

Title: The Safe Administration of Rapid Rituximab Infusion: An Evidence-Based Approach

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## **Abstract**

The goal of this study was to approach a global clinical issue that is imperative using an evidence-based approach to the investigation of the rapid administration of rituximab infusions for non-Hodgkin Lymphoma (NHL) and Chronic Lymphocytic Leukemia (CLL). This study focused on an evidence-based approach to improving patient safety, drawing on the Joanna Briggs Institute's model of evidence-based health care with its particular emphasis on evidence synthesis, evidence generation and evidence transfer.

The study consists of two central phases. The first phase is a comprehensive systematic review (CSR), which informed the design of a subsequent primary study that constitutes the second phase.

The specific systematic review question was: *"How safe is it to administer rituximab rapidly for NHL and CLL patients?"* The objective was to identify and synthesise the existing published and unpublished literature on the use of rapid rituximab infusion as an alternative infusion rate and its safety. The systematic review found that rapid rituximab infusion is not safe for chronic lymphocytic leukemia (CLL) patients yet it is safe for non-Hodgkin Lymphoma (NHL) patients. However, there was insufficient evidence to address other aspects of clinical concern related to the safe administration of the rapid infusion of rituximab. Therefore, a retrospective cohort study was conducted in Royal Adelaide Hospital (RAH), South Australia to elicit evidence that informs our current understanding of rapid rituximab infusion. The findings of the study identified high lymphocyte counts as the sole predictor of the occurrence and frequency of adverse drug events such as hypotension, hot flushes and itchiness. The evidence generated from the systematic review and primary study was transferred into a clinical guideline on administering rapid rituximab infusion safely and a pamphlet

for patients who are receiving the rapid regimen was developed.

# Declaration

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PROGRAM: Doctor of Philosophy

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And to God, who makes all things possible.

## **Chapter 1. Introduction to the study**

The intention of this thesis was to focus on a global clinical issue that is imperative and relevant in everyday clinical practice in oncology, using an evidence-based approach for the benefit of both clinicians and patients who are diagnosed with non-Hodgkin Lymphoma (NHL) and Chronic Lymphocytic Leukemia (CLL). This study consists of two major phases: firstly, a comprehensive systematic review (CSR); and secondly, a retrospective cohort study.

The principal review question was: *How safe is it to administer rituximab rapidly for NHL and CLL patients?* The objectives of the systematic review were to consider both the existing published and unpublished literature on rapid rituximab infusion as an alternative infusion rate that of off label use, and to synthesise the available evidence regarding its safe use. The findings from the systematic review recommend that rapid rituximab infusion is not safe for CLL patients yet it is safe for NHL patients. However, there was insufficient evidence to address other aspects of safe administration of rapid infusion. Therefore, a retrospective cohort study was conducted at the Royal Adelaide Hospital (RAH), South Australia to generate evidence on our current understanding of rapid rituximab infusion. The principal aim of this study was to determine the predictors of the occurrence, count and severity of adverse drug events.

### **Researcher's Clinical Experience in this Field of Study**

I am an oncology nurse and have worked in one of the two largest cancer centres in Singapore for 11 years. The cancer centre is located in National University Hospital. It is a principal teaching hospital for the National University Singapore Yong Loo Lin School of Medicine and consists of approximately 1000 beds. I specialise in administering cytotoxic therapy such as chemotherapy and immunotherapy in both

oncology and haematology patients. In addition to treating people with cancer, I am experienced in providing nursing care for patients with autoimmune/immune disorders and patients undergoing haematopoietic stem cell transplant.

## **Emergence of Monoclonal Antibody Therapy for Cancer Treatment**

The main treatments for cancer revolve around surgery, chemotherapy and radiotherapy. In recent years, monoclonal antibody therapy, which is more tolerable and possibly incurs less toxicity for patients, has emerged to replace and/or complement existing therapies. As the technology in monoclonal antibody therapy has advanced, it has become part of the mainstream therapy for some diseases, such as non-Hodgkin lymphoma (NHL) and rheumatoid arthritis (RA). Monoclonal antibody therapy is administered in single form or in combination with chemotherapy for curative reasons. It is also used as a maintenance therapy subsequently when patients achieve a complete remission from their diseases.

## **Side Effects of Cancer Treatment**

From clinical observations comparing chemotherapy and monoclonal antibody therapy, chemotherapy can cause immediate side effects and continually affect a patient's quality of life for weeks, and even months, after completion of treatment. Therefore, it can take up to several weeks for a cancer patient to recover fully from one course of chemotherapy to the next course of chemotherapy. However, patients find that monoclonal antibody therapy is more tolerable in comparison to chemotherapy. This is because monoclonal antibody therapy causes less immediate and long-term adverse effects, with the exception of anaphylactic shock and infusion-related reactions. Adam and Weiner<sup>1</sup> describe such reactions as mechanism-independent toxicity and mechanism-dependent toxicity. An example of the

monoclonal antibody therapy that is the focus of this thesis is rituximab (Mabthera, Rituxan) which is one of the drugs that I have most commonly used in the clinical setting.

## **Prevalence and Incidence of non-Hodgkin Lymphoma**

Based on the United States (US) statistics, the prevalence of non-Hodgkin lymphoma (NHL) was 454,378 including men and women in 2008.<sup>2</sup> In comparison with Australia, the incidences of lymphoid cancer in men and women were 4116 and 3160 in 2007. It was the most common hematological cancer in Australia.<sup>3</sup> Comparatively in Singapore, 1083 men and 758 women were diagnosed with NHL from 2005-2009. Lymphoma was ranked top 8 and 9 of the most common cancer in Singapore among men and women.<sup>4</sup> The statistics have reflected the enormous amount of rituximab being used by NHL patients in the west as well as in Asia.

## **Rituximab in Chemotherapy Regimen for non-Hodgkin Lymphoma**

Rituximab is usually administered in combination with chemotherapy. The sequence of intravenous administration starts with Rituximab (R) followed by chemotherapy, for example, Cyclophosphamide (C), Doxorubicin (H) and Vincristine (O). Oral Prednisolone (P) as part of the chemotherapy regimen, is given over 5 days, and the first dose is usually given in the morning with the rest of the drugs. This regimen is also known as RCHOP. Using acronyms to indicate a regimen of chemotherapy is a standard practice internationally. Therefore, the subsequent chapters of this thesis use such acronyms to refer to types of chemotherapy regimen.



## **Administration Rate of Rituximab**

The administration of rituximab is more complicated when compared to chemotherapy administration. It involves a carefully calculated infusion rate to be given over a defined duration. When rituximab is administered at the first cycle, the infusion rate is initiated at 50 mLs/ hr for 1 hour. The concentration of 1 mL is equivalent to 1mg. As a patient tolerates the drug (as assessed by the manifestation of normal body temperature, blood pressure, pulse and respiratory rate), the next infusion rate is escalated to 100 mLs/ hr for 30 minutes. When perfectly tolerated, the dose is increased by increments of 50mL per 30 minutes until a maximum rate of 400 mL/ hr is achieved or the infusion is completed. Vital signs monitoring is done every 15 minutes for the first hour, then every 30 minutes for each increment of infusion rate until the completion of the treatment, which is typically 5-6 hours depending on the total volume of dilution. If the patient tolerates the first cycle without grade 3 or 4 adverse drug events, the second and subsequent cycles are infusing over 3-4 hours. The infusion starting rate is different from the first cycle, starting at 100mL/hr for 30 minutes following by 100mL increments every 30 minutes until the maximum rate of 400 mL/hr or until the completion of infusion. The variation of duration of infusion is varied slightly among individual who is dependent on the total dosage or total volume. (Table 1)

*Table 1 Standard infusion rate for rituximab*

	<b>Standard rate (mL/hr)</b>
First Infusion	50mL/hr x 1 hour
	100mL/hr x 30 mins
	150mL/hr x 30 mins
	200mL/hr x 30 mins
	250mL/hr x 30 mins
	300mL/hr x 30 mins
	350mL/hr x 30 mins
	400mL/hr x 30 mins
	400mL/hr for remainder
	400mL/hr for remainder
Second & subsequent infusion	100mL/hr x 30 mins
	200mL/hr x 30 mins
	300mL/hr x 30 mins
	400mL/hr for remainder
Increase infusion rate only if vital signs are as follows: Systolic blood pressure (SBP) within 20 mmHg of baseline, Heart rate (HR) >60 or <120, Temperature < 38.3 degree Celsius	

The Common Terminology Criteria for Adverse drug event (CTCAE) version 4, page 1<sup>5</sup> an adverse drug event (AE) is

*any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure.*

There are five grades<sup>5</sup> used to measure the severity of an adverse drug event: grade 1 (mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated); grade 2 (moderate; minimal, local or noninvasive intervention indicated); grade 3 (severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling); grade 4 (life-threatening consequences; urgent intervention indicated); and grade 5 (death).

## **Duration of Rituximab Therapy**

As part of the cancer treatment protocol, patients usually not only receive one cycle of therapy but multiple cycles to make up a course of treatment. For example, RCHOP is given over six cycles and is considered to be one course of treatment that seeks to achieve a cure. When patients demonstrate complete response morphologically with no evidence of cancerous cells in the lymph nodes, bone marrow and/or clinically in remission, rituximab as monotherapy can be given as maintenance therapy every 2-3 month for up to 2 years.

## **Clinical Observation of a Patient's Tolerance of Rituximab**

From my personal and clinical observation, if a patient can receive the first infusion without severe adverse reactions, the subsequent infusions are usually uneventful. Therefore, patient refusal of vital signs monitoring commonly occurs in the clinical setting. These patients complain that blood pressure measurement is an extremely

uncomfortable and painful procedure. Therefore, patients prefer to inform nurses if they are feeling unwell rather than allowing the nurses perform vital signs monitoring on a regular intervals.

Up until now, drug manufacturers' guidelines recommend close monitoring in all cycles of rituximab infusions regardless of the outcomes of the first or subsequent cycle of infusion because of the possibility of a possible fatal infusion-related adverse drug event. Under such circumstances when patients request lesser vital signs monitoring, nurses tend to modify the monitoring schedule in accordance with patient preference and assess a patient's physical condition continuously or at the stipulated times without performing the vital signs measurement as specified by the drug manufacturers. Furthermore, currently in my practice institute, no specific institutional policy is generally available to address this issue.

### **The Clinical Burden of Rituximab Infusion**

The purpose of lengthy rituximab infusion is to prevent patients experiencing any acute adverse drug events that could be potentially fatal. However, lengthy rituximab infusion over 3-4 hours, particularly during the second and subsequent infusion cycles results in an increased healthcare burden of more staff time, costs and resources as nurses spend more time monitoring patients. To elaborate further, rituximab is usually administered in the ambulatory setting. Some cancer centres have instituted varied fees based on the length of infusion, for example, a patient will need to pay more if the duration of infusion exceeds 2 hours.

## **Global Interest in Seeking Alternative Administration Rates for Rituximab Infusion**

Many clinicians and health care providers are interested in alternative methods to administer rituximab over a shorter time period. This is because they need to meet the increasing demand from the cancer patients who require rituximab therapy and the consequent demands on healthcare providers' time and resources, while at the same time respecting and incorporating patient preferences - the hallmark of evidence-based health care.

## **Chapter 2. Background to the study**

### **Theoretical Framework**

#### **The Historical Emergence of Evidence-based Health Care (EBHC)**

Evidence-based practice (EBP) is the hallmark of high quality medical care. The evidence-based movement was largely initiated by Professor David Sackett from the University of Oxford in the early 1990s in the guise of evidence-based medicine (EBM). He and colleagues defined EBM as:

*The conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research.*<sup>6</sup>

EBP is not limited to EBM and the underpinning knowledge of EBM is now applied to other health care disciplines such as nursing and allied health. The term evidence-based health care (EBHC) was coined by Professor Alan Pearson and colleagues through the establishment of The Joanna Briggs Institute (JBI) in the mid-1990s. The JBI collaborates with all health care professionals to generate evidence through rigorous research activities: synthesising the evidence by conducting comprehensive systematic reviews; translating the best available evidence into clinical guidelines; and using the evidence through best practice implementation projects. This model is a cyclical process that aims to improve global health.

#### **The Joanna Briggs Institute (JBI) Model of EBHC**

There are three world leading international, independent organisations promoting evidence-based health care, specifically: the Joanna Briggs Institute (JBI), the Cochrane Collaboration and the Campbell Collaboration. The JBI model of evidence-based healthcare recognises that evidence is generated through research, theory and practice.<sup>6</sup> It identifies numerous sources of evidence, for example, from randomised

controlled trials, observational studies, human experiences and expert opinion. The JBI model differs from the approaches of the Cochrane and Campbell Collaborations by adopting a broader perspective of evidence. The Cochrane Collaboration focuses on effectiveness studies using randomised controlled trials. The JBI model emphasises a holistic approach and is able to address diverse questions that arise out of the clinical setting.

### **Framework of the JBI Model**

The JBI model of evidence-based health care consists of four key components: evidence generation, evidence synthesis, evidence transfer and evidence utilisation.<sup>7</sup>

#### ***Evidence Generation***

Under the structure of the JBI model of EBHC, evidence refers to a fact that is true. It classifies evidence into four categories: evidence of feasibility, of appropriateness, of meaningfulness and of effectiveness. Under this model, evidence is generated through research, experience and the formation of discourse. It considers both qualitative and quantitative data as empirical. As long as the generation of evidence is sound and grounded within a paradigm that matches the methodology and method accurately, it is considered to be valid and acceptable in this model.

#### ***Evidence Synthesis***

Evidence synthesis is the pooling of the results of primary research studies, re-analysing the primary data and presenting the results, which may or may not support the original claims, from an individual research study. Evidence synthesis is pragmatically achieved through conducting a systematic review.

#### ***Evidence Transfer***

When there is sufficient evidence available to support the implementation of practice, it is necessary to transfer the evidence from a systematic review to another design for

easy access and quick reading. The most common approaches to this process include clinical practice guidelines, best practice information sheets and evidence summaries. The JBI is making ongoing efforts to transfer the evidence into consumer-focused pamphlets in order to increase the uptake of the evidence by health care providers, patients and clients.

### ***Evidence Utilisation***

Evidence utilisation is the final step in the JBI model to improve global health. It is the most difficult act to carry out as it involves change not only targeted at individuals but also on a large scale involving groups, communities, and countries. Action research is the most widely used strategy to engage people in change and to preserve the outcome of the change. Using clinical audit through best practice implementation projects has resulted in many successful stories.<sup>8, 9</sup> For example, nurses' compliance of bath bathing and hand hygiene in in-patients oncology wards. As a result, clinical practice change based on best practice is increasingly valued globally.

In summary, the JBI model of EBHC is extremely useful in providing the framework to guide the health care industry on how to use evidence strategically in improving patients' health or medical outcomes in different ways. This study focuses on the utilisation of the JBI model in evidence synthesis, evidence generation and evidence transfer to address a patient safety issue – specifically whether there is a safe alternative infusion rate of rituximab.

Part 1 of the subsequent literature review examines the history of rituximab and particularly the following: indications; mechanism of action; pharmacodynamics; pharmacokinetics; route of administration; dosage; administration rate; premedication; and adverse reactions. It focuses on early trials leading to approval by the FDA (Food and Drug Administration) in the United States for public use. Part 2 of



the review focuses on the literature related to adverse drug events resulting from rituximab infusion. Part 3 of the review explores the predictors of adverse drug events resulting from rituximab infusion.

## **Literature Review**

### **Part 1: Historical background of Rituximab**

#### ***Burden of Cancer***

The American Cancer Society has released a report on cancer incidences in the US this year. The report has estimated 1,638,910 new cases of cancer will be diagnosed in 2012 and 557,190 people are estimated to die from cancer.<sup>10</sup> Cancer has been the number one cause of death in Singapore since 2007. The latest available statistics (of 2009) reveal that cancer remains the top ranked cause of death in the Singapore population, amounting to 29.3% of the total number of deaths.<sup>11</sup> Lymphoma and leukemia ranked number 9 (2.6%) and 10 (2.4%) respectively in both females and males of the total number of deaths in the period 2005-2009.<sup>4</sup> Of the total numbers of reported cancer through the Singapore Cancer Registry for 2005-2009, there were 4.5% of male and 3% of female diagnosed with lymphoma.<sup>4</sup>

#### ***Prevalence and Incidence of Non-Hodgkin Lymphoma and Chronic Lymphocytic Leukemia***

Lymphoma can be categorised into two main subgroups: Hodgkin lymphoma (HD) and non-Hodgkin lymphoma (NHL). This study focuses on NHL. In the United States (US), 454,378 people are living with NHL; and estimated 19,320 (29.11%) people had died from the disease in 2011.<sup>2</sup> The recent statistics' update has predicted that incidence of NHL will be 70130 in 2012.<sup>10</sup> Although the number of patients with NHL is somewhat lesser in comparison to other type of cancers, if treated, the overall 5 years survival rate is promising, ranging from 51.8% to 81.1% depending on the stage of disease.<sup>2</sup> Therefore, it is worthwhile to spend a significant amount of effort to

determine how NHL patients can be treated effectively without compromising their safety.

The prevalence of CLL is less common as compare to NHL. The American Cancer Society has estimated 16060 new incidences of CLL in 2012 and 4580 people will be dying from this cancer.<sup>10</sup>

Considering the life expectancy of Singapore residents is 81.4 years old at birth.<sup>11</sup> When we based on the US statistics in 2008, the median age at diagnosis of NHL was 66 and people died from NHL at 75 years old. As mentioned previously, conventional chemotherapy can cause many unwanted side effects and advancing age is becoming a key factor when clinicians determine whether or not a patient is fit to receive treatment. However, with the invention of rituximab (Mabthera, Rituxan), elderly patients are given a new hope to continue receiving standard treatment for a cure and with low toxicity.

### ***Indications for Rituximab***

In November 1997, FDA<sup>12</sup> approved rituximab (Rituxan, IDEC Pharmaceuticals Corp., San Diego, California, and Genentech Inc., South San Francisco, California) for relapsed or refractory CD20 positive low-grade NHL, particularly in follicular lymphoma patients.<sup>13</sup> Until then, the following diagnoses indicated the use of rituximab as part of treatment:<sup>14</sup>

- CD 20 positive, previously untreated, stage III/IV Follicular, B-cell non-Hodgkin Lymphoma;
- CD 20 positive, relapsed or refractory low grade or Follicular, B-cell non-Hodgkin Lymphoma;

- CD 20 positive, Diffuse Large B-cell non-Hodgkin Lymphoma (DLBCL) in combination with chemotherapy;
- CD 20 positive Chronic Lymphocytic Leukemia (CLL) in combination with chemotherapy; and
- Severe Rheumatoid Arthritis intolerance to at least one tumour necrosis factor (TNF) antagonist therapy in combination with Methotrexate.

Although rituximab has been used in Rheumatoid Arthritis (RA)<sup>15</sup> and dermatology,<sup>16</sup> for the purpose of this discussion, the focus is on NHL and CLL. This is because they are both haematological malignancies that affect the blood, lymph nodes and bone marrow. Thus, the homogeneity of the population can be maintained for the subsequent systematic review. NHL originates from cancerous lymphocyte cells within the lymph nodes. Conversely, CLL originates from the bone marrow. There are 4 main types of leukemia; CLL is categorised as chronic (C) because of its slow and gradual build up of disease characteristics. The middle letter of CLL differentiates the leukemia origins from myeloid (M) or lymphoid (L) cell lines.

### ***Classification Tool for NHL and CLL***

For the purpose of this study, all classifications of lymphoma specifically for NHL and CLL are acceptable. Current available NHL classifications are derived from the Working Formulation, World Health Organisation (WHO), and the Revised European-American Lymphoma classification.<sup>17</sup> The International Statistical Classification of Diseases and Related Health Problems (ICD) also categorises NHL and CLL.

### ***The Mechanism of Rituximab Action***

In plain language, rituximab kills CD 20 positive lymphocytes. There are three mechanisms commonly used to describe how rituximab triggers binding between human antibodies and tumour cells leading to cell death. These mechanisms were tested in an animal study using 4 monkeys.<sup>18</sup> Zhou et al.<sup>19</sup> described them in the following terms. The first mechanism is called antibody-Dependent Cellular Cytotoxicity (ADCC). When rituximab's fragment antigen binding (Fab) domain binds to antigens on the surface of CD-20 cells, the human (fragment crystallisable) Fc domain of the drug is able to draw human immune effector cells, natural killer cells, monocytes and macrophages causing either cell lysis or phagocytosis. The second mechanism is called Complement-Dependent Cytotoxicity (CDC). The Fc domain of rituximab activates the complement system leading to cell lysis. The third mechanism is called apoptosis (programmed cell death)<sup>20, 21</sup> through the presence of crosslinking with a secondary antibody.<sup>22</sup> The programmed cell death refers to the cells' condition when they are programmed to die in a single timeframe involving a series of morphological changes and DNA degradation.<sup>20</sup> Of these three mechanisms, CDC emerged as the most potent<sup>23</sup> and effective mechanism for cell killing.<sup>24</sup> In an in vitro study, Cardarelli et al.<sup>23</sup> observed that Burkitt's lymphoma (BL) cell line is the most sensitive to CDC killing.

In addition to these three mechanisms, rituximab has a direct action against tumor activity through intracellular signaling pathways without activating the host immune system.<sup>25</sup> One study<sup>26</sup> has suggested that a combination of various cytotoxic drugs such as Bendamustine, Cladribine, Doxorubicin and Mitoxantrone enhance the chemosensitising for cell killing - a synergising effect.<sup>25</sup>

### ***Pharmacodynamics and Pharmacokinetics of Rituximab***

The pharmacodynamics of rituximab is described as follows: when rituximab is infused at standard rates intravenously, it is absorbed directly, resulting in rapid depletion of circulating B-lymphocytes. After 3-6 months completion of the treatment, the drug remains detectable in the serum blood.<sup>27, 28</sup> Rituximab is then excreted through the reticuloendothelial system via phagocytosis and catabolism.<sup>13</sup> However, the exact pathway is uncertain. The mean half-life of rituximab is 60 hours (11 to 105 hours) at the initial dose. Conversely, a Japanese study reports a longer mean half life of  $387.7 \pm 188.9$  hours at  $375 \text{ mg/m}^2$ .<sup>28</sup> The concentrations of rituximab in the patients' body were measured from 0.8 to 518  $\mu\text{g/mL}$  at pre-infusion level, and 3-4 to 963 $\mu\text{g/mL}$  at post-infusion level respectively.<sup>29</sup> Two years later, a similar result was reported in another study.<sup>30</sup> It recorded pre-infusion levels from 0-898  $\mu\text{g/mL}$  to post-infusion levels of 582to 1177 $\mu\text{g/mL}$ . Based on the above mentioned reports, it is suggested that an increase in the number of rituximab doses may increase its half-life.<sup>18</sup>

### ***Efficacy and adverse drug events of Rituximab Clinical Trials***

#### ***Phase I Clinical Trial for 4 Weekly Rituximab in NHL***

Melaney et al. conducted the first phase I clinical trial in 1994.<sup>31</sup> The trial recruited 15 patients with relapsed low grade B-Lymphoma so they could be treated with a single dose of 10, 50, 100, 250 or 500  $\text{mg/m}^2$ , respectively. The research team collected patients' circulating CD-20 cells and monitored them for any adverse reactions. Nearly half of the patients recruited to the trial demonstrated some response. The most often occurring acute adverse drug events were fever following by nausea, rigor, orthostatic hypotension and bronchospasm. Three years later, in 1997, the same investigators, Melaney et al.<sup>29</sup> conducted a second phase I clinical trial to evaluate the safety, pharmacokinetics and biological effects of the different doses of

IDEC-C2B8. Prior approval of rituximab by FDA, it was named as IDEC-C2B8. In this trial, they recruited 20 relapsed low or intermediate or high grade Lymphoma patients to receive weekly infusion at 125, 250 or 375 mg/m<sup>2</sup>. Six patients demonstrated partial remission and five patients indicated some response. The trial selected 375mg/m<sup>2</sup> to be used for the subsequent phase II clinical trial.

*Phase II Clinical Trial for 4 Weekly Rituximab in Low Grade NHL*

Rituximab dosage at 375mg/m<sup>2</sup> weekly for 4 weeks was effective for patients with relapsed or low grade FL in a phase II clinical trial. The trial<sup>29</sup> involved multi-site research centres in the US. There were 37 patients with a median age of 58 (29-81 years old) recruited to the study. Seventeen patients achieved clinical remission (3 complete, 14 partial remission). The intention to treat response was 46%. As the number of infusions increased, the infusion's duration was shortened. In terms of the safety profile, 32 (86.5%) patients experienced adverse drug events during the trial; six out of 32 patients developed grade 3 or grade 4 adverse drug events (there were 12 events in total), which were mostly long-term side effects. Acute adverse drug events or infusion-related reactions were mostly grade 1-2 including fever, chills, respiratory symptoms and hypotension. These reactions occurred during initial infusion and diminished in subsequent infusions. Based on the findings from this trial, a Japanese trial<sup>28</sup> studied the same regimen to assess if Japanese relapsed B-cell Lymphoma patients would be similar. This was a small scale study using only 12 patients. Of these, two showed complete response and there was a partial response in five patients. The acute adverse drug events were mostly grade 1 and 2 associated with flu-like symptoms and skin reactions. The grade 3 events were related to haematological toxicities, which were temporary. A UK trial also used the same regimen for 48 patients.<sup>32</sup> Of those patients, only 10 out of 42 NHL or low grade

Lymphoproliferative Disease (LPD) patients achieved partial remission. For the safety profile, 14 patients developed 20 adverse drug events. Of these events, 14 were grade 1 and six were grade 2. There was no difference in the frequency of the occurrence of events in patients with high circulating neoplasms cells in comparison to those without. Fifteen out of 20 adverse drug events occurred at the initial infusion which was similar to what was found in other studies.<sup>29, 33, 34</sup> The most common events were fever, rigors, pain, headache, hypotension and nausea.

#### *Phase II Clinical Trial for 8 Weekly Rituximab in Low Grade NHL*

From 1999 onwards, the phase II clinical trial shifted the focus from the efficacy of rituximab 375mg/m<sup>2</sup> as monotherapy from 4 weekly to 8 weekly for patients with relapsed or refractory low grade FL. This study<sup>30</sup> reported that 57% of 37 patients demonstrated a response to treatment. Although this is a single arm study, five patients showed complete response and 14 patients had a partial response that was slightly higher compared to previous studies using weekly rituximab for 4 weeks.<sup>28, 29, 33, 34</sup> Almost all the patients experienced some degree of adverse drug events, recording 188 episodes of adverse drug events among 34 patients. The adverse drug events during infusion were fever, chills, asthenia, nausea and headache. Similar to other studies<sup>28, 29, 33, 34</sup>, the reactions were primarily associated with the first infusion and declined with subsequent infusions. Four patients developed grade 3 acute adverse drug events chiefly comprising urticaria and chills.

#### *Phase II Clinical Trial of Rituximab in Progressive Intermediate Grade NHL*

The first trial<sup>35</sup> to report the use of rituximab in patients with progressive intermediate grade NHL after high dose chemotherapy and peripheral stem cell transplant occurred in 1999. This was a retrospective case series study with only seven patients involved. Of these patients, the overall response rate was 86% with one patient achieving

complete remission. Forty-one adverse reactions were recorded with 28 adverse drug events associated with initial infusion.

In the same year, the first randomised control trial<sup>33</sup> of rituximab was conducted involving patients with intermediate and high grade NHL in Europe and Australia. A total of 54 patients were randomised into two arms. Arm A consisted of 28 patients (8 cycles of weekly infusion of rituximab at 375mg/m<sup>2</sup>) and arm B, 26 patients (1 cycle of rituximab at 375mg/m<sup>2</sup> following by weekly at 500mg/m<sup>2</sup>). Five patients responded fully and 12 had a partial response for both arms. There was no statistical difference between the two arms. Almost all patients experienced adverse drug events during infusion; however, the majority of these events were grade 1 and 2. Nine patients from each arm experienced grade 3 or 4 adverse drug event; arm B exhibited a slightly higher percentage than arm A. The most commonly reported adverse drug events were associated with fever, rigors, hypothermia and oedema. The frequency and severity of adverse drug events declined in subsequent cycles.

#### *Phase II Clinical Trial for Rituximab in NHL with Bulky Disease*

This trial was one of the earliest studies evaluating the effectiveness of rituximab in low and intermediate NHL with bulky disease.<sup>36</sup> The definition of bulky disease is the presence of at least one lesion measuring >10cm at its greatest diameter. The trial recruited 31 patients with 28 of them evaluated for response to treatment. One patient demonstrated complete remission and 12 experienced partial remissions. The most commonly occurring acute adverse drug events were fever and chills. Similar to other trials,<sup>28-30, 33, 34</sup> these events were grade 1 and 2, and associated with initial infusion.

#### *Phase II Clinical Trial for Rituximab in Less Common NHL*

Rituximab has also been evaluated in a phase II clinical trial for less common B-cell malignancies.<sup>37</sup> Thirty six out of 131 patients who were diagnosed as Mantle Cell



Lymphoma (MCL), Immunocytoma or Small B-cell Lymphocytic Lymphoma (SLL) responded to rituximab with a complete or partial remission, with an overall response rate of 27%. The most commonly occurring acute adverse drug events were fever, chills and pain. They occurred mostly in the first infusion. In this study, 8 patients were not able to complete the treatment and were withdrawn from the study because of adverse drug events.

*Phase III Clinical Trial for 4 Weekly Rituximab in Low Grade NHL*

Thirty-one centres in the US and Canada conducted a phase III clinical trial<sup>34</sup> to assess the effectiveness and safety of rituximab at 375mg/m<sup>2</sup> weekly for 4 cycles in patients with relapsed low grade FL. One hundred and sixty-six patients were included in this trial and of those patients, 48% responded to the treatment. The initial infusion-related reactions were grade 1 and 2 fever and chills. Only 12% and 4% of patients had grade 3 and 4 events respectively. The findings of this trial led to the approval of rituximab for indolent B cell Lymphoma (Rituxan; IDEC Pharmaceuticals, San Diego, CA, and Genentech, Inc, San Francisco, CA) by the FDA on 26 November 1997.<sup>38</sup>

A Swiss group of clinical researchers used the same regimen<sup>38</sup> to evaluate the effectiveness of rituximab for patients with follicular and Mantle Cell Lymphoma (MCL). FL patients achieved a better response rate of 52% versus 22% as compared to MCL<sup>39</sup> Similar to other studies,<sup>38</sup> the most common adverse drug events<sup>38</sup> were grade 1 and 2 fever and chills associated with the first infusion.<sup>39</sup>

The above studies mainly employed rituximab as a form of monotherapy. The following discussion examines the extended application of rituximab in combination with chemotherapy, radiotherapy, and monoclonal antibody therapy in treating NHL. It is followed by a discussion of clinical trial findings and safety profiles in CLL.

*Phase II Clinical Trial for Rituximab in Combination with Chemotherapy in NHL*

The most popular chemotherapy regimen is rituximab in combination with CHOP (Cyclophosphamide, Doxorubicin, Vincristine and Prednisolone) for NHL. One study reported a very high response rate of 95% by using this regimen in 40 indolent (low-grade) B cell Lymphoma patients.<sup>40</sup> Another regimen - RIME (Rituximab, ifosfamide, mitoxantrone, etoposide) - was used in 22 B cell NHL patients prior to autologous stem cell transplant (ASCT). The overall response to treatment was 90% and minimum toxicities were reported.<sup>17</sup> The other examples of regimen include RC (Rituximab, Chlorambucil)<sup>41</sup>, RICE (Rituximab, Ifosfamide, Carboplatin, Etoposide), RDHAP (Rituximab, Cisplatin, Arac, Dexamethasone)<sup>42</sup> and RFCM (Rituximab, Fludarabine, Cyclophosphamide, Mitoxantrone).<sup>43</sup>

*Phase II Clinical Trial for Rituximab in Combination with Radiotherapy in NHL*

A study<sup>44</sup> looking at rituximab in combination with radiotherapy was conducted in 1999. The aim of the first phase I/II clinical trial was to evaluate the efficacy and safe use of rituximab in combination with Yttrium-90 Ibritumomab Tiuxetan for refractory or relapsed B cell NHL. The overall response rate was 67% in 51 patients. As the treatment modality involved radiotherapy, grade 3 or 4 adverse drug events were associated with haematologic toxicity such as thrombocytopenia.

*Phase II Clinical Trial for Rituximab in Combination with Interferon-alpha 2a in NHL*

Rituximab has also been used in combination with Interferon-alpha 2a for NHL. A phase II clinical trial<sup>45</sup> was conducted in patients with relapsed low grade NHL to evaluate the clinical activity and safety of utilising Interferon-alpha 2a with rituximab. Sixty-four patients were recruited to this study and 70% responded to the treatment with 33% ending up in complete remission. In terms of adverse drug events, 53 patients experienced 272 episodes. The most commonly reported acute events were

fever and hypotension. The long-term effects of therapy were bone marrow suppression and especially leucopenia.

#### *Phase II Clinical Trial for Rituximab in Stem Cell Transplant*

The role of Rituximab in stem cell transplant can be applied for stem cell harvesting; pre- and post-stem cell transplant. Buckstein et al.<sup>46</sup> administered one dose of 375mg/m<sup>2</sup> rituximab 2 days before the stem cell mobilisation and 8 cycles after the Autologous Stem Cell Transplant (ASCT). The preliminary results from this study suggest that the use of rituximab prior to stem cell harvesting yielded higher CD 34 counts when compared to a control group. McGuirk et al.<sup>47</sup> used rituximab in combination with irradiated donor lymphocyte to treat 2 patients who underwent allogenic stem cell transplant and developed Epstein-barr virus associated with Lymphoproliferative Disease (LPD). Both patients responded to treatment initially but the first one died 43 days post-infusion. The second patient remained well after 6 months post-rituximab infusion. In 2000, Milpied et al.<sup>48</sup> used rituximab for transplant patients including both bone marrow and solid organs to treat B cell LPD and yielded an overall response rate of 69%. Patients with bone marrow transplants demonstrated a higher response rate of 83% in comparison to 65% in solid organ transplant patients.

#### *Phase I Clinical Trial for Rituximab in CLL*

The use of rituximab in CLL started much later than NHL. In 2001, a phase I clinical trial<sup>49</sup> was conducted to investigate the maximum tolerated dose for CLL and other leukemia patients. Fifty patients received the first dose of rituximab 375mg/m<sup>2</sup> over 6 to 12 hours. In subsequent cycles (2-4), each patient was assigned to different groups with a higher dose including 500, 650, 825, 1000, 1500 and 2250mg/m<sup>2</sup>. Each infusion was administered weekly for 4 weeks. The overall response rate combining all levels of doses was 40%. The majority of the study population consisted of CLL

patients and a subgroup analysis demonstrated that CLL patients responded at 500mg/m<sup>2</sup>, 1000mg/m<sup>2</sup>-2250mg/m<sup>2</sup>. None of the patients in the 650mg/m<sup>2</sup> and 825mg/m<sup>2</sup> responded to rituximab. During the first infusion at 375mg/m<sup>2</sup>, almost all patients (94%) developed grade 1 or 2 adverse drug events such as fever and chills. Six (12%) patients experienced grade 3 or 4 adverse drug events. Patients appeared to tolerate the higher doses in subsequent infusions better. Indeed, only 3 out from 35 patients in the group of the dose range of 500mg/m<sup>2</sup> to 1500mg/m<sup>2</sup> experienced a grade 1 adverse drug event (hypotension, nausea and malaise). In the highest dose group (2250mg/m<sup>2</sup>) 8 out of 12 patients experienced grade 2 adverse drug events (fever, chills, nausea and malaise).

#### *Phase II Clinical Trial for Rituximab in CLL*

In Germany, researchers conducted a phase II clinical trial<sup>50</sup> involving 6 centres. The trial used rituximab in combination with Fludarabine for CLL patients. In the trial protocol, the administration of Fludarabine in 25mg/m<sup>2</sup> occurred in weeks 1, 5, 9, and 13 for 5 days in each week. In weeks 9 and 15, rituximab was given in combination with Fludarabine. The first rituximab infusion in week 9 was administered over 3 days where dosage was “stepped up”. Subsequently, rituximab alone was given at week 17 and 21. The overall response rate was 87% in 27 patients. Patients reported mostly acute adverse drug events including chills, fever and erythema graded at 1 and 2 and associated with the first infusion.

The evidence generated from the previous study informed the conduct of a randomised clinical trial<sup>51</sup> of rituximab in combination with Fludarabine in a sequential or concurrent regimen. In the sequential regimen, Fludarabine (25mg/m<sup>2</sup>) was first administered daily for 5 days and repeated every 28 days for a total of 6 cycles followed by 4 weekly Rituximab (375mg/m<sup>2</sup>). In the concurrent regimen,

rituximab was administered on days 1 and 4 concurrently with Fludarabine in cycle 1. In the subsequent 5 cycles, only rituximab was administered on day 1. A total of 104 patients were recruited to the study with 53 and 51 patients randomly assigned to the sequential and concurrent arm respectively. There were seven patients in the concurrent regimen who received an escalation rate so that Rituximab infusion was completed within 1-4 hours. Patients in the concurrent regimen achieved an overall response rate of 90% versus 77% in the sequential regimen. Patients in concurrent regimens demonstrated better response rate but experienced infusion-related side effects. One hundred percent of patients experienced grade 1 or 2 adverse drug events such as fever, chills/rigors, dyspnea and hypotension associated with the initial infusion. There were 9 (20%) patients who also experienced grade 3 and 4 adverse drug events. However, compared to the 7 patients who received an escalation rate of Rituximab, none of the patients reported grade 3 or 4 adverse drug events. In the sequential regimen, infusion-related side effects were observed in 9 (5%) patients. Of these 9 patients, only 1 patient developed grade 3 hypotension.

Despite the multiple trials conducted for different kind of cancer, the FDA approved the use of rituximab is only for four types of cancer patients.<sup>52</sup> There were clinical trials conducted for non-cancer conditions as well, namely: Multiple Sclerosis (MS),<sup>53</sup> Refractory Thrombotic Thrombocytopenic Purpura (TTP),<sup>54</sup> Systemic Lupus Erythematosus (SLE),<sup>55</sup> Epidermolysis Bullosa Acquisita (EBA)<sup>22</sup> and Rheumatoid Arthritis (RA)<sup>56</sup> that would not be discussed in this study.

### ***The Route of Rituximab Administration in Clinical Trials***

The Food and Drug Administration approved the intravenous route of rituximab administration. However, other modes of administration are used in the clinical setting. Clinical trials have examined intralesional and intrathecal rituximab

administration. A case report<sup>57</sup> published in 2000 involving 2 patients with cutaneous B cell Lymphoma states that cutaneous tumours were cured with intralesional rituximab. The two patients suffered pain during injection transiently and one of them reported increased temperature. Otherwise, they tolerated the injection well and there were no reported systematic adverse drug events. One year later, another study<sup>58</sup> reported on 3 cutaneous B cell Lymphoma patients with CD 20 expression who responded to the intralesional rituximab therapy.

Non-Hodgkin Lymphoma may lead to metastasises in the central nervous system (CNS). A patient with indolent Follicle center-Hodgkin Lymphoma was reported to have developed facial nerve palsy and right side paralysis with severe headache. This patient did not respond to radiotherapy and developed lower extremity weakness and back pain after radiotherapy. High dose steroid therapy did not alleviate any of the symptoms. Subsequently, the patient was given rituximab 800mg weekly for 4 weeks. This patient was able to walk and the neurological symptoms declined. Intrathecal chemotherapy alternating with rituximab for 5 months was administered and the patient responded to treatment completely.<sup>59</sup> Thus, intraventricular rituximab appears to be feasible for NHL with CNS involvement.<sup>60</sup>

The newest method of administration of rituximab is subcutaneous and a pilot study<sup>61</sup> has demonstrated the feasibility and effectiveness of administering one dose of 20mg intravenously followed by subcutaneous 20mg thrice weekly for 6-12 weeks in 4 CLL patients.

### ***The Dosage of Rituximab in Clinical Trials***

The rituximab's dosage varies across different years of clinical trials. In the initial trial in 1997,<sup>44</sup> the dosage was 250mg/m<sup>2</sup>. In another study,<sup>28</sup> 250mg/m<sup>2</sup> was used as the starting dose, escalating to 375mg/m<sup>2</sup> if the patient tolerated the initial dose.

Depending on the overall treatment plan or disease that is intended to treat, there is a difference in the number of cycles of rituximab administration. A dose of 375mg/m<sup>2</sup> once weekly for 4 weeks was the proposed dosage in earlier clinical trials seeking approval from the FDA in 1997.<sup>17, 28, 29, 32, 34, 35, 37, 44, 62</sup> The average dose was 711mg ranging between 562-825mg in those clinical trials.<sup>29</sup> From 1999 onwards, it was reported that 375mg/m<sup>2</sup> once weekly for 6-8 weeks was more effective.<sup>29, 30, 63</sup>

A dose of 375mg/m<sup>2</sup> has been approved for indolent lymphoma.<sup>14</sup> For more aggressive lymphoma, one study tested a dose of 500mg/m<sup>2</sup> during the phase I clinical trial; 500mg/m<sup>2</sup> was considered to be the maximum tolerated dosage. In this study,<sup>33</sup> the first group of patients received 375mg/m<sup>2</sup> once weekly for 8 weeks and the second group of patients received 375mg/m<sup>2</sup> on day 1 followed by 500mg/m<sup>2</sup> on day 8 once weekly for 7 weeks.

In the stem cell transplant setting, 375mg/m<sup>2</sup> was administered 2 days before stem cell collection followed by 8 cycles of maintenance therapy after autologous stem cell transplant. The purpose of administering a rituximab infusion prior to stem cell collection is to achieve in vitro purging.<sup>46</sup> In the radioimmunotherapy trial,<sup>44</sup> the rituximab was given either at 100 or 250mg/m<sup>2</sup> prior radiation followed by 375mg/m<sup>2</sup> weekly for 4 weeks. For treating cutaneous B-cell lymphoma, intralesional rituximab was given 3 times per week. Each injection consisted of 3mls of stem solution (10mg/mL). The cycle was repeated for 6 cycles every 28 days.<sup>57</sup>

### ***The Administration Rate of Rituximab***

According to manufacturers' guidelines, the acceptable range of rituximab concentration after dilution is between 1-4mg/mL.<sup>64</sup> However, the majority of trials adopted a preferred concentration of 1mg in 1mL.<sup>28-30, 62</sup> For the rituximab administration rate, many trials continued to follow the drug manufacturers'

recommendation to start the initial rate at 50mg/hr for the first hour and an escalation of rate of 50mg/hr increments every 30 minutes to a maximum of 300mg/hr.<sup>30, 33, 44</sup> The second and subsequent infusion would be given at 100mg/hr and increased to 200mg/hr following by 300mg/hr every 30 minutes to a maximum rate of 400mg/hr.<sup>33, 37, 44</sup> Therefore, the initial infusion was completed on average within 5 hours with subsequent infusions completed within 3.1 to 4.5 hours.<sup>33</sup> One study<sup>7</sup> started the initial infusion rate at 50mg/hr for 30 minutes and escalated it every 30 minutes to a maximum rate of 200mg/hr. The subsequent infusions began at 200mg/hr. Therefore, the initial infusion took 5.6 hours (range 1.5-12.7) on average to complete and subsequent infusions were completed at 4.5, 4.4 and 4.2 hours in cycles 2, 3 and 4 respectively. As the number of cycles increased, their duration shortened.<sup>29</sup> Other studies have taken the more conservative approach compared to the above mentioned studies. Two studies<sup>28, 62</sup> used an initial infusion rate of 25mg/hr for one hour with escalation of 100mg/hr at the next hour with a maximum rate of 200mg/hr. Another study<sup>35</sup> does not report the specific infusion rate but reported “a slow infusion over 3-5 hours”.

### ***The Premedication of Rituximab in Clinical Trials***

A premedication comprising antipyrexia, antihistamine and corticosteroids is recommended prior to rituximab infusion to reduce the likelihood of fatal adverse reactions.<sup>14</sup> Varying types of combination of premedication have been used in clinical trials. The most commonly used premedication is 650mg oral Paracetamol and 20-50 mg oral or intravenous Diphenhydramine. Patients typically receive these medications 30 minutes prior to infusion.<sup>33, 35, 44, 51</sup> The same drugs have been used in other trials but with higher or lower dosages. One trial<sup>17</sup> used a higher dosage of oral Paracetamol (1000mg) and Diphenhydramine hydrochloride (50 to 100mg). Another trial<sup>28</sup> used a



smaller dosage of oral Paracetamol (500mg) and oral Diphenhydramine (30mg). Besides Diphenhydramine, one trial<sup>37</sup> used Chlorpheniramine as an antihistamine instead. Another trial<sup>62</sup> replaced Paracetamol with Ibuprofen (200mg) in combination with Chlorpheniramine Maleate (2 mg). One trial<sup>50</sup> used exceptionally minimal premedication of oral Paracetamol (1000mg) given 30 minutes prior infusion.

### ***The Measurement of Adverse Drug Events in Clinical Trials***

There are three instruments most often used to measure adverse drug events resulting from rituximab infusion. The most commonly adopted measurement tool was developed by the National Cancer Institute (NCI) and this tool has evolved, with different versions emerging corresponding to publication of clinical trials and of the National Cancer Institute (NCI) Adult Toxicity Criteria from 1997-1999<sup>29, 30, 33, 44</sup> and the National Cancer Institute Common Toxicity Criteria (NCI CTC) version 2 from 2000-2003 respectively.<sup>37, 50, 51</sup> In two clinical trials conducted by a Japanese Clinical Oncology group, an expanded version of NCI adult toxicity criteria<sup>28, 65</sup> and the World Health Organization (WHO) 3-point scale from Grade I-III (mild, moderate, severe) were used to measure the severity of adverse drug events.<sup>32</sup> All these tools are similar to each other. Although the NCI measurement tools use scales of 0-4 or 1-5, these scores are equivalent to mild, moderate, severe and death when reporting the adverse drug event.

### ***The Management of Adverse Drug Events in Clinical Trials***

Regardless of the severity of an adverse drug event, the first step in managing events linked to the administration of rituximab is temporarily interrupting the infusion rate.<sup>29, 33, 37, 28, 50, 51</sup> When the signs and symptoms are resolved, the infusion rate is usually re-started at half of the previous rate.<sup>33, 37, 50</sup> Intravenous hydration and oral Allopurinol 300mg daily are administered for patients who are at risk of tumour lysis

syndrome.<sup>33, 37, 51</sup> Other supportive medications used to alleviate the symptoms are antipyretics,<sup>28, 51</sup> antihistamines,<sup>28, 51</sup> analgesics<sup>51</sup> and corticosteroids.<sup>28, 51</sup>

Adverse drug events related to rituximab infusion typically are manageable. However, there are reported incidences of rituximab induced cytokine release syndrome leading to death. One case study reported that a CLL patient suffered cardiopulmonary arrest leading to death 9 hours after receiving rituximab. The signs and symptoms leading to the death were believed to be mediated by the cytokine release syndrome. The patient started with chills followed by progressive hypotension, breathlessness with basal crepitation in the lungs and tachycardia. In subsequent hours, the patient developed hypoxemia, deterioration of kidney function and pulmonary infiltration.<sup>66</sup>

### ***Summary***

The part 1 literature review has identified the development of rituximab application for various clinical diagnoses in clinical trials and presented the current state of science concerning rituximab infusion. The next section of literature review will further discuss on the adverse drug events of rituximab infusion

## **Part 2: Adverse Drug Events of Rituximab Infusion**

Rituximab was the first monoclonal antibody approved for cancer treatment by the FDA in the US in November 1997.<sup>67</sup> In this study, adverse drug events could be classified into acute (during and within 24 hours post infusion) or long term reactions (days to months). The focus of the study will be on acute adverse drug events.

### ***Incidence of Adverse Drug Events***

Monoclonal antibodies, such as rituximab, are known to cause infusion-related adverse reactions.<sup>68</sup> The incidence of first cycle infusion-related reactions has been reported to be as high as 77%, with 7% being grade 3 and 4 adverse drug events, and 33% with 2% grade 3 and 4 adverse drug events at next infusions.<sup>14</sup> In clinical trials

where rituximab was infused at a slower rate, the most common adverse reactions were infusion reactions such as fever, lymphopenia, chills, infection, and asthenia for lymphoid malignancies. In CLL, the most common adverse reactions are infusion reactions and neutropenia.<sup>52</sup> Infusion reactions have been described as hypotension, fever, chills, rigors, urticaria, bronchospasm, angioedema (sensation of tongue and throat swelling), nausea, fatigue, headache, pruritus, dyspnoea, rhinitis, vomiting, flushing and pain at the cancer site.<sup>14</sup> Adverse reactions usually occur at the beginning of the first infusion within 30 minutes to 2 hours.<sup>14, 52, 68</sup> Other possible and more serious adverse reactions are tumour lysis syndrome (TLS), mucocutaneous reaction, progressive multifocal leukoencephalopathy, hepatitis B reactivation with fulminant hepatitis, infection, cardiac arrhythmias, renal toxicity, bowel obstruction and perforation.<sup>14, 52</sup>

### ***Clarification of Terminology Used: Adverse Drug Events***

In the literature, different terminologies are used to describe drug-related reactions, for example, adverse drug event,<sup>69, 70</sup> adverse drug event,<sup>71, 72</sup> adverse reaction,<sup>73, 74</sup> and toxicity.<sup>75, 76</sup> Despite the variety of terms used, the FDA label (package insert)<sup>14</sup> has adopted the National Cancer Institute (NCI) severity grading system in order to standardise reporting for adverse reactions. The most commonly used NCI severity grading scales are the Common Toxicity Criteria (CTC)<sup>77</sup> or the Common Terminology Criteria for Adverse drug events (CTCAE)<sup>5</sup> using a scale of 0-4 for CTC or 1-5 for CTCAE. Examples of CTC and CTCAE are documented in Appendix I. CTCAE is the revised version of CTC. In this thesis, the terms ‘adverse drug events’ and ‘adverse reactions’ are most frequently used. However, other terms, namely ‘toxicity’ or ‘drug reactions’ are used where appropriate.

### ***Mechanism of Adverse Drug Events Resulting from Rituximab Infusion***

Dillman<sup>78</sup> suggests that monoclonal antibodies react with circulating tumour cells which can lead to a reaction called cytokine release syndrome, or in severe cases, cytokine storm. Cytokines are a group of polypeptide proteins<sup>79</sup> which are small cell signaling protein molecules that are secreted by the glial cells of the nervous system and numerous cells of the immune system. They are a group of signaling molecules used extensively in intercellular communication.<sup>79</sup> Cytokines are produced and secreted by many cell types, mainly macrophages and whenever cells are removed by the spleen or the liver.<sup>78</sup> Examples of cytokines include interleukins (IL), interferons (IFNs), tumour necrosis factors (TNF) and colony-stimulating factors (CSFs). The clinical presentation of cytokine release syndrome can include fever, nausea, chills, hypotension, tachycardia, asthenia, headache, rash, scratchy throat, tongue and throat swelling and dyspnea.<sup>79</sup> One study<sup>80</sup> reports that the level of some cytokines (IL-6, IL-8, TNF- $\alpha$  and IFN- $\gamma$ ) positively correlated with adverse reactions in patients who developed hypotension, hypoxemia or dyspnea. However, only the correlation for IL-8 was found to be statistically significant, with a  $p$  value = 0.02.<sup>80</sup>

In contrast, levels of complement activation products such as CH50 and C3 have not shown any correlation with adverse reactions.<sup>80</sup> Van Der Kolk et al.<sup>81</sup>, however, found that high levels of C3b/c are associated with severe side effects. They reasoned that rituximab can cause rapid complement activation<sup>22</sup> within the immune system, leading to further activation of macrophages and mast cells, consequently resulting in the further release of C3b/c and C4b/c. However, these results should be treated with caution since the sample was limited to 5 patients. Other theories suggest that infusion-related adverse drug events are linked to tumour cell agglutination. This mechanism is proposed by Kunzmann et al. in a case report study.<sup>82</sup> However, a study

by Sivakumaran<sup>83</sup> suggested otherwise in that ex-vivo evidence shows that a colloid solution with serum blood leads to tumour cell agglutination. Colloid solution is a commonly used fluid used to manage peripheral circulatory failure for patients who become hemodynamically unstable after experiencing infusion-related events.

### ***Risks of Adverse Drug Events***

There are several risk factors contributing to cytokine release syndrome. High numbers of circulating CD-20 positive blood tumor cells are believed to be one of the key risk factors associated with serious adverse reactions namely severe rigors, fever, bronchospasm, hypoxemia and thrombocytopenia.<sup>80</sup> Winkler et al.<sup>84</sup> supported this finding in their study which records peaks of TNF-  $\alpha$  and IL-6 at 90 minute in a cytokine release syndrome among patients with lymphocyte counts exceeding  $50.0 \times 10^9/L$ ,  $p = 0.049$ . However, another study<sup>80</sup> reported contradictory findings and suggests that disease type, prior therapy, absolute tumor blood count number, extensive nodal involvement and tumor CD-20 expression might not correlate with adverse reactions except increasing age,  $p = 0.02$ .

### ***Long-Term Complications Resulting from Rituximab Infusion***

Different types of acute adverse reactions and long-term complications have been identified from the rituximab standard rate infusion. However, few studies have examined the long-term impact of rapid rituximab infusion on patients' conditions with respect to short-term acute toxicity. One study<sup>85</sup> monitored patients' cardiac toxicity following a rapid Rituximab infusion starting at 50mg/hr and increasing gradually to 700mg/hr as a maximum rate. Thirty-two patients participated in the study and none showed any clinically relevant Electrocardiogram (ECG) alterations. Furthermore, there was no significant change in other measures of cardiac health (Troponin I levels or mean Left Ventricular Ejection Fraction (LVEF)). However,

mean levels of Brain Natriuretic Peptide (BNP - a polypeptide secreted by the ventricles of the heart in response to excessive stretching of heart muscle cells) - did increase significantly after 24 hours of rapid rituximab infusion. Although BNP increased significantly, they remained within the normal range with the deviation occurring in one patient. Therefore, the investigators concluded that the rise of the BNP was non-specific but fluid overload could not be ruled out.

Another study<sup>85</sup> showed that 13 patients who received rituximab in combination with Adriamycin-based chemotherapy had a reduction in LVEF >10% compared to their pre-treatment baseline 3 months later. These patients recovered normally but another 6 patients who had LVEF that decreased >15% compared to baseline levels, did not recover to an acceptable range. Adriamycin is known to cause cardiac toxicity.<sup>86</sup> The patients who had not received Adriamycin did not show a decrease in LVEF. The patients in the study were followed for up to two years. Patients who had shown the decrease in LVEF following rituximab treatment did not show any episode of cardiac failure or signs and symptoms of cardiomyopathy after two years. Therefore, the investigators suggest that rituximab may increase the risk of cardiac toxicity when combined with other drugs but otherwise have no severe clinical consequences to a patient's long-term cardiac health.

### ***Summary***

Part 2 of the literature review has clarified the terminology used for adverse drug event; reported on the occurrences, mechanisms and risk of adverse drug events. Also, few evidence examine on the long-term complications resulting from standard and rapid rituximab infusion. The next section will identify the factors associated with the occurrence and severity of adverse drug events in relation to the standard rate of rituximab infusion.

### **Part 3: Predictors of Rituximab Induced Adverse Drug Events**

There are numerous factors associated with the occurrence and severity of adverse drug events following standard or rapid rituximab infusion.

#### ***Age***

Fourteen studies<sup>71-74, 76, 85, 87-94</sup> of rapid rituximab infusion do not investigate age as a possible factor for considering rapid infusion and only report that those aged 18-92 years tolerate rapid infusion. In the studies involving standard infusion rates, it is documented in the FDA label those aged 65 and older more often develop supraventricular arrhythmias.<sup>52</sup> However, another study reported that patients aged 60 and older tolerated rituximab well in combination with standard chemotherapy in indolent or aggressive lymphomas.<sup>95</sup> An age  $\leq 60$  versus  $> 60$  years old is one the five factors used to build FLIPI (Follicular Lymphoma International Prognostic Index) for optimal treatment for patients.<sup>96</sup> Age is used as a prognostic factor for survival but it is unclear in the literature if age could predict the risk of patients experiencing adverse drug events.

#### ***Gender***

Gender is a routinely collected demographic characteristic in most research studies. It is known that gender influences coronary heart disease<sup>97</sup> but it is not commonly associated with cancer. It is reported in one study that the female gender was associated with grade 3 or greater haematological toxicity (leucopenia, neutropenia, thrombocytopenia, anemia).<sup>62</sup> However, another study<sup>94</sup> did not find any significant difference in gender as a predicted risk factor for adverse drug events. A recent epidemiological<sup>98</sup> report suggests that NHL is more often diagnosed among men and that, therefore, future research analysis should consider gender as a variable.

### ***Co-morbidity***

One study has reported that the prevalence of co-morbidity among NHL patients was 66% in those aged 60 years and over.<sup>99</sup> Cardiovascular disease and hypertension are the most commonly reported co-morbidities.<sup>99</sup> This study also identified that the presence of co-morbidities often led to dose reduction in chemotherapy usage and in survival rates<sup>99</sup> Another study suggested that patients with pre-existing cardiac and pulmonary condition are at risk of developing infusion-related reactions<sup>52</sup>

Physiologically, the rapid infusion of any fluids may possibly cause fluid overloading leading to pulmonary edema particularly amongst patients with pre-existing heart failure. However, Gotter et al.<sup>100</sup> argued that fluid overload - especially in patients with heart disease - may not necessarily explain fluid accumulation. They propose that other factors such as neurohormone and inflammatory activation, renal dysfunction and inappropriate use of some medications are related to fluid redistribution leading to fluid accumulation in the peripheral organs and lungs.

Rapid infusion of 500mL of fluids over 60 minutes is commonly seen in some chemotherapy regimens. In the researcher's institute, a regimen of Cytarabine in BEAM (Carmustine, Etoposide, Cytarabine and Melphalan) is diluted in 500mLs of normal saline and administered over 60 minutes. This regimen is regarded as a conditioning regimen before stem cell transplant and has been evaluated in clinical trials.<sup>101</sup> Therefore, it is not uncommon to administer the drug rapidly in the oncology setting.

### ***Diseases associated with the use of Rituximab***

For which rituximab is approved by FDA for only FL and DLBCL (subtype of NHL),<sup>14</sup> there is a considerable interest among the clinicians in using rapid rituximab for different types of NHL such as MCL (Mantle Cell Lymphoma), BL (Burkitt



Lymphoma),<sup>71</sup> and MZL (Marginal Zone Lymphoma).<sup>88</sup> Only one study<sup>94</sup> has examined different subtypes of NHL associated with the occurrence of adverse drug events with reference to rapid rituximab infusion. This study did not confirm that a diagnosis of B-cell malignancy would increase the risk of the occurrence of adverse drug events.

### ***Staging of NHL***

Staging is critical in cancer in order to optimise treatment as well as serve as a useful prognostic factor. Three systems are available for staging NHL: Ann Arbor, WHO classification and International Prognostic Index (IPI).<sup>102</sup> In the Ann Arbor system there are 4 stages. Stage I is defined as the involvement of a single lymph node region. Stage II is the involvement of two or more lymph node regions on the same side of the diaphragm. When the lymph node involvement occurs at both sides of the diaphragm, it is called stage III. Stage IV is represented by disseminated disease in other organs such as the liver, lungs and bone marrow. Clinically, stages III/IV are considered to be advanced diseases. The initial chemotherapy treatment is the same regardless of the stage. However, patients with stage IV disease will require stem cell transplant as a curable option. The WHO classification is used for categorising lymphoma rather than describing its severity and this classification is based on the morphology of the cell. Typically, it divides them into B-cell or T/NK cell and/or blastic or mature appearance. IPI considers five factors, namely age, performance status, lactate dehydrogenase level, involvement of extranodal site and stage of disease. The presence of each factor is assigned as score 1. The adding up of the overall scoring further classifies patients into the low or high risk group.

Only one study has identified that bone marrow involvement is associated with grade 3 or greater haematological toxicity. In this study, all of the included patients had

lymphoma and staged using the Ann Arbor scale; therefore, as mentioned earlier, bone marrow involvement represented stage IV disease.<sup>62</sup> In other words, stage IV disease is associated with the occurrence of adverse drug events.

### ***Premedication***

Infusion-related toxicity is commonly associated with monoclonal antibodies such as rituximab. As recommended by the drug manufacturer, premedication prior to rituximab infusion aims to prevent or minimise adverse drug events during infusion. However, clinical studies report otherwise. Antihistamine is not needed in some areas as the occurrence of events occurs primarily at cycle 1 and 2 in cetuximab cases.<sup>103</sup> Steroids as part of the premedication are used occasionally to minimise adverse reactions.<sup>14</sup> However, two studies concluded that no severe adverse drug events were found in patients who did not get corticosteroid as a premedication<sup>71</sup> or who received chemotherapy without steroid content.<sup>72</sup> Premedication prior to rituximab infusion appears to play no explicit role in preventing or reducing the occurrence of adverse drug events.

### ***Blood counts***

A high number of circulating malignant cell ( $\geq 25,000/\text{mm}$ ) has been associated with the risk of developing a reaction.<sup>52</sup> Winkler et al.<sup>84</sup> reported that 11 CLL or NHL patients with lymphocyte counts exceeding  $50.0 \times 10^9/\text{L}$  experienced an increased frequency of adverse drug events.

A B-CLL patient with leucocytosis of  $111.9 \times 10^9/\text{L}$  developed severe adverse drug events 90 minutes into rituximab infusion.<sup>104</sup> The reactions included throat irritation, chills and fever. The symptoms were managed and resolved using Pethedine. Immediately after infusion, this patient developed fever, chills, tachycardia, nausea and vomiting that progressed into tumour lysis syndrome and disseminated

intravascular coagulation. Eventually, the patient was hospitalised; after discharge from the hospital, he continued to receive Rituximab treatment without experiencing any additional adverse drug events or complications.<sup>104</sup>

In the following year, Bryd et al.<sup>105</sup> embarked on a case series study to investigate the roles of high circulating malignant cells in 5 patients with prolymphocytic leukemia, chronic lymphocytic leukemia and diffuse large B-cell lymphoma. The findings were that patients experienced rapid tumour clearance and developed significant adverse drug events such as fever, rigors, bronchospasm and hypoxemia; another medical complication associated with this group of patients was tumour lysis syndrome. The investigators suggested that a stepping up regimen should be recommended. Although premedication was administered, it was not effective in preventing the adverse drug events. Many studies suggest that high lymphocytes counts are clearly associated with the occurrence of adverse drug events, but that this does not predict the risk of toxicity.<sup>75</sup> Besides lymphocyte counts, high lactate dehydrogenase (LDH) has been found to significantly relate to a larger number of fever episodes.<sup>62</sup>

### ***Tumour load***

Besides patients' blood counts, one study<sup>106</sup> suggested that patients with lower tumour mass and/or that have received chemotherapy prior to rituximab administration experience fewer side effects. The investigators proposed that rituximab should be administered after chemotherapy to reduce the burden of CD 20 circulating in the blood stream.

### ***Influence of initial infusion***

Brelin<sup>79</sup> argues that cytokine release syndrome is often associated with the initial cycle of monoclonal antibody infusion and subsides with the subsequent cycles. Her comments are supported by at least five clinical trials.<sup>28-30, 34, 107</sup> She hypothesises that

the high percentage of targeted cell binding with monoclonal antibody is the etiology of cytokine release syndrome.

### ***Dosing***

One study has evaluated the effects of dose on treatment outcomes and toxicity between 500mg/m<sup>2</sup> and 375mg/m<sup>2</sup>.<sup>108</sup> This randomised phase II trial compared the overall response rate and tolerability of rituximab among DLBCL, MCL and other intermediate or high grade B-cell lymphoma. Twenty-eight patients in arm A received rituximab 375mg/m<sup>2</sup> weekly for 8 weeks and 26 patients in arm B received rituximab 500mg/m<sup>2</sup> for the first week followed by 500mg/m<sup>2</sup> weekly for another 7 weeks. Five patients demonstrated a complete response in arm A and one in arm B. In terms of partial response, five were observed in arm A and seven in arm B. Twenty six patients experienced 125 episodes of adverse drug events in arm A and twenty three patients experienced 143 episodes of adverse drug events in arm B. There was no statistical difference between the two arms.

### ***Summary***

Part 3 of this literature review has identified many studies on the potential risk factors for the occurrence of adverse drug events resulting from either standard or rapid rate of Rituximab infusion. However, no study has investigated whether those factors provide any predictive value for the incidence of adverse drug events.

Gathering the information from the literature review, the benefits of rapid rituximab infusion are clearly evidenced in the literature.<sup>71, 94</sup> However, the occurrences of adverse drug events are common and could possibly increase treatment cost and staff time. Despite the rapid infusion rate not being adopted by the drug manufacturers, many medical centres have widely adopted the new infusion regimen. Therefore, it is important that the available research is systematically analysed to determine its

validity and if valid, presented to clinicians to consider in their treatment options for individual patients.

## **Chapter 3. Study Methods**

This study consists of two phases: firstly, Phase 1 which is a systematic review to synthesise the best available evidence in relation to rapid rituximab infusion; and secondly, Phase 2, which is a retrospective cohort study to identify the potential predictors of the adverse drug events of rapid rituximab infusion.

### **Phase 1: The Systematic review**

The systematic review - also known as synthesis research - followed a protocol approved previously by a group of experts from The Joanna Briggs Institute to guide the review process.

### **The Systematic Review Protocol**

#### **Background to the Review**

In 2009, statistics from the US showed that the number of people diagnosed and living with NHL and CLL numbered 452,723 and 85,713 respectively.<sup>109</sup> The diagnosis of NHL and CLL is continuously rising, partially due to increased life expectancy. To date, 1.5 million patients worldwide have been treated with rituximab.<sup>74</sup> Ageing is considered as one of the key risk factors for CLL.<sup>110</sup> Therefore, it is anticipated that many will require rituximab as part of their treatment regimen.

The prolonged infusion of rituximab (sometimes totaling as much as 4-5 hours per infusion) has a substantial impact on health care providers; it challenges them to work within limited resources such as space constraints, human resources and long waiting times for patients to receive their treatment on schedule. In addition patients or insurance companies have to pay more for long infusion hours as some medical centres charge treatment fees based on the duration of the infusion.<sup>71</sup> In 2004, it was reported that more than 1200 patients had received rapid infusions (total duration over 90 minutes) of rituximab in Canada.<sup>92</sup> In addition, staff working in 20 independent

NHS trusts from the United Kingdom (UK) were interviewed about their rituximab administration policy and it was reported that 70% of second and subsequent rituximab infusions were administered over 90 minutes and 5% over 60 minutes.<sup>74</sup>

As a result, many medical centres from different regions across the world including the US, Canada, Europe, the Middle East and Asia have conducted research studies<sup>72-74, 76, 85, 87-89, 91-93, 111-116</sup> to evaluate the feasibility and safety of rapid rituximab infusion. The majority of these studies are related to the safety of infusion rates with the assumption that the efficacy of rituximab is not compromised by the rate of infusion. Only one study examines both the efficacy and safety of rapid rituximab infusion concurrently.<sup>90</sup> The results suggest that rapid infusion is as effective as conventional rate infusion in patients with Diffuse Large B-Cell Lymphoma (DLBCL), a subtype of NHL. The advantage of rapid rituximab infusion is clearly evidenced in some of these studies.<sup>71, 73</sup> They demonstrate that rapid rituximab infusion is safe and able to translate into cost savings, better resource utilisation and increased patient satisfaction. However, one study<sup>117</sup> highlights the downside of the cost issue where the occurrence of the adverse drug events can require more staff time (33%) resulting in higher human resource costs. Nonetheless, the benefit of rapid rituximab infusions has been well articulated in terms of cost savings and better resource utilisation without compromising effectiveness.

### **Significance of the Systematic Review**

Currently, there are no published systematic reviews that have examined the safety of rapid administration of rituximab. This systematic review was undertaken to identify the best available evidence to inform clinical practice. This is because overestimating a risk may inhibit an effective treatment that can potentially provide a cure and improve people's quality of life. Conversely, underestimating a risk may cause health

care providers, especially doctors and nurses, to be unprepared for potential adverse reactions that endanger patients' lives.

### **Justification of the Population of Interest for the Systematic Review**

The FDA first approved of rituximab for non-cancer diagnoses such as RA in February 2006.<sup>14</sup> Five years later, the drug was extended to include other autoimmune diseases and to be administered rapidly over a shorter duration.<sup>118</sup> Larsen and Jacobsen<sup>118</sup> conducted a prospective study of 54 patients with various kinds of autoimmune diseases (Wegeners Granulomatosis, RA, SLE, Primary Sjogrens Syndrome and other inflammatory conditions) in Denmark to elicit the prevalence, nature and severity of infusion-related reactions resulting from rapid rituximab infusion. Although the study intervention differed from the rapid infusion regimen used by oncologists/haematologists (will be discuss later in chapter 4), the dosage used was standard for every participant at 1000mg in 500mLs of normal saline. Instead of using 20/80% of total dose for determining administration rates by oncologists/haematologists, the study set the infusion rate at 200mL/hr in first the 30 minutes and 400mLs/hr in the remaining 60 minutes. Premedication was given to all participants prior to the infusion (of Prednisolone 100mg, oral Fexofenadine 180mg and oral Paracetamol 1 g). The study reports 5 (9.2%) infusion-related adverse reactions related to rhinitis, cough/dyspnea and fatigue. Two patients experienced grade 1 severity reactions as measured by the NCI CTCAE Version 3; 1 and two patients experienced grade 2 and 3 adverse reactions respectively. The authors conclude that a rapid infusion regimen is safe and time-saving for health care professionals without compromising patient safety.

Although rapid infusion has been used for non-cancerous patients, the population of interest in this systematic review only consisted of adult cancer patients with NHL



and CLL. This is because these are the cancer populations approved by the FDA for cancer therapy to date. The population characteristics at any level of performance status, presence or absence of any co-morbidity and at any stage of disease were also included in the review. The results from the review were treated separately with individual analysis for NHL and CLL.

### **Justification of Outcome Measure for the Systematic Review**

For the purpose of this systematic review, the primary outcome was the measurement of the presence or absence of acute adverse drug events, and their severity, on different scales or ranking frameworks proposed by the investigators of the primary studies. Examples of these adverse drug events include hypotension, fever, chills, rigors, urticaria, bronchospasm, angioedema (sensation of tongue and throat swelling), nausea, fatigue, headache, pruritus, dyspnoea, rhinitis, vomiting, flushing and pain at the disease site. The commonly validated tools used for measuring the outcomes were National Cancer Institute Common Toxicity Criteria (NCI CTC) and National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE).

### **Potential Confounding factor for Outcome measure**

In addition to the precautionary measures of closely monitoring the rate of infusion and vital signs monitoring, Paracetamol, Diphenhydramine<sup>71, 76, 79, 80</sup> and Corticosteroids<sup>74, 90</sup> are usually administered 30 minutes before rituximab infusion with the purpose of minimising infusion reactions. Therefore, it is necessary to collect information on premedication as it will be the potential confounding factor.

### **Justification of Intervention of Interest for the Systematic Review**

Rituximab can cause fatal adverse drug events and the pharmaceutical manufacturer (Roche) recommends a very careful administration regimen<sup>52</sup> for rituximab infusion.

The recommended initial rate for infusion is 50mg/hr. If patients tolerate the drug without any severe acute adverse reactions and vital signs are stable, the infusion rate can be gradually increased at 50mg/hr every 30 minutes to a maximum of 400mg/hr. When patients tolerate the first infusion, the future infusion rate can be started at 100mg/hr and gradually increased at 100mg/hr every 30 minute to a maximum rate of 400mg/hr. The dosage of rituximab is calculated based on the patient's body surface area. The recommended dosage for the treatment of Lymphoma is 375mg/m<sup>2</sup> on Day 1 for each cycle up to 6-8 cycles.<sup>14</sup> The interval between cycles usually takes approximately 3 weeks. The recommended dosage for CLL is slightly different to NHL, as 375mg/m<sup>2</sup> is prescribed on Day 1 at first cycle and followed by 500mg/m<sup>2</sup> for subsequent 5 cycles.<sup>14</sup> Therefore, with the regimen recommended by the pharmaceutical manufacturers, the initial and subsequent duration for completion of the infusion in each cycle will take 5-6 hours and 3-4 hours respectively.<sup>52</sup>

The variation in the administration rate between the initial and subsequent infusion is due to the rapid breaking down of the circulating B lymphocytes following the initial infusion, which causes more adverse reactions to occur. In subsequent cycles, when the number of B lymphocytes has fallen in the blood stream, lesser adverse reactions occur.<sup>79</sup> As a result, it is safer for the subsequent infusion to run at a rapid rate. This also explains why patients may react to the first infusion but have no severe adverse reactions to subsequent infusions.

For the purpose of this systematic review, rapid rituximab infusion was defined as rituximab infusion completed in 120 minutes or less in the second or subsequent cycles of infusion. The most common rapid infusion rate is to complete in either 60<sup>71</sup>,<sup>87</sup> or 90<sup>74, 85</sup> minutes. The standard infusion rate would refer to the pharmaceutical manufacturer recommendation as above.

## **Justification Types of Study Included in the Systematic Review**

Randomised controlled trials (RCT) are considered to be the gold standard for studying harm.<sup>119</sup> However, the majority of studies<sup>71, 73, 74, 76, 87, 90, 112, 113</sup> examining the tolerability and safety of rapid rituximab infusion are in fact case series. For the purposes of this review, it considered both experimental and non-experimental studies that reported on the definition, number, seriousness and severity of adverse drug events to rapid rituximab infusion. Other factors considered include a clear description of the scale of measurement and the mode and timing of data collection on adverse drug events. The mode of data collection can be either active such as measurement of vital signs or passive through self-reporting from patients or both.<sup>119</sup>

## **Review objective**

The objective of this review was to critically appraise, synthesise and present the best available evidence related to the safety of rapid rituximab infusion in adult patients with NHL and CLL.

## **Review questions**

The specific review questions to be addressed were:

1. What is the frequency of acute adverse drug events from rapid rituximab infusion versus standard infusion?
2. How severe are the acute adverse drug events from rapid rituximab infusion versus standard infusion?
3. What are the treatments for patients if they develop acute adverse drug events from rapid rituximab infusion versus standard infusion?
4. What is the mortality rate of patients who develop acute adverse drug events from rapid rituximab infusion versus standard?

5. What are the types, dosages and routes of administration of premedication given to patients prior to rapid rituximab infusion?

## **Criteria for considering studies for this review**

### ***Types of studies***

This systematic review considered experimental, quasi-experimental and observational studies that reported on the definition, number, seriousness and severity of adverse reactions of rituximab at rapid infusion rates.

### ***Types of participants***

The participants of interest included adults 18 years old and above, scoring between 0-4 in the Eastern Cooperative Oncology Group Performance Status (ECOG) or any functional assessment tool used by primary investigator of the study, with any co-morbidity including but not limited to cardiac and respiratory diseases and one of the following diagnosis:

- a) Patients with non-Hodgkin lymphoma
  - i) Based on histology findings of any stage from I to IV based on Ann-Arbor staging<sup>120</sup>
  - ii) Any subtypes including but not limited to Diffuse Large B Cell Lymphoma (DLBCL), Follicular Lymphoma, Mantle Cell Lymphoma (MCL) and Burkitt's Lymphoma
  - iii) Who receive rituximab as monotherapy or combination with any type of chemotherapy including but not limited to CHOP (Cyclophosphamide, Doxorubicin, Vincristine and Prednisone), and CVP (Cyclophosphamide, Vincristine and Prednisone)
  - iv) Prior exposure to rituximab infusion

- b) Patients with Chronic Lymphocytic Leukemia
  - i) Based on cytology or phenotype findings
  - ii) Any stage from O-IV based on Rai classification or any stage from A-C based on Binet staging<sup>121</sup>
  - iii) Who receive rituximab as monotherapy or in combination with any type of chemotherapy including but not limited to Fludarabine and FC (Fludarabine,Cyclophosphamide)
  - iv) Prior exposure to rituximab infusion

Patients who were diagnosed with autoimmune diseases such as Thrombotic Thrombocytopenic Purpura (TTP), Autoimmune Haemolytic Anaemia (AIHA), Systemic Lupus Erythematosus, Epidermolysis Bullosa Acquisita (EBA) and Rheumatoid Arthritis (RA) were excluded from this review as they are autoimmune diseases, and their pathogenesis is different from cancer.

### ***Types of interventions***

The intervention of interest was a description of the protocol(s) for rapid infusion of rituximab..

### ***Comparators***

The comparator group was a description of standard of care-existing protocol(s) for infusion of rituximab.

### ***Types of outcome measures***

The primary outcomes measures of interest were:

1. Frequency, type and severity of acute adverse drug events
2. Cycles of infusion completed by the number of patients without acute adverse drug events

3. Types, dosages and route of administration of premedication including but not limited to PO Paracetamol 1g, IV Diphenhydramine 25mg and IV Hydrocortisone 100mg

The secondary outcomes measures of interest were:

1. Number of patients who continued the rapid rituximab infusion regardless of acute adverse drug events
2. Number of patients who were discontinued from the study due to adverse drug events
3. Type of treatment rendered to patients after acute adverse drug events
4. All causes of mortality including death caused by the underlying diseases or the complication arises from the therapy

## **Review methods**

### ***Search strategy***

On 17 July 2010, before undertaking this systematic review, the Cochrane Library, Joanna Briggs Institute Library of Systematic Review, MEDLINE and the Database of Abstracts of Review of effect were searched and no systematic reviews on this topic were found. The key words used in the initial search were ‘Rituximab’, ‘Rituxan’, ‘Mabthera’, ‘rapid’ and ‘infusion’. Endnote was used to manage the returned results.

The search strategy was started in 5 September 2010. It aimed to find both published and unpublished studies. A three-step search strategy was developed to guide the systematic review. MESH terms from PubMed were used to determine the words used to search in MEDLINE and CINAHL. The first search from MEDLINE and CINAHL was undertaken followed by analysis of the text words contained in the title and abstract, and the text terms used to describe the article. A second search used all the

identified keywords and index terms to search across all accessible databases and websites. As some databases are different in their search features, search terms varied different when searching them. Therefore, the search strategy was focused on the key search term-rapid rituximab infusion that appeared in the title or abstract. Thirdly, the reference lists of all identified reports and articles were searched for additional studies. (Appendix II).

Rituximab was approved for therapeutic use by the FDA in the US in 1997. Therefore, the search started from 1997 until October 2010 with no language restrictions. After the initial search across the databases, search alerts were set up from October 2010 to July 2011 to be updated on further development of study on rapid rituximab infusion.

For those studies published in languages other than English (such as Dutch), reviewers from the Joanna Briggs Institute Collaborating Centres were asked to assist in critical appraisal and data extraction.

The primary authors were contacted for further details of studies when abstracts were found in conference proceedings.

Databases searched included the following:

1. PubMed
2. Web of Science
3. Scopus
4. Cochrane Central Register of Controlled Trials
5. Science Direct
6. CINAHL
7. Scifinder

## 8. Mednar

Furthermore, Loke et al.<sup>122</sup> from the Cochrane Adverse Effects Methods Group recommended an exhaustive search for adverse affects which includes the following resources:

1. FDA post-market drug safety information
2. <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/default.htm>
3. European Public Assessment Reports from the European Medicines Evaluation Agency
4. [http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar\\_search.jsp&jsenabled=true](http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&jsenabled=true)
5. Current Problems in Pharmacovigilance  
<http://www.mhra.gov.uk/Publications/Safetyguidance/CurrentProblem sinPharmacovigilance/index.htm>
6. Australian Adverse Drug Reactions Bulletin  
<http://www.tga.gov.au/adr/aadrb.htm>
7. Roche  
<http://www.roche-australia.com/portal/eipf/australia/au/corporate>
8. Agency for Healthcare Research and Quality (AHRQ)  
<http://www.ahrq.gov>
9. Health Technology Assessment Programme (HTA)  
<http://www.hta.ac.uk>
10. US National Institutes of Health, ClinicalTrials.gov  
<http://www.clinicaltrials.gov>



## **Assessment of Methodological Quality**

Following a detailed examination, those articles that appeared to match the inclusion criteria were appraised by 2 reviewers independently. I was the primary reviewer and a peer who was trained in comprehensive systematic review was the secondary reviewer. We assessed the methodological validity of the articles prior to inclusion in the review using the standardised critical appraisal instruments from the Joanna Briggs Institute Meta Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI). There are nine criteria in JBI-MAStARI. The important criterion used to determine the study of high quality is: clear definition of included population; identification of confounding factors; objective and reliable in outcome measurement; statement of duration to follow up; descriptions of patients withdraw from the study; and appropriate used of statistical analysis. (Appendix III) Any disagreements that arose between the reviewers were resolved through discussion with a third reviewer.

### ***Data collection***

Data were extracted from the non-experimental studies that fulfill the inclusion criteria using a standardised data extraction tool from the JBI-MAStARI. The tool has two sections. The first section consists of information namely study design, setting, participants, interventions, author's conclusions and reviewer's conclusion. The second section includes description and scale of outcome measurement and results from the primary study. (Appendix IV)

### ***Data synthesis***

The included primary studies were case series studies with only a single group in each study. Therefore, for the purposes of this review, the effect size from the pooled results was presented using proportion meta-analysis using Stats Direct (statistical

software).<sup>123</sup> In this analysis, the software transforms proportions to logits, which can take on any numerical value.<sup>124</sup> The pooled proportion is calculated based on Der Simonian and Laird weights for the random effects model.<sup>123</sup> Statistical heterogeneity was assessed using Cochran Q.<sup>123</sup> When statistical pooling was not possible, the findings were presented in a narrative summary.

## **Phase 2: Retrospective Cohort Study**

### **Background to the Retrospective Cohort Study**

Rituximab (Rituxan/Mabthera) is a chimerical monoclonal antibody that acts directly against the CD-20 antigen, a hydrophobic transmembrane protein located on the surface of normal and malignant B cells.<sup>14</sup> It was the first monoclonal antibody approved for cancer treatment by the Food and Drug Administration (FDA) in the United States (US) in 1997.<sup>67</sup> The FDA specifically approved the use of rituximab for diagnoses including non-Hodgkin Lymphoma (NHL), Chronic Lymphocytic Leukemia (CLL) and Rheumatoid Arthritis (RA).<sup>14</sup> In addition to these diagnoses, the application of rituximab has expanded rapidly to include other disease conditions such as Multiple Sclerosis,<sup>53</sup> Refractory Thrombotic Thrombocytopenic Purpura,<sup>54</sup> Systemic Lupus Erythematosus,<sup>55</sup> Epidermolysis Bullosa Acquisita<sup>22</sup> Burkitt's Lymphoma (BL), Central Nervous System(CNS) Lymphoma, Hodgkin's lymphoma (HL with lymphocyte predominant), Mucosal Associated Lymphoid Tissue (MALT), Lymphoma (gastric and non-gastric), Splenic Marginal Zone Lymphoma (MZL), Waldenstrom's Macroglobulinemia,<sup>18</sup> Chronic Immune Thrombocytopenic Purpura (ITP), refractory pemphigus vulgaris, treatment of systematic autoimmune diseases (other than rheumatoid arthritis), and treatment of steroid-refractory chronic Graft-Versus-Host Disease (GVHD).<sup>27</sup>

As discussed earlier, rituximab can cause potentially fatal adverse drug events. Therefore, according to the pharmaceutical manufacturer's (Roche) recommendation, the initial rate for infusion is 50mg/hr. If patients are able to tolerate the drug without any severe acute adverse reactions and vital signs are stable, the infusion rate can be gradually increased by 50mg/hr every 30 minutes to a maximum of 400mg/hr. When patients tolerate the first infusion well, the subsequent infusion rate can begin at

100mg/hr and gradually increased by 100mg/hr every an interval lasting 30 minutes to a maximum rate of 400mg/hr. The dosage of rituximab is calculated based on the patient's body surface area. Therefore, with an average of 1.7m<sup>2</sup> body surface area, the initial and subsequent duration for completion of an infusion in each cycle will take 5-6 hours and 3-4 hours respectively.<sup>52</sup>

Lengthy rituximab infusion over 3-4 hours at a second and subsequent cycle of infusion has resulted in an increasing health care burden of more staff, cost and time being used.<sup>71, 73, 74, 125, 126</sup> There is an exponential growth in the literature reporting changes to rituximab infusion rates based on individual institutions' experiences.

Therefore, a systematic review<sup>127</sup> was conducted to critically appraise, synthesise and present the best available evidence in relation to the safety of using rapid rituximab infusion over 60 or 90 minutes. However, a systematic review alone will not necessarily lead to clinical practice change. This is because the process of administering rapid rituximab infusions involves three prominent stakeholders: pharmacists, medical clinicians and nurses from the ambulatory setting. Several clinical questions are evident. Pharmacists are concerned with dilution and concentration; medical clinicians are cautious about using off label administration that could create potential medico-legal issues; and nurses are interested in the pattern of vital signs monitoring. To use rapid rituximab safely, other information is needed to guide practice change particularly in relation to the diagnoses, specific patients' characteristics, and the role of premedication or treatment regimens that may impact on the occurrence and severity of acute adverse drug events.

The central focus of inquiry is patient safety in the context of administering rapid rituximab based on the best available evidence.

## **Study Objectives**

The primary objective of this retrospective study was to identify factors that could predict which patients would experience acute adverse drug events resulting from rapid rituximab infusions in order to make recommendations for a comprehensive clinical guideline for rapid rituximab administration.

The secondary objective of the study was to identify the type, severity and management of acute adverse drug events.

## **Specific Aims of the Study**

The primary aims of the study were:

1. To explore any correlations between characteristics of patients and treatment used with the occurrence, frequency and severity of acute adverse drug events from rapid rituximab infusions.
2. To determine the predictors of the occurrence, frequency and severity of adverse drug events.
3. To calculate the odds ratio for the variation among the identified variables.

The secondary aims of the study were:

1. To identify patterns of nurse assessment used to detect adverse drug events resulting from rapid rituximab infusion.
2. To discover any new factors that cause adverse drug events.
3. To provide evidence for other cancer populations aside from NHL and CLL concerning the safety in using rapid rituximab infusion.

## **Research question**

What is/are the best predictors: patients' age, gender, diagnosis, stage of disease, presence of cardiac or lungs co-morbidity, number of courses, number of cycles, type

of treatment, dosage based on body surface area, use of premedication, blood counts including white blood cells, absolute neutrophils, lymphocytes and lactate dehydrogenase (LDH) in predicting the occurrence, frequency and severity of the adverse drug events.

### **Hypotheses**

1. Age is an indicator for predicting the occurrence, frequency and severity of adverse drug events resulting from rapid rituximab infusion.
2. Circulating lymphocyte counts is an indicator that predicts the occurrence, frequency and severity of adverse drug events resulting from rapid rituximab infusion.
3. Level of lactate dehydrogenase is an indicator that predicts the occurrence, frequency and severity of adverse drug events resulting from rapid rituximab infusion.

### **Operational definitions used for variables identified for data collection**

1. Age: The year at which the patient received rapid rituximab infusion.
2. Gender: The condition of being female or male.
3. Diagnosis: The identification of a diagnosis was collected based on the medical Oncologist's and Haematologist's description which is readily available in the individual patient's medical notes.
4. Stage of disease: The classification of stage of disease as identified from patients' medical notes and whichever classification used by the medical oncologist and haematologist was accepted.

5. Presence of cardiac or lungs co-morbidity: Any medical condition available in the patients' medical notes which were related to cardiac and/or lung problems, for example hypertension, ischemic heart disease, congestive cardiac failure, asthma, chronic obstructive airway disease and others.
6. Number of courses: Treatment in chemotherapy as measured by course. A course of treatment can consist of numerous cycles of chemotherapy.
7. Number of cycles: A cycle is a smaller unit measured under a course of treatment. An infusion of rapid rituximab is equal to a cycle of treatment.
8. Type of treatment: Type of treatment refers to whether rituximab was given as monotherapy or in combination with chemotherapy.
9. Dosage based on body surface area: The prescribed dosage of rituximab is calculated based on the body surface area. The formula of body surface area could be calculated using the Dubois and Dubois formula<sup>128</sup> or the Mosteller formula.<sup>129</sup>
10. Premedication: Three types of premedication were used in this study; antihistamine, antipruritic and corticosteroids
11. White blood cell counts: A group of blood cells that lack haemoglobin, are colourless and with a nucleus which is responsible for the immune system. They consist of neutrophils, basophils, eosinophils, lymphocytes, monocytes. The normal white blood cell count is  $4-11 \times 10^9/L$ .<sup>130</sup>
12. Circulating lymphocyte counts: The lymphocyte count is part of the product of the total white blood cell count (WBC) and fraction of lymphocytes on the WBC differential.<sup>131</sup> Normal lymphocyte counts are measured as  $1.00-3.50 \times$

$10^9/L$  according to the Royal Adelaide Hospital's (RAH) laboratory's reference.<sup>130</sup>

13. The absolute neutrophil count (ANC) is equal to the product of the white blood cell count (WBC) and the fraction of polymorphonuclear cells (PMNs) and band forms noted on the differential analysis. The normal level of ANC is  $2.8-7.5 \times 10^9/L$ .<sup>130</sup>
14. Lactate dehydrogenase (LDH): Normal serum LDH level is defined as 110-230 U/L according to the Royal Adelaide Hospital's laboratory's reference.<sup>130</sup>
15. Adverse drug event: An adverse drug event is defined as any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medical treatment (drug therapy) that may or may not be considered related to the medical treatment.<sup>5</sup>
16. Severity of adverse drug event: The severity of an adverse drug event is graded from 1-5 using the National Cancer Institute Common Terminology Criteria for Adverse drug events (CTCAE) Version 4.<sup>5</sup>

## **Study Design**

A quantitative method using a retrospective design was used in this study. This design was chosen because it was the most practical, time efficient, economical and it involved no potential risks to patients. It was also able to address the research questions sufficiently. In addition to its practicality, this design also allowed for the examination of multiple variables concurrently as well as a focus on rare events.<sup>132</sup>

There are two potential disadvantages related to retrospective design: firstly, the inability to establish causal effect between variables; and secondly, referral bias for the general correlation studies. However, the predictors that were chosen for the



analysis were based on the pathophysiology of the occurrence of the adverse drug events and therefore the inability to establish causal effect would not constitute a threat in this study. Secondly, referral bias is not a threat as this study had identified patients with a specific diagnosis to be included and the follow up on the occurrence of adverse drug event was short in duration.

### **Sampling**

Convenience sampling was chosen as patient information was readily available in the Cancer Centre or in-patient wards of RAH. A list of patients was generated by the Cancer Centre's pharmacist as a starting point to identify the potential samples. All the medical records of patients, with and without a diagnosis of cancer, who were treated in the Cancer Centre of RAH from Jan 2007- Feb 2011 with rapid rituximab infusions, were screened for the following inclusion criteria:

1. Any diagnosis except that of cancer must be confirmed by biopsy.
2. Any stages of disease or cancer range from stage I-IV.
3. Received rituximab alone or in combination with other chemotherapy at second and subsequent infusions.
4. Presence of any co-morbidity for example but not limited to hypertension and diabetes mellitus.
5. Age 18 years old and over.

Exclusion criteria:

Patients who received rapid rituximab infusion in RAH but not treated by either a medical oncologist or haematologist were excluded from the study. This was because the application of rituximab also extended to non-cancerous diagnoses such as

autoimmune diseases. People who are less than 18 years old were excluded from the study because RAH Cancer Centre does not provide rituximab infusions for children.

Four hundred and eighty-seven patients were screened for potential to be recruited into the study and 294 (73.5%) patients met in the inclusion criteria and their medical records were available for evaluation during the study period.

### **Sample size calculation**

Power analysis estimation of sample size was calculated using the following formula:

The value of alpha =0.05<sup>133</sup>

The effect size =0.3 (medium effects)<sup>134</sup>

To detect a medium effect of an estimated 10 predictors, an estimated sample size of 120 patients are required for regression analysis using graph.<sup>133</sup>

### **Study Protocol**

Patients were given rapid rituximab infusion that was over 90 minutes' duration in total. In the first 30 minutes, patients received 20% of the total dose of rituximab. When patients tolerated this, as assessed by the vital signs results and the nil reporting of any discomfort, the remaining 80% dose of rituximab was administered over 60 minutes. Prior to rituximab administration, patients were given premedication to prevent or reduce the adverse drug events. Depending on the treatment, PO Paracetamol 1g, PO Loratidine 10mg, and IV Hydrocortisone 100mg were usually given to patients who received rituximab as monotherapy. For patients who received rituximab in combination with chemotherapy, an antiemetic such as Tropisteron 5mg per oral was administered. All of these premedications were administered 30 minutes prior to rituximab infusion.

Whenever patients experienced acute adverse drug events, rituximab infusion was interrupted temporarily. Depending on the signs and symptoms of the adverse drug events, additional antihistamine, analgesic, antiemetic and corticosteroid were administered promptly. Patients who developed adverse drug events at grade 3 and above were hospitalised for further monitoring and management. When the adverse drug events subsided, the rituximab infusion was resumed at the slower rate or half of the rate from the previous rate. However, rituximab could be discontinued if patients developed severe adverse drug events.

Patients' vital signs monitoring including temperature, heart rate, respiratory rate and blood pressure performed by nurses before, during and after the infusions at baseline, 30-minute, and 90-minute.

### **Data management**

The researcher collected the data by reviewing patients' medical records including patients' progress notes, blood tests results, chemotherapy prescription and administration charts, and nursing monitoring charts. The data was extracted firstly using pen and paper (Appendix VII); subsequently, it was entered onto an Excel spreadsheet for importing to statistical software for further statistical analysis. The data from the form served as a back-up file as well in the event of unforeseeable technical fault or failure. It also assisted in minimising error during the process of data entry.

Only the researcher and her supervisors were allowed to access the research data and results. A hard copy of the data was kept at the researcher's personal work station under lock and key. The soft copy of the data was kept in the researcher's desktop with specific ID and password protection. Patient identifiers were used to retrieve the

medical records initially. However, a case number was assigned to each patient during data extraction. Only the case number was used for data entry and analysis. Therefore, patients were de-identified once information had been transferred into the Excel spreadsheet for data entry.

In summary, the researcher took full responsibility for all steps from the retrieval of case notes to the data extraction, data entry, data analysis and the return of the patient case notes to the Medical Record Office at the RAH.

### **Ethics and Human Subjects Issues**

Ethical approval was sought from The Royal Adelaide Hospital and The University of Adelaide's Human Research Ethics Committees. The researcher applied for a waiver of the Ethics Consent form and it was approved as patient identifiers were not needed after the data extraction was completed. Although patient identifiers were used initially, they were de-identified once the data analysis was done. Patient information was kept confidential throughout the research study.

### **Statistical Analysis**

The Statistical Software SAS 9.2 and SAS Enterprise Guide 4.3 were used to analyse the results. Descriptive analysis was performed for demographic data and descriptive data. A multivariate model was developed to quantify the independent influence of predictor variables on the probability of an adverse drug event using a generalized estimating equation (GEE) method on a repeated measurement.<sup>135, 136</sup>

The initial analysis was performed to check if the outcome variables were reported in every subcategory for individual independent variable. If this assumption was not met, a generalized estimating equation model would not be able to converge the algorithm. Therefore, recoding of variables in lesser categories was necessary. For

example, age was collected as continuous variable initially. It was recategorised into groups that consisted of at least one adverse drug event in each group for data to be converged. Subsequently, univariate analysis based on Wald statistics for Type 3 GEE analysis,  $p < 0.05$  was used to identify if any of the predictors correlated with the outcome variables and therefore could be chosen for multivariate analysis in the final model. The results of the multivariate analysis were presented in L'Beta estimate, standard error, confidence limits, Chi-square and probability (P). The Proc Genmod command in SAS 9.2 does not automatically produce an odds ratio statement - which is presented as an L'Beta estimate in the output table.<sup>137</sup> Therefore, command of exponential (exp) has to be included if one wants to estimate odd ratio.

The form of GEE analysis varied with different outcome variable. For example, to identify predictors of the occurrence and severity of adverse drug events during infusion, log binomial generalized estimating equations (GEEs)<sup>136</sup> were used. Log Poisson GEEs were used when the number of adverse drug events was calculated. Predictors to be considered include age, gender, diagnosis, stage of disease, presence of cardiac and/or lung co-morbidity, number of courses, number of cycles, type of treatment, dosage base on body surface area, type of premedication, white blood cell counts, absolute neutrophil counts, lymphocyte counts and LDH level.

Generalised estimating equation (GEE) was proposed<sup>135</sup> to analyse longitudinal data which consisted of repeated observations over time on the same set of units and closely correlated. It is an extended model from a generalised liner model using a non-linear link function to examine issues of non-independence between observations and non-normally distributed outcome variables. These may constitute a binary or count data. This model is more robust in comparison to other regression models (logistic regression, repeated measure ANOVA) which require an assumption of a

normal distribution and independent observation being fulfilled before using the model.

The GEE was performed using the statistical software SAS 9.2. The following example is used to clarify the use of this statistical method<sup>137</sup>:

Let  $y_{ij}$ ,  $j = 1, \dots, n_i$ ,  $i = 1, \dots, K$ , represent the  $j$ th measurement on the  $i$ th subject. There are  $n_i$  measurement on subject  $i$  and  $\sum_{i=1}^k n_i$  total measurement. The statistical formula is presented below as follows:

$$S(\beta) = \sum_{i=1}^k D_i V_i^{-1} (Y_i - \mu_i(\beta)) = 0$$

And  $\beta$  = Parameters of estimate;  $Y$  = vector of measurement;  $\mu$  = vector of mean;  $V$  = covariance matrix of vector measurement;  $D$  = a matrix of derivative of element.

The two link functions that were used in the subsequent example were:

logit (for binomial distribution)  $g(\mu) = \log(\mu/1-\mu)$

log (for Poisson distribution)  $g(\mu) = \log(\mu)$

The associated variance function in binomial distribution for binary outcome is presented as  $V(\mu) = \mu(1-\mu)$  and for Poisson distribution for count outcome is  $V(\mu) = \mu$ .  $g$  = link function.

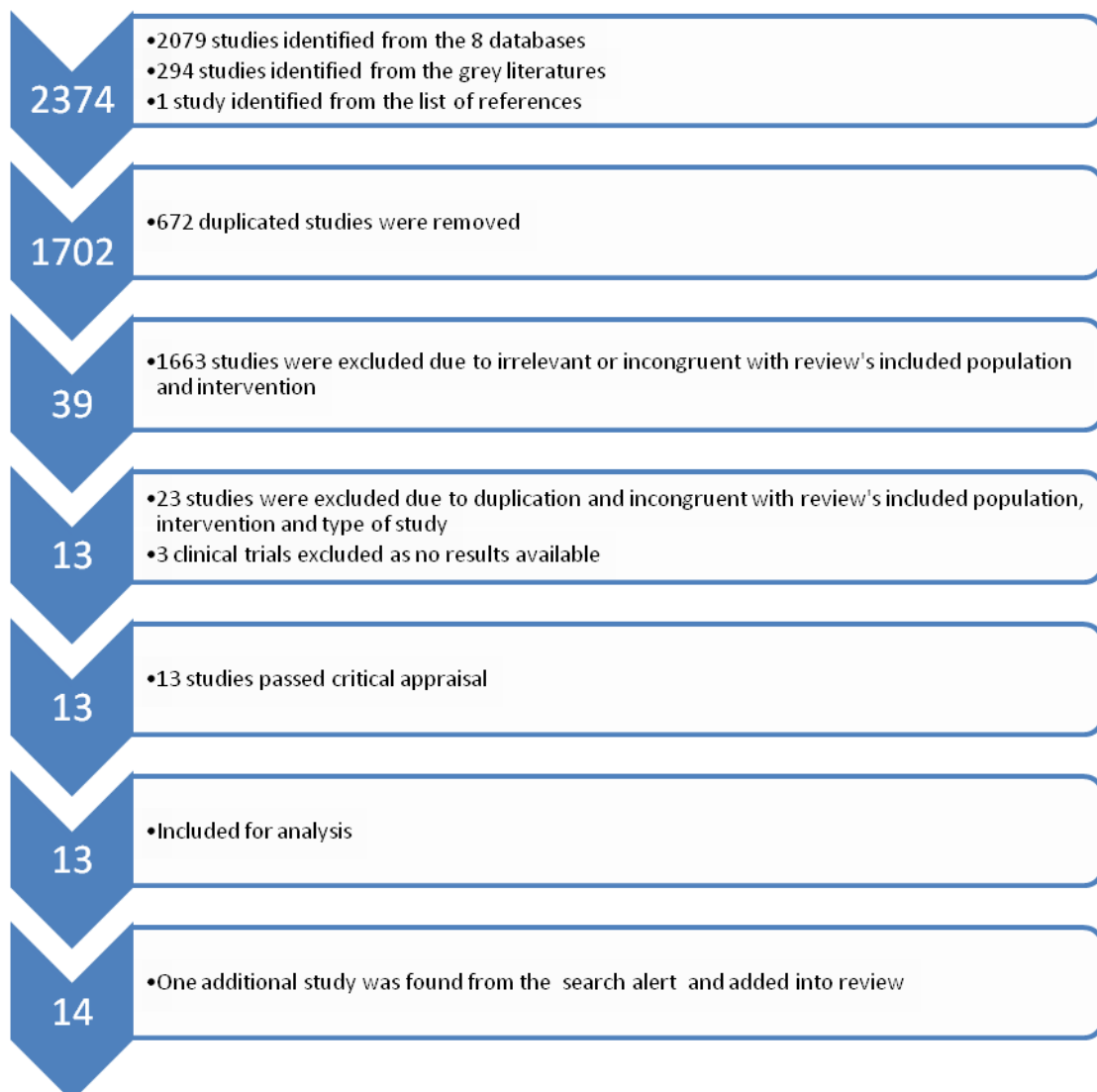
A sample of coding for the analysis is attached in Appendix VII

## **Chapter 4. Results from Phase 1: Systematic Review**

### **Description of studies**

A total of 2079 and 294 studies were retrieved from 8 commercially published and grey literature electronic databases, respectively, on completion of the search in October 2010. An additional study was found through the reference lists to give a total of 2374 studies. Of these, 672 duplicated studies were removed. The remaining 1702 study titles and abstracts were examined for a match with the inclusion criteria and it was found that 1663 studies were either irrelevant or incongruent with the inclusion criteria. Only 39 studies appeared to match the inclusion criteria and full texts were retrieved for further examination. After detailed examination, 13 studies qualified for inclusion based on methodological quality assessment and 23 studies were excluded. A further three clinical trials<sup>64, 138, 139</sup> from the 39 studies appeared to match the inclusion criteria but they were not included since their results would not be published until the end of 2010 or early 2011. One study was available in Dutch. Therefore, this report was sent to the Joanna Briggs Institute's Collaborating Centre in Belgium for critical appraisal. The Dutch study<sup>140</sup> was excluded because approximately one third, i.e. 29.4% out of 17 patients, were treated for either AIHA or Idiopathic Thrombocytopenic Purpura (ITP). These are autoimmune diseases and were not included in the review inclusion criteria. Of the remaining 22 studies excluded after detailed examination these included discussion papers,<sup>75, 105, 141-143</sup> duplicated studies<sup>125, 126, 144-149</sup> and incongruent with the review inclusion criteria related to population,<sup>114, 140</sup> intervention<sup>51, 80, 111, 113, 115, 116</sup> or outcome measures.<sup>85, 112</sup> Figure 1 highlights the process of study selection for this review. All 13 included studies scored at least 5 out of 9 criteria during methodological assessment using the JBI-MAStARI appraisal instrument. Therefore, 13 studies were included in this

review for analysis. After the initial search, a search alert was set up to monitor potential studies published after the search was conducted. One study<sup>94</sup> was found to meet the review inclusion criteria and passed the methodological assessment between October 2010 and July 2011. Therefore, this paper was added to the review. (Figure 1) Details of the studies included in the review are presented in Appendix V. Studies excluded from the review and reasons for their exclusion are detailed in Appendix VI.



*Figure 1. Process of Study Selection from 1997 until July 2011*



## **Methodological quality**

All 14 included studies in the analysis were observational studies. Each study design was a case series without a comparison group. Each used convenience sampling depending on the availability of the patients who sought treatment at the study site. The sample definition was reported based on age, diagnosis and treatment regimen. The other characteristics of patients who were identified included type of premedication, especially steroids usage, presence of bulky disease (>7cm) or advance stage III and IV diseases and presence of leucocytosis (Total White Blood Cells of >25,000). Although some of the studies did not mention the name of the instrument used to measure the outcomes, they reported adverse drug events using Grades, which could implicitly imply the use of NCI CTC or NCI CTAE. These are standard tools used globally for grading adverse drug events.

This review focused on the acute adverse drug events of rapid rituximab infusion and therefore, studies that reported adverse drug events during infusion and the subsequent 1-2 hours following completion were included. Only one patient withdrew from the rapid infusion regimen but was included in the analysis due to a Grade 3 adverse drug event. Some of the outcome measures were determined objectively using a thermometer or a manual or digital sphygmomanometer. However, the majority of outcomes were measured subjectively and depended on patients' self-reporting and observations made by the nurses in charge of the rituximab infusion. Descriptive analyses were used to describe patient characteristics, numbers of patients and numbers of cycles of rapid rituximab infusion completed by the patients. Reports on the type of adverse drug events, description of the treatment rendered to patients who developed adverse drug events and the outcome after the treatment were also included.

Patient diagnosis was clearly reported by the included studies (Appendix V). 766 patients were included in the analysis with the majority being NHL, n= 735 (96%), followed by CLL, n= 15 (2%) and other diagnoses n= 16 (2%) that were not stated in the inclusion criteria. However, it was decided to include these 16 patients with other diagnoses because the result of frequency of adverse reactions was not reported based on individual diagnosis. Only two studies<sup>71, 93</sup> reported patient Eastern Cooperative Oncology Group (ECOG) scoring and one study<sup>71</sup> presented patients' co morbidities such as hypertension and diabetes. Three studies<sup>85, 87, 93</sup> reported the presence of bulky disease and seven studies<sup>72, 73, 85, 87, 89, 92, 94</sup> identified if the patients were in a stage of leucocytosis during rapid rituximab infusion. Most studies<sup>71-73, 76, 85, 87-94</sup> stated the type of chemotherapy regimens used except in one study<sup>74</sup> which did not mention it in the report.

Two common rapid rituximab infusion regimens were reported by the majority of included studies. The first rapid rituximab infusion regimen lasted over 30 minutes for 20% of the total dose. When the patients tolerated the infusion well, the remaining 80% was infused for over 60 minutes. Therefore, the total duration of infusion was 90 minutes. Eleven studies<sup>71-73, 76, 87, 89-94</sup> used a 90-minute regimen and the remaining three studies used a 60-minute regimen. There were two methods of rapid rituximab infusion over 60 minutes. The first study<sup>85</sup> used a constant rate throughout 60 minutes. The second study<sup>88</sup> used the rate of 100mg/hr for the first 15 minutes. When patients tolerated the infusion well, the rate was increased to 500mg/hr. The third study<sup>74</sup> did not explain how the rituximab was administered rapidly over 60 minutes.

The adverse drug events were measured by NCI CTC version 2<sup>76</sup> or NCI CTC version 3<sup>85</sup> or CTCAE version 3<sup>73, 89</sup> or CTCAE version 4<sup>94</sup> in six studies and one study<sup>90</sup> did not specify the version used. The type of adverse drug events were clearly described

in seven studies<sup>71, 72, 76, 85, 91, 93, 94</sup> Of those studies that did report adverse drug events, six<sup>71, 72, 85, 89, 93, 94</sup> specified the exact time when the adverse drug events occurred and five<sup>71, 72, 76, 89, 94</sup> clearly described the management of the adverse reactions.

All the studies<sup>71-74, 76, 85, 87-94</sup> reported the use of antipyretic and antihistamine as part of the premedication regimen before rapid rituximab infusion. A slight variation was noted across all these studies in terms of their route of administration and dosage. Eight studies<sup>72-74, 90, 91, 93, 94</sup> also included corticosteroids as premedication.

The majority of studies<sup>71, 73, 76, 85, 87-90, 92-94</sup> were conducted in outpatient or ambulatory settings in several countries including Saudi Arabia, Singapore, the United States, Ireland, the United Kingdom, Spain, Argentina, France and Denmark. Only one study<sup>72</sup> was conducted in both inpatient and outpatient settings. Two studies<sup>74, 91</sup> did not state the research setting in their reports.

## **Descriptive Analysis of Results**

A total of 766 patients were included in the review. They completed a total of 2330 cycles of rapid rituximab infusion. A total of 29 acute adverse drug events were reported in the studies. Of these 29 events, 17 were grade 1, five were grade 2 and one was grade 3 in NHL patients. Twelve of the grade 1 adverse drug events were reported in the 90-minute regimen while the remaining five were reported for the 60-minute regimen in the NHL group. Only one grade 1 adverse drug event occurred in the 60-minute regimen in one of the CLL patients. There were five occurrences of adverse drug events which were not clearly reported in either the NHL or CLL group. Of these five adverse drug events, four were grade 1 and one was grade 3 in the 90-minute regimen (Table 2).

*Table 2. Frequency and severity of acute adverse drug events among NHL and CLL patients in 90- and 60 minute- regimens*

Population	Regimen	Study	ΩGrade				Total number of adverse reactions	Total number of patients	Total number of cycles
			1	2	3	4			
NHL	90 min	Al Zahrani 2009					0	21	126
		Chiang 2010	2	2			4	79	269
		Corey 2007		1			1	46	135
		El Agnaf 2007					0	17	73
		Gibbs 2007					0	61	250
		Salar 2006	1	1			2	70	319
		Sehn 2007	1				1	205	565
		Statham 2006	1	1			2	23	62
		Soria 2008	2				2	37	-
		Swan 2010	5		1		6	13	32
	60 min	Provencio 2006	5				5	40	233
Tuthill 2009						0	54	105	
CLL	90 min	Milone 2007	4		1		5	¥ 31	67
	60 min	Aurran 2005	1				1	69	94
		Total	22	5	2		29	766	2330

¥ Among 31 patients, 4 were CLL and 27 were NHL. It was not stated in which group of patients that the 5 adverse reactions occurred. Several attempts were made to contact primary authors, but they were not contactable.

ΩGrade 1: Intervention not indicated  
Grade 2: Non-urgent medical intervention indicated  
Grade 3: Hospitalisation indicated  
Grade 4: Life-threatening and urgent medical intervention indicated

The most commonly reported acute adverse drug events were rash (5 patients) followed by: fever and chills (4 patients); abdominal pain (4 patients); nausea and vomiting (4 patients); hypotension (3 patients); bradycardia (3 patients); and sore throat (1 patient). However, one study did not specify the type of reaction. Rash, fever and chills were more prominent among NHL patients (Table 3). It was unclear whether CLL or NHL patients complained more of abdominal pain. The onset of acute adverse drug event ranged from 30 minutes into the infusion to immediately post-rapid rituximab infusion. Treatments were not needed for grade 1 adverse drug events as they were usually self-limiting. For grade 2 adverse drug events, temporary interruption of the rapid infusion and supplement of additional drugs namely antiemetic, antihistamine and opioid eased the symptoms. Only one patient withdrew from the 90-minute rapid rituximab regimen due to abdominal pain (Table 4). No deaths were reported in any of the studies.

Table 3. Type, time of event and treatment of adverse drug events in NHL patients

		Study	Grade of Adverse Reaction	Type of Adverse Reaction	Time of Event	Treatment of Adverse Reactions	Withdraw from Study / Death
NHL	90 Min	Chiang 2010	1	Nausea & vomiting	Immediately post-rapid infusion	Not stated	No
			1	Nausea & vomiting	Immediately post-rapid infusion	Not stated	No
			2	Nausea & vomiting	70 min into the infusion	IV Metoclopramide given	No
			2	Chills & rigors	45 min into infusion	IV Diphenhydramine 25mg given and restarted infuse at a slower rate	No
		Corey 2007	2	Rigors & back pain	5 min post- rapid infusion	Meperidine 12.5mg given	No
		Salar 2006	1	Abdominal discomfort	30 min into infusion	No intervention, the symptoms resolved spontaneously	No
			2	Sore throat	30 min into infusion	Infusion rate was reduced	No
		Sehn 2007	1	Unclear	Unclear	Unclear	No
		Statham 2006	1	Hypotension	Unclear	No intervention	No
			2	Rash	Unclear	Rapid infusion was discontinued temporary and antihistamine was given	No
		Soria 2008	1	Skin erythema	During rapid infusion	Not stated	No
			1	Skin erythema	During rapid infusion	Not stated	No
		Swan 2010	1	Hypotension	During rapid infusion	No intervention	No
			1	Hypotension	During rapid infusion	No intervention	No
	1		Bradycardia	During rapid infusion	No intervention	No	
	1		Bradycardia	During rapid infusion	No intervention	No	
	1		Bradycardia	During rapid infusion	No intervention	No	
	3		Nausea, vomiting & syncope	30 min into infusion	Rapid infusion was discontinued temporary and anti emetic was given	No	
	60 min	Provencio 2006	1	Fever	During rapid infusion	Not stated	No
			1	Chills	During rapid infusion	Not stated	No
			1	Chills	During rapid infusion	Not stated	No
			1	Rash	During rapid infusion	Not stated	No
			1	Rash	During rapid infusion	Not stated	No

*Table 4. Type, time of event and treatment of adverse drug events in CLL patients*

Population	Regimen	Study	Grade of Adverse Reaction	Type of Adverse Reaction	Time of Event	Treatment of Adverse Reactions	Withdraw from Study / Death
CLL	90 min	Milone 2007 <sup>∞</sup>	1	Hypotension	Not stated	Not stated	No
			1	Chest pain	Not stated	Not stated	No
			1	Abdominal pain	Not stated	Not stated	No
			1	Abdominal pain	Not stated	Not stated	No
			3	Abdominal pain	Not stated	Not stated	Yes
	60 min	Aurran 2005	1	Not stated	Not stated	Not stated	No

<sup>∞</sup> This study consisted of both NHL and CLL patients. It was not stated which group of patients developed acute adverse reactions

All the studies used antipyretics, more specifically Acetaminophen/Paracetamol as a premedication for rapid rituximab infusion. The dosage of this medication ranged from 375 mg to 1000mg either in the form of tablet(s) or injection. The most common antihistamine was either oral or parenteral Diphenhydramine 25-50mg followed by parenteral Chlorphenamine 10mg, oral Dexchlorpheniramine 5mg and oral Hydroxyzine 20mg. The common choice of corticosteroids was parenteral Hydrocortisone 100mg, Prednisolone 100mg and Methylprednisolone (Table 5).

*Table 5 Type, name, route and dosage of premedication used in NHL and CLL patients*

Population	Regimen	Study	Antipyretic			Antihistamine			Steroids		
			Route	Name	Dosage (mg)	Route	Name	Dosage (mg)	Route	Name	Dosage (mg)
NHL	90 min	Al Zahrani 2009	PO	Paracetamol	1000	PO	Hydroxyzine	20	NS	NS	NS
		Chiang 2010	PO	Paracetamol	1000	IV	Diphenhydramine	25	NS	NS	NS
		Corey 2007	PO	Acetaminophen	625	IV	Diphenhydramine	25-50	NS	NS	NS
		El Agnaf 2007	PO	Acetaminophen	1000	IV	Chlorphenamine	10	IV	Hydrocortisone	100
		Gibbs 2007	PO	Paracetamol	1000	NS	Chlorphenamine	8	NS	Prednisolone	100
		Salar 2006	NS	Acetaminophen	NS	NS	Diphenhydramine	NS	NS	Methylprednisolone	NS
		Sehn 2007	PO	Acetaminophen	375	PO	Diphenhydramine	50	NS	NS	NS
		Statham 2006	NS	Paracetamol	NS	NS	Chlorphenamine	NS	NS	NS	NS
		Soria 2008	IV	Paracetamol	1000	PO	Dexchlorpheniramine	5	PO	Steroid	40
		Swan 2010	PO	Acetaminophen	650	IV	Diphenhydramine	25	IV	Hydrocortisone	100
	60min	Provencio 2006	IV	Paracetamol	1000	PO	Dexchlorpheniramine	5	NS	NS	NS
Tuthill 2009		PO	Paracetamol	1000	IV	Chlorphenamine	10	IV	Hydrocortisone	100	
CLL	90	Milone 2007	PO	Paracetamol	NS	IV	Diphenhydramine	NS	IV	Hydrocortisone	NS
	60	Aurran 2005	NS	Paracetamol	NS	NS	Diphenhydramine	NS	NS	Steroids	NS

Abbreviations: PO - Per Oral; IV – Parenteral; NS – Not Stated



The aim of this review was to examine the incidence and severity of acute adverse drug events from rapid rituximab infusion. This review has analysed results separately for NHL and CLL population. To account for possible heterogeneity present due to variations within the included interventions, a random effects model was used. Meta-analysis of proportions performed using random effects model (DerSimonian-Laird) showed a pooled proportion of 0.0304 (95%CI 0.01, 0.06) among eleven studies of 653 NHL patients. In other words, 3% of acute adverse drug events were reported among 653 NHL patients in 2137 cycles of rapid rituximab infusion (Figure 2). Significant heterogeneity was detected in the eleven studies,  $p = 0.01$ ,  $I^2 = 56.9\%$  (95%CI 0%, 76%) (Box 1). To overcome this heterogeneity, two studies utilising a 60-minute regimen were removed. The subsequent analysis using non-combinability as part of the random effects model shows homogeneity of studies,  $p = 0.1$  and  $I^2 = 40.8\%$  (95%CI 0%, 71.3%) (Box 2). Therefore, the pooled proportion in the nine studies of a 90-minute rapid rituximab infusion regimen among 559 patients in 1855 cycles is 0.026, equivalent to 2.6% (Figure 3). However, with an additional one study using a 90-minute regimen in NHL patients found from the search alert, significant heterogeneity was again detected in ten studies,  $p = 0.0001$ ,  $I^2 = 72.9\%$  (95%CI, 40.4%-84.2%) (Box 3). The new pooled results in the ten studies of 90-minute rapid rituximab infusion regimen for 572 patients in 1887 cycles is 0.0422, which is equivalent to 4.2% (Figure 4).

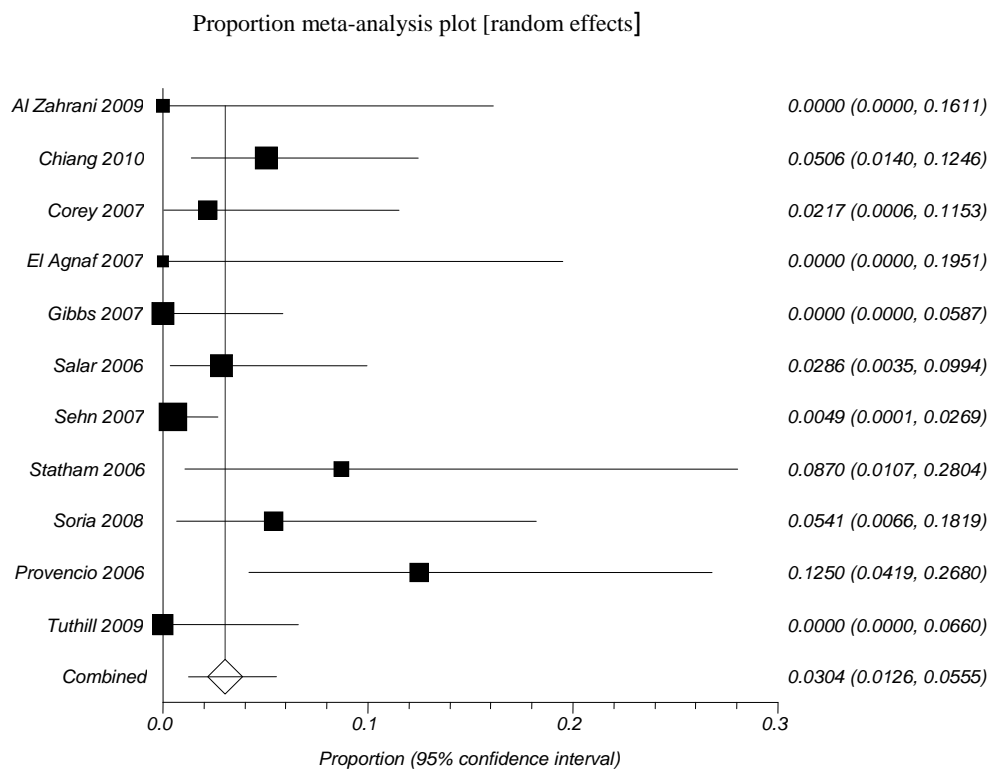


Figure 2. Proportion meta-analysis of acute adverse reactions in 11 studies (combination of both 90- and 60-minute regimens)

Cochran Q = 23.202124 (df = 10) P = 0.01

Moment-based estimate of between studies variance = 0.023475

I<sup>2</sup> (inconsistency) = 56.9% (95% CI = 0% to 76.4%)

Box 1. Non-combinability of studies for 11 studies (combination of 90- and 60-minute regimen)

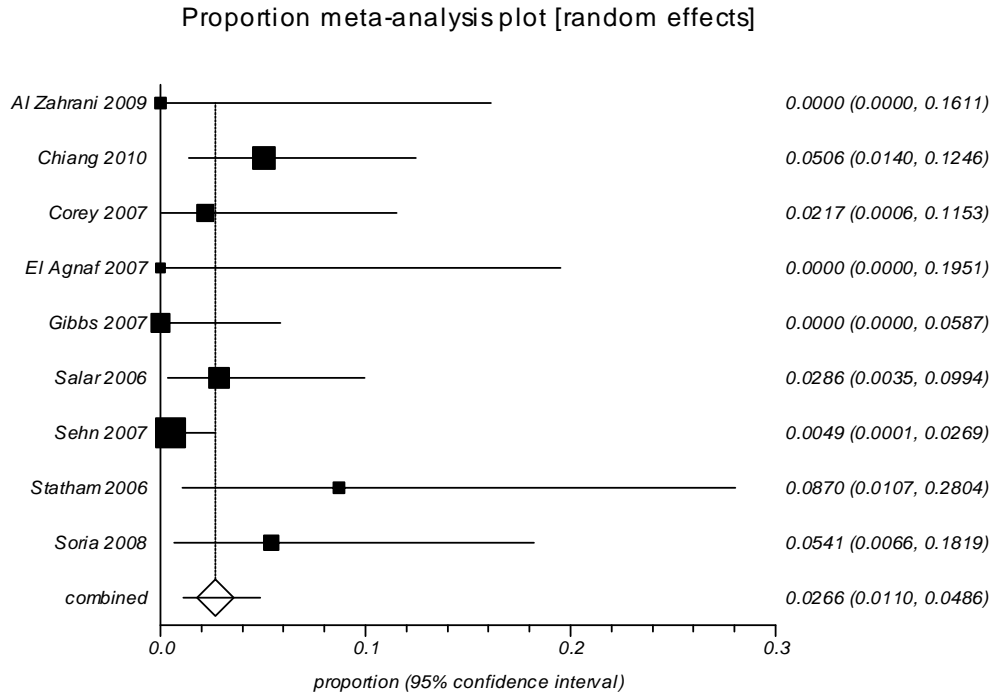


Figure 3. Proportion meta-analysis of acute adverse reactions in 9 studies (90-minute regimen) in NHL patients

Cochran Q = 13.510486 (df = 8) P = 0.0955

Moment-based estimate of between studies variance = 0.012044

I<sup>2</sup> (inconsistency) = 40.8% (95% CI = 0% to 71.3%)

Box 2. Non-combinability of 9 studies (90-minute regimen)

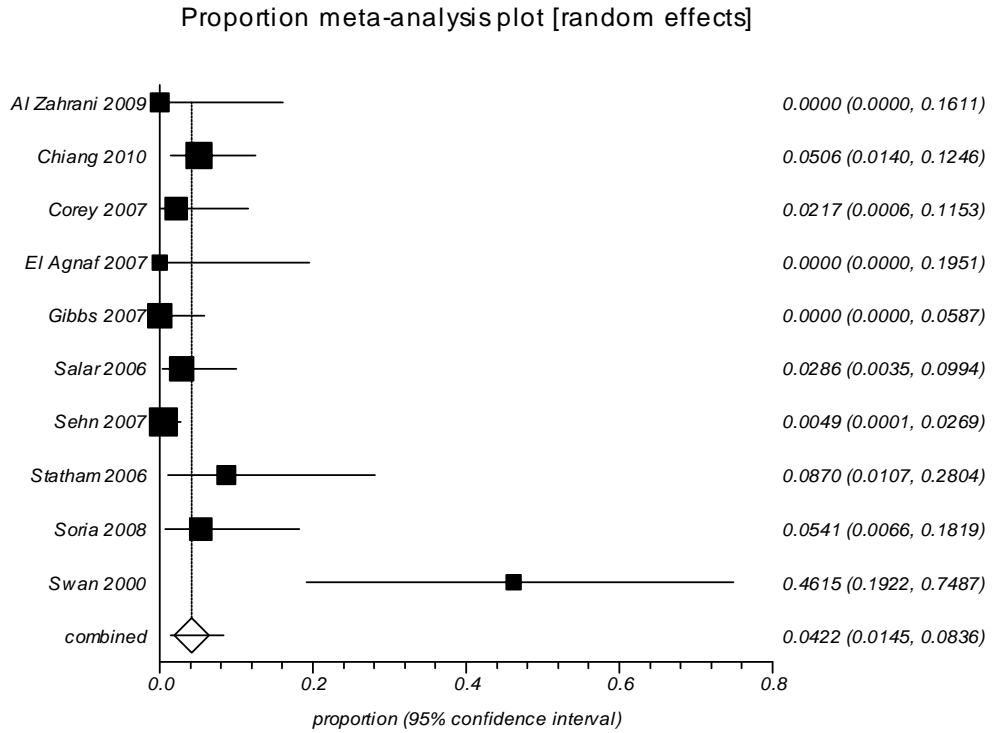


Figure 4. Proportion meta-analysis of acute adverse reactions in 10 studies (90-minute regimen) in NHL patients

Cochran Q = 33.269991 (df = 8) P = 0.0001

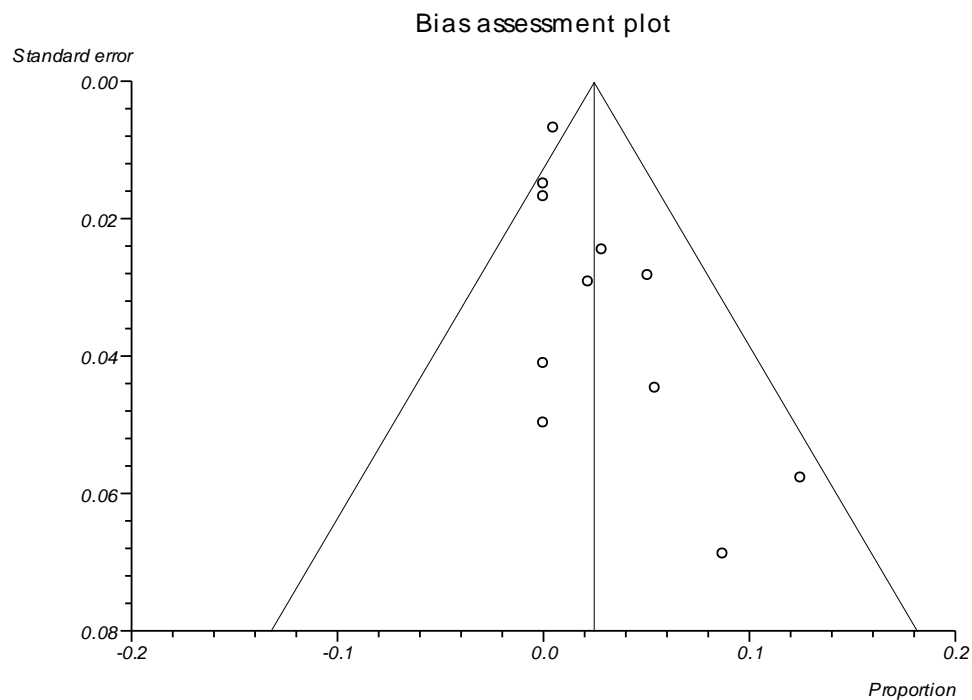
Moment-based estimate of between studies variance = 0.051214

I<sup>2</sup> (inconsistency) = 72.9% (95% CI = 40.4% to 80.2%)

Box 3. Non-combinability of 10 studies (90-minute regimen)

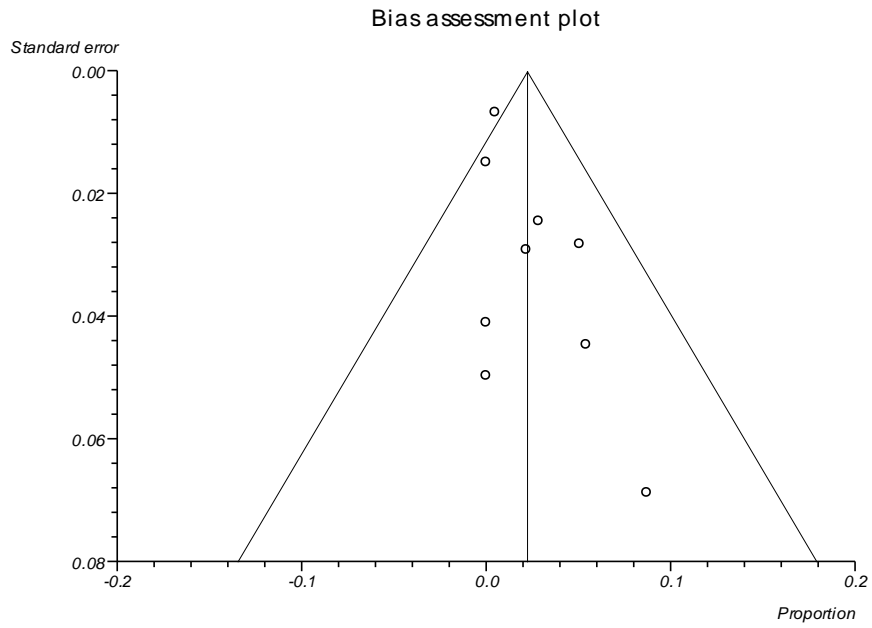
A Bias assessment plot was performed to detect any publication bias among the studies that could possibly skew the results. Both analyses done on the eleven and subsequent nine studies demonstrated that the studies were symmetrically distributed under the funnel plots. The statistical test, Harbord bias, further confirmed the absence of publication bias,  $p=0.25$  in Plot 1 and  $p=0.30$  in Plot 2 respectively. Even with an additional study found from the search alert included in the meta-analysis, no publication bias was detected as well,  $p = 0.10$  (Plot 3).

*Plot 1. Bias assessment plot and indicator for 11 studies (combination of 90 and 60-minute regimen) in NHL patients*



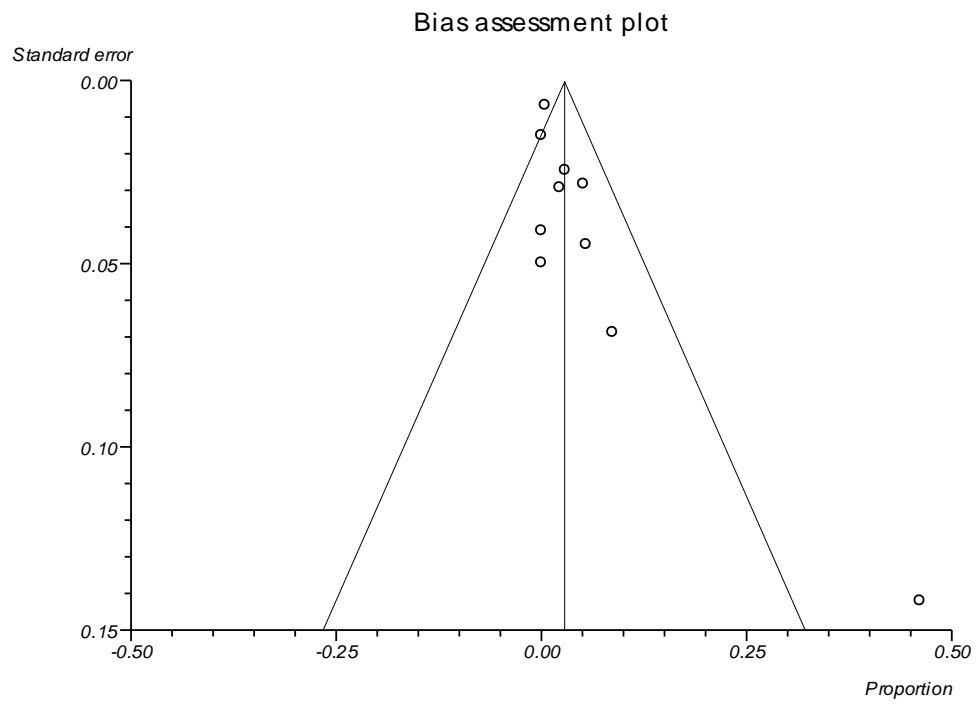
Harbord: bias = 1.83 (92.5% CI = -1.21 to 4.87) P = 0.26

Plot 2. Bias assessment plot and indicator for 9 studies (combination of 90-regimen) in NHL patients



Harbord: bias = 1.3 (92.5% CI = -1.17 to 3.77) P = 0.30

*Plot 3. Bias assessment plot and indicator for 10 studies (combination of 90-regimen) in NH patients*



Harbord: bias = 4.46 (92.5% CI = -0.57 to 9.48) P = 0.11

## **Summary of Non-Hodgkin Lymphoma patients in 60-minute Rapid Rituximab Regimen**

Two studies were included in this review only for NHL patients undergoing a 60-minute rapid rituximab regimen. In the study by Provencio et al.<sup>85</sup> only five out of a total of 40 patients who completed 233 cycles of rapid rituximab infusions developed grade 1 adverse drug events. These adverse drug events consisted of fever, chills and rash that occurred during the rapid rituximab infusions. The treatment for these reactions was not stated. No patient withdrew from the study. No corticosteroids were used as part of the premedication regimen. In the Tuthill et al. study,<sup>74</sup> no adverse drug event were reported among 69 patients who completed 94 cycles of rapid rituximab infusions. In this study, parenteral Hydrocortisone 100mg was used as part of the premedication.

## **Summary of Chronic Lymphocytic Leukemia patients in 90 and 60-minute Rapid Rituximab Regimen**

Only two studies included CLL patients and meta-analysis was not possible for the studies as one study used a 90-minute regimen and the other a 60-minute regimen. In Milone et al.'s study,<sup>91</sup> four patients were CLL and 27 patients were NHL who completed 67 cycles of rapid rituximab infusion. Four grade 1 acute adverse drug events were reported, although it was unclear which patients developed the adverse drug event. One patient from this study developed a grade 3 adverse drug event in a 90-minute regimen. It was unclear which group of patients developed adverse drug event as well. Several attempts were made to contact primary authors for more details but to no avail. The treatment for these adverse drug events was not stated in the study. Parenteral Hydrocortisone 100mg was used in the premedication.



In Aurran et al.'s study<sup>88</sup> a total number of 69 patients completed 94 cycles of rapid rituximab infusions. Eleven patients were CLL, the rest were 27 DLBCL, 22 FL, two Mantle Cell Lymphoma (MCL), three Marginal Zone Lymphoma (MZL), two Lymphopasmocytic, one Castelman Disease and one Idiopathic Thrombocytopenia Purpura. In this study, it was clearly stated that the only patient who developed grade 1 acute adverse drug event was a CLL patient. The type and treatment of the adverse drug event was not stated in the study. A corticosteroid was used but there was no mention of its specification.

## **Chapter 5. Results from Phase 2: Retrospective Cohort Study**

### **Patients' Characteristics**

#### **Age**

Two hundred and ninety-four (294) patients met the inclusion criteria and were available for evaluation. The median age of patients was 65 years ranging from 19 to 90. Of these 294 patients, 43 (14.6%) experienced adverse drug events arising out of rapid rituximab infusion. Sixteen (37.2%) out of 43 patients aged between 61-70 made up the most common age group experiencing adverse drug events resulting from rapid rituximab infusion. This was followed by the age group 51-60 years with 11 (25.6%) patients in this group developing adverse drug events. There were 6 (14%) patients in each of the age groups  $\leq 50$  and 71-80 who experienced the adverse drug events. Only 4 (9.3%) patients in the very old age group of 81-90 developed adverse drug events. Regardless of the difference between the number of occurrences of adverse drug events, there was no statistical difference between the groups who experienced the adverse drug event as compared to those without by stratification into 5 age groups,  $\chi^2 = 1.42$   $p = 0.84$  (Table 6).

#### **Gender**

Slightly more than fifty percent of the patients were male (55%). Twenty-six (60.5%) of these male patients experienced adverse drug events resulting from rapid rituximab infusion when compared to 17 (39.5%) female patients. There was no statistical difference between the two groups when stratified by gender,  $\chi^2 = 0.51$ ,  $p = 0.47$  (Table 6).

## **Diagnosis**

The patients in the study were broadly classified into 5 groups: non-Hodgkin lymphoma (NHL), acute and chronic lymphocytic leukemia (ALL and CLL), autoimmune diseases, lymphoproliferative diseases (LPD) and monoclonal gammopathy undetermined of significance (MGUS). The majority of patients (85%) were diagnosed with NHL including 2 main subtypes of NHL: DLBCL and FL. Thirty-four (79.1%) patients from the NHL group developed adverse drug events resulting from rapid rituximab infusion. This was followed by 6 (14%) patients from the Acute and Chronic Lymphocytic Leukemia group. One (2.3%) patient from each group of autoimmune disease, LPD and MGUS, also experienced an adverse drug event. There was no statistical difference in the occurrence of adverse drug events across the different groups of diagnoses,  $\chi^2 = 1.5$ ,  $p = 0.51$  (Table 6).

## **Stage of Disease**

Slightly more than half of the cancer patients were in an advanced stage of their disease. They were 173 (58.84%) staged III/IV and 24 (55.8%) patients experienced adverse drug events from rapid rituximab infusion. Compared to the earlier stage I/II, 4 (9.3%) patients developed adverse drug events. In this study, some diagnoses did not require staging such as autoimmune disease, LPD and MGUS. Thus, among patients in this group without staging or where staging information was not available in the medical notes, 15 (34.9%) of them experienced adverse drug events. There was no statistical difference between the stages of disease,  $\chi^2 = 5.93$ ,  $p = 0.05$  (Table 6).

### **Presence of Cardiac and Lung Disease as Co-morbidities**

Co-morbidities related to cardiac disease included hypertension, ischemic heart disease (IHD), atria fibrillation (AF), aortic sclerosis, cardiomyopathy, congestive cardiac failure (CCF), heart murmur, valvular heart disease, low injection function, mild aortic regurgitation and pericardia effusion. Respiratory-related co-morbidities included but were not limited to asthma, chronic obstructive airway disease (COAD)/ chronic obstructive pulmonary disease (COPD), and chronic lung fibrosis. Slightly more than half of the patients (55.1%) did not have any of the above mentioned co-morbidities yet experienced more adverse drug events compared to those who had cardiac or pulmonary co-morbidity. Twenty-eight (65.1%) of them without the presence of co-morbidity developed adverse drug events compared to 15 (34.9%) patients who had co-existing co-morbidity. However, this was not statistically significant,  $\chi^2 = 2.04$ ,  $p = 0.15$  (Table 6).

Table 6. Patients' Characteristics, N = 294

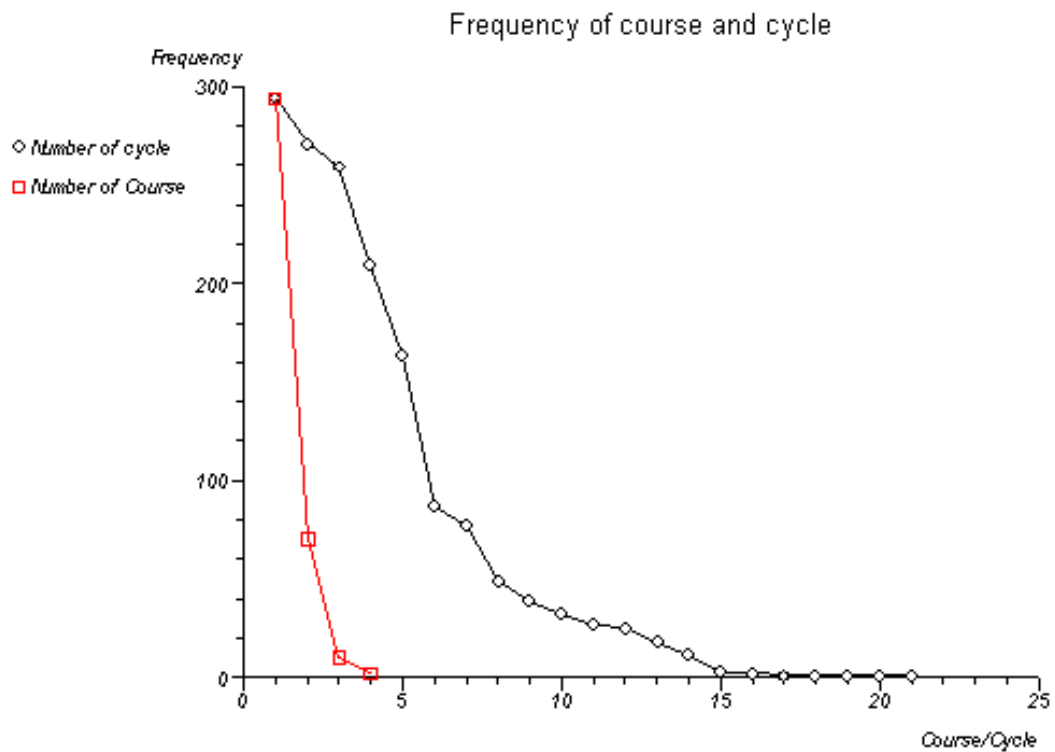
	Number without AR (%), N=251	Number with AR (%), N=43	Chi- Square( $\chi^2$ )	P value
<b>Age</b>			1.42	0.84
≤ 50	33 (13.1)	6 (14)		
51-60	54 (21.5)	11 (25.5)		
61-70	86 (34.3)	16 (37.2)		
71-80	54 (21.5)	6 (14)		
81-90	24 (9.6)	4 (9.3)		
<b>Gender</b>			0.51	0.47
Male	137 (54.6)	26 (60.5)		
Female	114 (45.4)	17 (39.5)		
<b>Diganosis</b>			1.5	0.51
Non hodgkin lymphoma	216 (86.1)	34 (79.1)		
Acute and chronic lymphocytic leukemia	22 (8.7)	6 (14)		
Autoimmune disease	4 (1.6)	1 (2.3)		
Lymphoproliferative disease	4 (1.6)	1 (2.3)		
Monoclonal gammopathy undetermined significant	5 (2)	1 (2.3)		
<b>Stage</b>			5.93	0.05
I-II	51 (20.3)	4 (9.3)		
III-IV	149 (59.4)	24 (55.8)		
Not applicable/not stage	51 (20.3)	15 (34.9)		
<b>Co-morbidity related to cardiac or respiratory diseases</b>			2.04	0.15
Yes	117 (46.6)	15 (34.9)		
No	134 (53.4)	28 (65.1)		-
<b>Course</b>			9.05	0.00*
1	199 (79.3)	25 (58.1)		
>1	52 (20.7)	18 (41.9)		
<b>Cycles</b>			3.28	0.19
1-4	109 (43.4)	22 (51.2)		
5-8	111 (44.2)	13 (30.2)		
>8	31 (12.4)	8 (18.6)		

\*p value is significant at 0.05

A course of chemotherapy treatment consists of varying the cycles of rituximab alone or in combination with chemotherapy. In this study, 294 patients received 376 courses of treatment. The median course was 1 and ranged from 1-4 courses. The majority of patients (78.2%) received only 1 course of treatment. (Figure 5) Twenty-five (58.1%) patients who received just one course of treatment experienced adverse drug events from rapid rituximab infusion. Among the 70 (23.81%) patients who received more than 1 course of treatment, 18 (41.9%) patients developed adverse drug events. Therefore, the difference between those who just received one course compared to those who received more than 1 course was statistically significant,  $\chi^2 = 9.05$ ,  $p = 0.00$  (Table 6).

Among the 376 courses of treatment, 294 patients received 1571 cycles of rapid rituximab infusion. On average, each patient received 4 cycles of rapid infusion, SD =3, ranging from 1-21 cycles (Figure 5). For the purposes of statistical analysis, the number of cycles were subdivided into 3 groups (1-4, 5-8 and >8 cycles). Twenty-two (51.2%) who received between 1-4 cycles developed adverse drug events resulting from rapid rituximab infusion as compared to 13 (30.2%) in between 5-8 cycles and 8 (18.6%) in >8 cycles respectively. The occurrence of adverse drug events was not statistically significant between the three groups (Table 6).

Figure 5. Number of courses and cycles of rapid rituximab infusion



### Type of Treatment

Patients’ treatment profiles were tabulated based on the number of courses of treatment. In this study, they were divided into groups only receiving rituximab as monotherapy or in combination with chemotherapy. Two-thirds of the patients (70.74%) received rituximab in combination with chemotherapy. Thirty-six (78.3%) patients who received Rituximab in combination with chemotherapy developed adverse drug events compared to 10 (21.7%) patients who received rituximab only (Table 7).

### Body Surface Area

The calculation of the rituximab’s dosage is based on a patient’s body surface area (BSA) which is based on height and weight. Taking into consideration the nature of the study setting, the physician would use the Mosteller formula<sup>129</sup> to calculate the patient’s body surface area and further adjust it before sending the prescription to the

pharmacy. In the pharmacy department, an online Dubois & Dubois formula<sup>128</sup> would be used to verify the physician's order. The most common reason for a physician to adjust the body surface area was to base the rituximab dosage on a rounded figure. Other reasons included considering patients' ideal weight for those overweight rather than the face value weight. In this study, data demonstrated that some physicians kept to the original calculation of body surface area (46.5%). Twenty-five (54.3%) patients who had the dosage prescription calculated exactly according to their body surface developed adverse drug events resulting from rapid rituximab infusion compared to 3 (6.5%) patients who had the BSA adjusted down and 18 (39.2%) patients who had the BSA adjusted up respectively (Table 7).

*Table 7. Patients' treatment profiles based on number of courses, N = 376*

	<b>Number without AR, N=330</b>	<b>%</b>	<b>Number with AR, N=46</b>	<b>%</b>
<b>Type of treatment</b>				
Rituximab alone	100	30.3	10	21.7
Rituximab combine with chemotherapy	230	69.7	36	78.3
<b>Dosage based on calculation of body surface area</b>				
Adjusted down	11	3.3	3	6.5
Exact	150	45.5	25	54.3
Adjusted up	168	51.2	18	39.2

## **Premedication**

The use of premedication varied from one cycle to another. Therefore, the frequency and type of premedication was based on treatment cycles. The most commonly used premedication prior to rapid rituximab infusion was corticosteroids, antihistamines and antipyretics. For the total number of 1513 cycles, 891 (56.7%) cycles used rapid rituximab infusion without using corticosteroids as premedication. An example of corticosteroid used in the study was Hydrocortisone. In 27 (47.4%) cycles using



steroids and 30 (52.6%) cycles without steroids respectively led to adverse drug events. All the cycles used antihistamines (Loratidine in this study). An adverse drug event was reported in 57 (100%) cycles of rapid rituximab infusion and no adverse drug event was recorded in 1514 cycles. Antipyretics such as Paracetamol were used in almost all cycles (99.4%). Adverse drug events occurred in fifty-six (98.2%) cycles for those who received antipyretics compared to one (0.8%) cycle in the group that did not receive antipyretics (Table 8).

*Table 8. Patients' use of premedication based on number of cycles, N= 1571*

	Number without AR, N=1514		Number with AR, N=57	
		%		%
<b>Steroid as premedication</b>				
Yes	650	42.9	30	52.6
No	864	57.1	27	47.4
<b>Antihistamine as premedication</b>				
Yes	1514	100	57	100
<b>Antipyretic as premedication</b>				
Yes	1505	99.7	56	98.2
No	9	0.3	1	0.8

### **Blood Count Level**

Four type of blood counts were collected based on the number of cycles. This was because routinely the physician would need to know if the patient was fit for the treatment especially when rituximab was administered in combination with chemotherapy. Occasionally, although no blood test was conducted prior to the rapid rituximab infusion, it would frequently be conducted one day after the infusion to measure the toxicity of the treatment. For patients who received only rituximab as monotherapy, no blood test would be done prior to rituximab infusion as rituximab would not cause marrow suppression and blood counts were likely to remain fairly

stable. Therefore, those blood tests that were conducted one day after infusion or more than 4 days prior to infusion were not included in the study. Full blood counts (also known as complete blood counts) encompassed three major elements of blood cells: total white blood cells, red blood cells and platelets. White blood cells can be subcategorised into neutrophils, eosinophils, basophils, lymphocytes and monocytes. Eight hundred and sixty-one (67.1%) of the total number of patients who had white blood cells sampled reported a normal range from  $4-11 \times 10^9/L$ . In the 23 cycles (50%) which had normal white blood cells, adverse drug events were reported. When compared to cycles where white blood cell counts were recorded, 15 low (32.6%) developed adverse drug events resulting from rapid rituximab infusion whereas in those with high white blood cells, an adverse drug event occurred in 8 (17.4) cycles. Similarly the majority (79.2%) of the absolute neutrophil counts were within normal range. Eleven (23.9%), 31 (67.4%) and 4 (8.7%) cycles led to adverse drug events in low, normal and high absolute neutrophil counts groups respectively. In terms of lymphocyte counts, most patients had low (48.8%) or normal (49.5%) lymphocyte counts. There were 23 (51.1%), 18 (40%) and 4 (8.9%) adverse drug events reported in low, normal and high lymphocytes group respectively. Lactate dehydrogenase (LDH) is enzyme released while tissues are breaking down in cancer. Measurement of LDH indirectly reflects the tumor load within the patient. In this study, slightly more than half of the patients (59%) had a normal LDH level followed by a high LDH level (39.6%). There were no adverse drug events reported in the low LDH group. Twenty-six (66.7%) and 13 (33.3%) developed adverse drug events in normal and high LDH groups respectively (Table 9).

Table 9. Patients' blood counts based on number of cycles, N=1571

	Number without		Number with	
	AR	%	AR	%
<b>Total White Blood Cell (x 10<sup>9</sup>/L)</b>				
<4 (Low)	323	26.1	15	32.6
4-11 (Normal)	838	67.7	23	50
>11 (High)	76	6.2	8	17.4
Total	1237		46	
<b>Absolute Neutrophil counts (x 10<sup>9</sup>/L)</b>				
<1.8 (Low)	151	12.3	11	23.9
1.8-7.5 (Normal)	981	79.7	31	67.4
>7.5 (High)	99	8	4	8.7
Total	1231		46	
<b>Lymphocytes (x 10<sup>9</sup>/L)</b>				
<1 (Low)	600	48.7	23	51.1
1-3.5 (Normal)	613	49.8	18	40
>3.5 (High)	18	1.5	4	8.9
Total	1231		45	
<b>LDH (U/L)</b>				
<110 (Low)	16	1.4	0	0
110-230 (Normal)	669	58.8	26	66.7
>230 (High)	453	39.8	13	33.3
Total	1138		39	

Missing data for Wbc= 288,ANC =294, lymphocytes=295, LDH=394

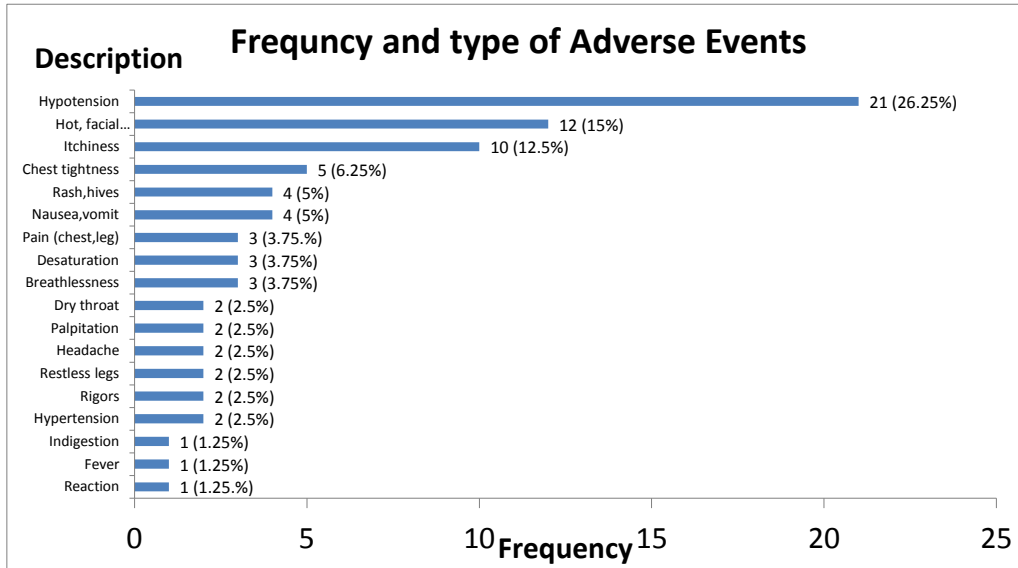
## **Frequency of Adverse Drug Events**

Of 294 patients who received rapid rituximab infusion, 43 patients experienced adverse drug events. Hence, the rate of adverse drug events was 14.6%. These patients experienced 57 episodes of adverse drug events because they could develop multiple adverse drug events within an infusion, cycle or a different course. A total of 80 adverse drug events were made up of 18 types of adverse drug events (Figure 6).

## **Type of Adverse Drug Events**

The most common occurrence of adverse drug events consisted of 21 episodes of hypotension (26.25%) followed by patients' complaints of feeling hot, facial flushing (15%) and itchiness (12.5%). The less common adverse drug events were: chest tightness (6.25%); rash, hives (5%); nausea, vomiting (5%); pain (3.75%); desaturation (3.75%); breathlessness (3.75%); dry throat (2.5%); palpitation (2.5%); headache (2.5%); restless legs (2.5%); rigors (2.5%); hypertension (2.5%); fever (1.25%); indigestion (1.25%) and not reported (1.25%) (Figure 6).

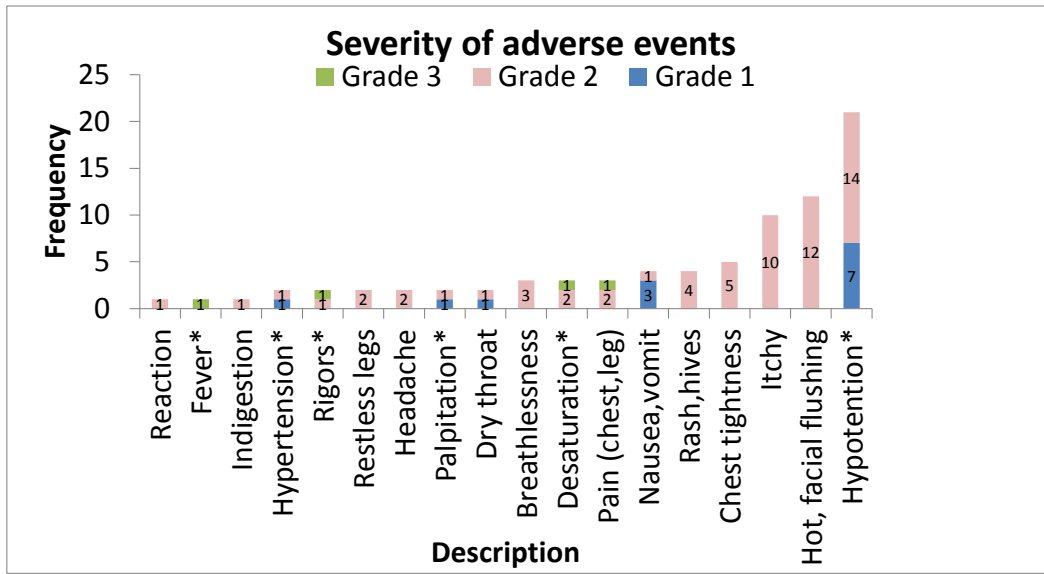
Figure 6. Frequency and Type of Adverse Drug Events



## **Severity of Adverse Drug Events**

The severity of adverse drug events was mostly grade 2 consisting of 63 (78.75%) episodes of adverse drug events namely reaction (the reaction was not described specifically), indigestion, hypertension, rigors, restless legs, headache, palpitation, dry throat, breathlessness, desaturation, pain, nausea, vomit, rash, hives, chest tightness, itchy, hot flushing and hypotension. Only 4 (5%) episodes of adverse drug event were graded as 3 and related to fever, rigors, desaturation and chest pain. The remaining 13 (16.25%) episodes of adverse drug events were rated grade 1 and included hypertension, palpitation, dry throat, nausea, vomiting and hypotension. Potential life-threatening signs and symptoms were fever, hypertension, rigors, palpitation, desaturation and hypotension (Figure 7).

Figure 7. Severity of adverse drug events, n=80



## **Timing of Occurrence of Adverse Drug Events**

Adverse drug events resulting from rapid rituximab could occur at any time; however, this study identified a common pattern of events unfolding. Most events occurred at 30, 60 and 90- minutes into the infusion (Figure 8). Using the Fisher-Freeman-Halton exact test, the  $p$  value was significant at 0.0185 which demonstrated a difference between the patterns of occurrence of adverse drug events (Figure 9). Although in 11 episodes the exact timing was not reported (“during infusion”, Figure 8), it was noted that 7 out of 11 episodes were linked to blood pressure. The measurement of blood pressure was taken at 0, 30, 60 and 90 minute intervals. Therefore, the most commonly occurring adverse drug events could be detected at 30, 60 and/or 90 minutes.



Figure 8. Timing of occurrence of adverse drug events, n = 57

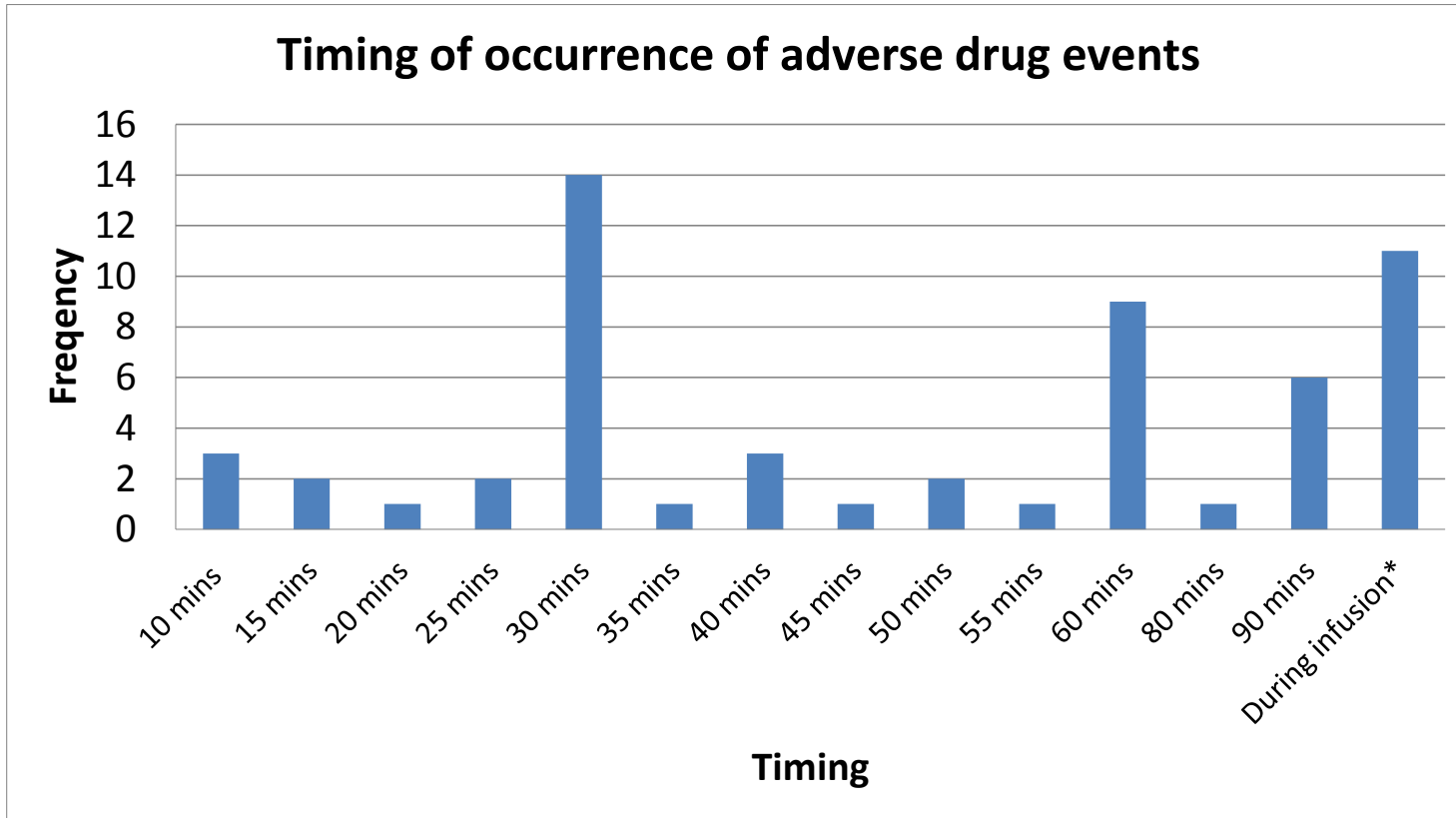
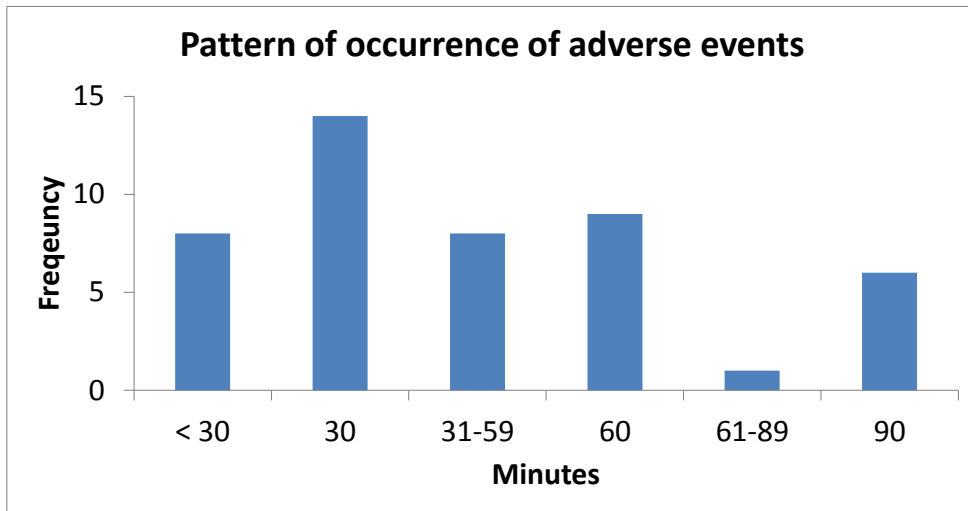


Figure 9. Pattern of occurrence of adverse drug events

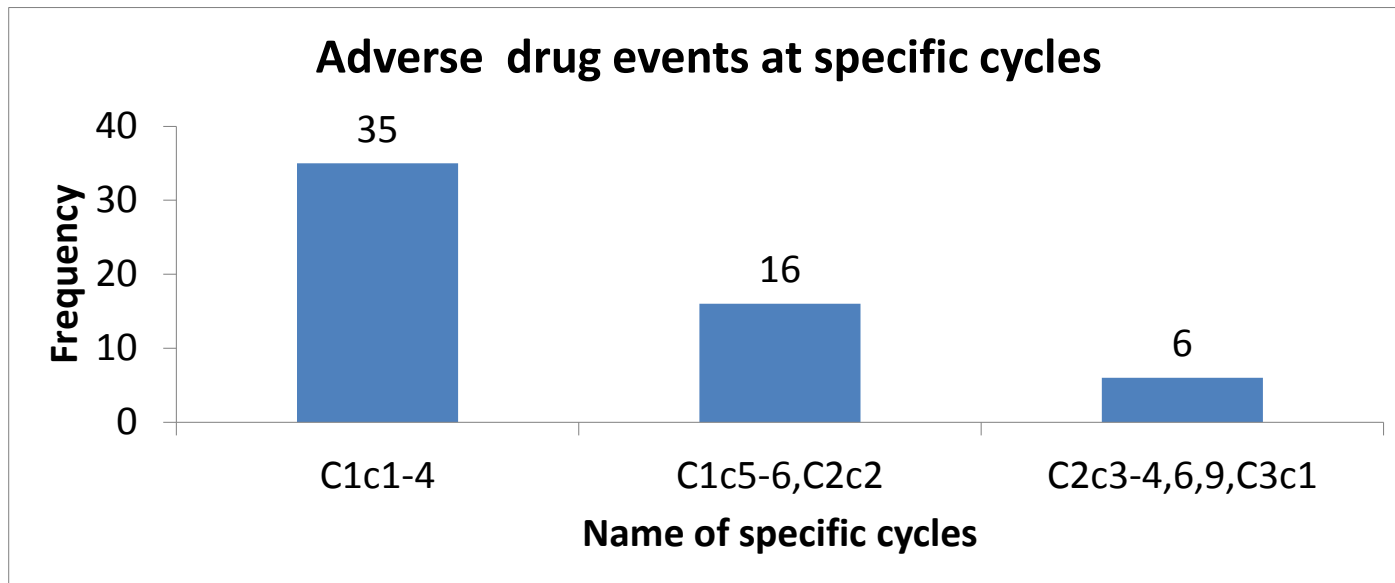


$P=0.0185$

## **Occurrence of Adverse Drug Events in Specific Cycles**

The peak number of adverse drug events was 35 (61.4%) episodes occurring in course 1 between cycles 1-4 of rapid rituximab infusion. This was followed by 16 (28%) episodes occurring in course 1 between cycles 5-6 and course 2 cycles 1-2. The least adverse drug events were 6 (10.6%) episodes occurring in course 2 cycles 3-4, 6, 9 and course 3. There was statistical significance between the three groups when the Fisher-Freeman-Halton exact test was applied,  $P = 0.0181$  (Figure 10).

Figure 10. Adverse drug events at specific cycles



$P = 0.0181$

Legend: C = course; c = cycle

## **Univariate Analysis using Log Binomial Generalised Estimating Equations**

Using log binomial generalised estimating equations, univariate analysis was performed for the individual independent variable of the occurrence of adverse drug events. The occurrence of adverse drug events was presented in dichotomous format, i.e. 1 = occurrence of adverse drug event; 0 = no occurrence of adverse drug event.

### **Age**

Patients in the 51-60, 61-70 and 81-90 age groups were 1.47 (95%CI 0.56, 3.85), 1.65 (95%CI 0.66, 4.11) and 1.32 (0.4, 4.4) odds likely to develop an adverse drug event in comparison to those  $\leq 50$  years of age. Conversely, the 71-80 age group had 0.92 (95%CI 0.28, 3.1) less chance of experiencing an adverse drug event compared to those who were aged  $\leq 50$  years. However, no statistical significance was found,  $p = 0.75$  (Table 10).

### **Gender**

Male patients had 1.47 (95%CI 0.77, 2.78) likelihood of experiencing an adverse drug event when compared to the female patients,  $p = 0.24$  (Table 10).

### **Diagnosis**

Patients diagnosed with acute/chronic lymphocytic leukemia, autoimmune disease or MGUS had 1.89 (95%CI 0.78, 4.6); 2.36 (95%CI 0.42, 13.4); 1.42 (0.18, 10.96) were more likely to develop an adverse drug event compared to those with NHL. On the other hand, patients diagnosed with lymphoproliferative disease were 0.64 (95%CI 0.09, 4.73)

less likely to experience an adverse drug event as compared to NHL,  $p = 0.54$  (Table 10).

### **Stage of disease**

Some of the patients suffering from the diseases such as autoimmune diseases, MGUS, LPD did not require staging or no information was available on their stage of disease. The odds for them of experiencing an adverse drug event as compared to those who were in stage I/II of the disease were 3.05 (95% CI 0.96, 9.74). Patients with stage III/IV had 1.66 (95% CI 0.55, 5.03) chance of developing an adverse drug event compared to those in stage I/II. These differences were not statistically significant,  $p = 0.09$  (Table 10).

### **Presence of cardiac or lung morbidity**

Patients experiencing cardiac or lung morbidity had 0.81 (95% CI 0.42, 1.58) less chance of experiencing an adverse drug event compared to those without,  $p = 0.54$ , hence this was not statistically significant (Table 10).

*Table 10 Association of patients' characteristics (Predictors) with the occurrence of adverse drug events*

Predictors	L'Beta Estimate	Standard Error	L'Beta		Chi-square	Pr>Chi Sq
			Confidence Limit			
<b>Age</b>						0.7524
51-60 vs ≤ 50	1.4658	0.7220	0.5582	3.8488	0.6000	0.4376
61-70 vs ≤ 50	1.6525	0.7678	0.6648	4.1080	1.1700	0.2797
71-80 vs ≤ 50	0.9234	0.5641	0.2789	3.0576	0.0200	0.8962
81-90 vs ≤ 50	1.3210	0.8093	0.3976	4.3892	0.2100	0.6495
<b>Gender</b>						0.2408
Male vs female	1.4657	0.4778	0.7737	2.7767	1.3800	0.2408
<b>Diagnosis</b>						0.5445
A/CLL vs NHL	1.8908	0.8563	0.7783	4.5933	1.9800	0.1596
Autoimmune disease vs NHL	2.3635	2.0920	0.4170	13.3964	0.9400	0.3312
LPD vs NHL	0.6446	0.6553	0.0879	4.7273	0.1900	0.6658
MGUS vs NHL	1.4181	1.4795	0.1835	10.9588	0.1100	0.7378
<b>Stage of disease</b>						0.0903
No stage vs Stage I-II	3.0502	1.8061	0.9557	9.7351	3.5500	0.0596
Stage III-IV vs Stage I-II	1.6570	0.9388	0.5458	5.0301	0.7900	0.3728
<b>Comorbidity (lung &amp; cardiac disease)</b>						0.5399
Yes vs No	0.8127	0.2750	0.4187	1.5774	0.3800	0.5399

\*p value is significant at 0.05

### **Number of courses**

Patients who received more than one course of treatment were 0.87 (95%CI 0.43, 1.77) less likely to experience an adverse drug event compared to those who only received one course of treatment,  $p = 0.70$ , which was not statistically significant (Table 11).

### **Number of cycles**

Patients who received 3-4, 5-6 and >7 cycles of rapid rituximab infusion were 0.58 (95%CI 0.31, 1.1), 0.37 (95%CI 0.16, 0.88) and 0.36 (0.17, 0.79) respectively less likely to experience an adverse drug event compared to those who received 1-2 cycles of rapid infusion. The odd ratio tended to decrease as the number of cycles of rapid rituximab increased,  $p = 0.03$  (Table 11)

### **Type of treatment**

Patients who received rituximab alone were 0.67 (95%CI 0.33, 1.37) less likely to develop an adverse drug event compared to patients who received Rituximab in combination with chemotherapy,  $p = 0.27$  (Table 11).

### **Dosage prescription based on body surface area**

Patients who had their prescribed dosage rounded down from their original calculated body surface area had 2.11 (95% CI 0.58, 7.64) probability of experiencing an adverse drug event compared to those where the exact calculated dosage based on body surface area was administered. Those with their body surface area rounded up from their original calculated body surface area had 0.74 (95%CI 0.38, 1.45) less chance of developing adverse drug event,  $p = 0.27$  (Table 11).



### **Use of corticosteroids as premedication**

Patients who received corticosteroids as premedication prior to rapid rituximab infusion had 1.48 (95% CI 0.8, 2.74) chance of experiencing an adverse drug event in comparison to those who did not receive corticosteroids as premedication,  $p = 0.22$  (Table 11).

### **Use of antipyretics as premedication**

Patients who received antipyretics as premedication prior to rapid rituximab infusion had 0.33 (95% CI 0.04, 2.58) chance of experiencing an adverse drug event compared to those who did not receive antipyretics,  $p = 0.29$  (Table 11).

### **Use of antihistamines as premedication**

The data on this variable was not converged during the analysis because there were too few occurrences of adverse drug events related to the use of antihistamines (Table 11).

### **Total white blood cell counts**

Patients with low and high total white blood cell count had odds of 1.68 (95%CI 0.89, 3.21) and 3.31 (1.42, 7.7) respectively of developing an adverse drug event compared to those with normal total white blood cell counts,  $p = 0.02$  (Table 11).

### **Lymphocyte counts**

Patients with low and high lymphocyte counts had odds of 1.31 (95%CI 0.68, 2.5072) and 7.57 (2.49, 23.04) respectively of developing an adverse drug event compared to those with normal lymphocyte counts which is statistically significance,  $p = 0.00$  (Table 11).

### **Lactate dehydrogenase level**

The data on this variable was not converged during the analysis because there were too few occurrences of adverse drug events at any level of LDH (Table 11).

### **Absolute neutrophil count**

Patients with low and high absolute neutrophil counts had odds of 2.31 (95%CI 1.14, 4.67) and 1.28 (0.43, 3.77) respectively of developing adverse drug events as compared to those with normal absolute neutrophil counts. This did not prove to be statistically significant,  $p = 0.07$  (Table 11).

In summary, age, gender, diagnosis, stage of disease, presence of cardiac or lung morbidity, number of courses, type of treatment, calculation of body surface area, corticosteroid premedication, antipyretic premedication and absolute neutrophil counts were not found to be significantly associated with the occurrence of an adverse drug event. Only the number of cycles, total white blood cell and lymphocyte counts were found to have statistically significant associations with the occurrence of adverse drug events. For the antihistamine and LDH predictors, data was not converged during the analysis because the occurrences of adverse drug events in each group were too few.

Table 11. Association of patients' treatment characteristics (Predictors) with the occurrence of adverse drug events

Predictors	L'Beta Estimate	Standard Error	L'Beta Confidence Limit		Chi-square	Pr>Chi Sq
<b>Course</b>						0.7010
2 > 1	0.8706	0.3141	0.4292	1.7659	0.1500	0.7010
<b>Cycle</b>						0.033*
3-4 vs 1-2	0.5826	0.1900	0.3075	1.1040	2.7400	0.0976
5-6 vs 1-2	0.3728	0.1639	0.1575	0.8824	5.0400	0.0248*
>7 vs 1-2	0.3633	0.1451	0.1661	0.7948	6.4300	0.0112*
<b>Type of treatment</b>						0.2736
Rituximb alone vs combination chemotherapy	0.6707	0.2447	0.3280	1.3713	1.2000	0.2736
<b>BSA</b>						0.2691
Round down vs exact	2.1063	1.3842	0.5810	7.6368	1.2800	0.2570
Round up vs exact	0.7445	0.2526	0.3829	1.4477	0.7600	0.3846
<b>Premedication: steroid</b>						0.2162
Yes vs No	1.4769	0.4657	0.7961	2.7401	1.5300	0.2162
<b>Premedication: Antipyretic</b>						0.2932
Yes vs No	0.3349	0.3486	0.0435	2.5754	1.1000	0.2932
<b>Premedication: Antihistamine</b>						-
Yes vs No	-	-	-	-	-	-
<b>Total white blood cell counts</b>						0.0157*
Low vs normal	1.6848	0.5530	0.8854	3.2060	2.5300	0.1120
High vs normal	3.3083	1.4267	1.4207	7.7036	7.7000	0.0055*
<b>Lymphocyte counts</b>						0.0016*
Low vs normal	1.3055	0.4347	0.6797	2.5072	0.6400	0.4234
High vs normal	7.5679	4.2982	2.4862	23.0368	12.7000	0.0004*
<b>Lactate dehydrogenase level</b>						-
Low vs normal	-	-	-	-	-	-
High vs normal	-	-	-	-	-	-
<b>Absolute neutrophil counts</b>						0.0676
Low vs normal	2.3053	0.8302	1.1381	4.6693	5.3800	0.0204
High vs normal	1.2786	0.7048	0.4340	3.7667	0.2000	0.6557

\*p value is significant at 0.05

## **Univariate Analysis using Log Poisson Generalised Estimating Equations**

Patients could develop more than one adverse drug event in one cycle. Therefore, univariate analysis was performed to model the number of adverse drug events (counts). Using log Poisson generalised estimating equations, univariate analysis was performed for each individual independent variable (also known as a predictor) of adverse drug events.

### **Age**

Patients in the 51-60, 61-70 and 81-90 age groups have odds of 1.54 (95%CI 0.61, 3.94), 1.89 (95%CI 0.77, 4.67) and 1.96 (0.52, 7.37) of developing an adverse drug event compared to those aged  $\leq 50$  years. Conversely, those aged 71-80 have odds of 0.93 (95%CI 0.29, 2.97) of experiencing an adverse drug event in comparison to those who are  $\leq 50$  years old. There is thus no statistically significant difference,  $p = 0.52$  (Table 12).

### **Gender**

Male patients have odds of 1.74 (95%CI 0.92, 3.27) for experiencing an adverse drug event compared to the female patients,  $p = 0.09$ , which is not statistically significant (Table 12).

### **Diagnosis**

Patients diagnosed with acute/chronic lymphocytic leukemia, autoimmune disease and MGUS had odds of 1.9 (95%CI 0.8, 4.53); 4.08 (95%CI 0.82, 20.42); 1.26 (0.18, 8.90) of developing an adverse drug event compared to those with NHL. On the other hand,

patients diagnosed with lymphoproliferative disease were 0.59 (95%CI 0.08, 4.15) less likely to experience an adverse drug event compared to NHL,  $p = 0.28$  (Table 12).

### **Stage of disease**

Some of the patients suffering from the diseases such as autoimmune diseases, MGUS, and LPD did not require staging or no information was available on their stage of disease. The likelihood of them experiencing an adverse drug event compared to those who in stage I/II of the disease were 3.39 (95%CI 1.1, 10.48). Patients with stage III/IV disease had odds of 1.84 (95% CI 0.61, 5.54) of developing an adverse drug event compared to those in stage I/II,  $p = 0.06$  (Table 12).

### **Presence of cardiac or lung morbidity**

Patients who had cardiac or lung morbidity were 0.82 (95%CI 0.42, 1.62) less likely to experience an adverse drug event compared to those without,  $p = 0.57$  (Table 12).

Table 12. Association of patients' characteristics (Predictors) with the number of adverse drug events

Predictors	L'Beta Estimate	Standard Error	L'Beta Confidence Limit		Chi-square	Pr>Chi Sq
<b>Age</b>						0.521
51-60 vs ≤ 50	1.5439	0.7379	0.6050	3.9395	0.8300	0.3635
61-70 vs ≤ 50	1.8942	0.8731	0.7675	4.6748	1.9200	0.1658
71-80 vs ≤ 50	0.9253	0.5506	0.2883	2.9700	0.0200	0.8962
81-90 vs ≤ 50	1.9643	1.3258	0.5232	7.3744	1.0000	0.3172
<b>Gender</b>						0.0882
Male vs female	1.7351	0.5608	0.9209	3.2691	2.9100	0.0882
<b>Diagnosis</b>						0.2802
A/CLL vs NHL	1.8956	0.8430	0.7929	4.5320	2.0700	0.1504
Autoimmune disease vs NHL	4.0828	3.3532	0.8164	20.4196	2.9300	0.0867
LPD vs NHL	0.5897	0.5872	0.0838	4.1519	0.2800	0.5959
MGUS vs NHL	1.2637	1.2589	0.1794	8.9045	0.0600	0.8142
<b>Stage of disease</b>						0.0583
No stage vs Stage I-II	3.3899	1.9529	1.0960	10.4847	4.4900	0.0341
Stage III-IV vs Stage I-II	1.8394	1.0342	0.6111	5.5366	1.1800	0.2784
<b>Comorbidity (lung &amp; cardiac disease)</b>						0.5711
Yes vs No	0.8216	0.2851	0.4162	1.6218	0.3200	0.5711

### **Number of courses**

Patients who received more than one course of treatment had odds of 1.0 (95%CI 0.5, 2.03) of experiencing an adverse drug event compared to those who only received one course of treatment,  $p = 0.99$  (Table 13).

### **Number of cycles**

Patients who received 3-4, 5-6 and >7 cycles of rapid rituximab infusion were 0.52 (95%CI 0.27, 1.02), 0.32 (95%CI 0.14, 0.76) and 0.4 (0.18, 0.88) respectively were less likely to develop an adverse drug event compared to those who received 1-2 cycles of rapid infusion,  $p = 0.03$  (Table 13).

### **Type of treatment**

Patients who received rituximab alone had 0.64 (95%CI 0.32, 1.31) less chance of developing an adverse drug event compared to patients who received rituximab in combination with chemotherapy,  $p = 0.22$  (Table 13).

### **Dosage prescription based on body surface area**

Patients who had their prescribed dosage rounded down from their original calculated body surface area had odds of 1.68 (95% CI 0.50, 5.62) of experiencing an adverse drug event compared to those using their exact calculated dosage based on body surface area. Those with their body surface area rounded up from their original calculated body surface area had odds of 0.66 (95%CI 0.34, 1.28) of developing an adverse drug event,  $p = 0.22$  (Table 13).

### **Use of corticosteroids as premedication**

Patients who received corticosteroids as premedication prior to rapid rituximab infusion had odds of 1.68 (95% CI 0.92, 3.08) of experiencing an adverse drug event compared to those who did not receive corticosteroids,  $p = 0.09$  (Table 13).

### **Use of antipyretics as premedication**

Patients who received antipyretics as premedication prior to rapid rituximab infusion were 0.40 (95% CI 0.06, 2.55) less likely to experience an adverse drug event compared to those who did not receive antipyretics,  $p = 0.33$  (Table 13).

### **Use of antihistamines as premedication**

The data was not converged during the analysis because there were too few occurrences of adverse drug events in either group (Table 13).

### **Total white blood cell counts**

Patients with low and high total white blood cell counts had odds of 1.6 (95%CI 0.81, 3.16) and 3.03 (1.31, 7.04) respectively of developing adverse drug events compared to those with normal total white blood cell counts. The  $p = 0.031$ . There no statistical significance emerged (Table 13).

### **Lymphocyte counts**

Patients with low and high lymphocyte counts had odds of 0.97 (95%CI 0.5, 1.9) and 5.98 (2.04, 17.54) respectively of developing adverse drug events compared to those with normal lymphocyte counts,  $p = 0.00$  (Table 13).

### **Lactate dehydrogenase level**

The data was not converged during the analysis because there were too few occurrences of adverse drug events concerning the level of LDH (Table 13).



### **Absolute neutrophil counts**

Patients with low and high absolute neutrophil counts had odds of 2.26 (95%CI 1.08, 4.72) and 1.09 (0.38, 3.11) respectively of developing adverse drug events compared to those with normal absolute neutrophil counts,  $p = 0.09$  (Table 13).

In summary, age, gender, diagnosis, stage of disease, presence of cardiac or lungs morbidity, number of courses, type of treatment, calculation of body surface area, corticosteroids premedication, antipyretics premedication and absolute neutrophil count were not found to be significantly associated with the number of adverse drug events. Only the number of cycles, total white blood cell, and lymphocyte counts were found to be statistically and significantly associated with the number of adverse drug events. For the antihistamine and LDH predictors, data was not converged during the analysis because there were too few adverse drug events in each group. Hence, only the number of cycles and lymphocyte count predictors were selected for the multivariate model. Total white blood cell counts were excluded from the model of potential multicollinearity effect.

Table 13. Association of patients' treatment characteristics (Predictors) with the number of adverse drug events

Predictors	L'Beta Estimate	Standard Error	L'Beta Confidence Limit		Chi-square	Pr>Chi Sq
<b>Course</b>						0.9905
2 > 1	1.0043	0.3608	0.4966	2.0308	0.0000	0.9905
<b>Cycle</b>						0.0299
3-4 vs 1-2	0.5245	0.1769	0.2708	1.0160	3.6600	0.0557*
5-6 vs 1-2	0.3243	0.1417	0.1377	0.7638	6.6400	0.0100*
>7 vs 1-2	0.3954	0.1607	0.1782	0.8772	5.2100	0.0225*
<b>Type of treatment</b>						0.2245
Rituximb alone vs combination chemotherapy	0.6441	0.2333	0.3167	1.3099	1.4800	0.2245
<b>BSA</b>						0.2219
Round down vs exact	1.6821	1.0346	0.5038	5.6157	0.7100	0.3978
Round up vs exact	0.6552	0.2236	0.3357	1.2788	1.5400	0.2153
<b>Premedication: steroid</b>						0.0903
Yes vs No	1.6847	0.5187	0.9213	3.0804	2.8700	0.0903
<b>Premedication: Antipyretic</b>						0.3344
Yes vs No	0.4036	0.3794	0.0639	2.5473	0.9300	0.3344
<b>Premedication: Antihistamine</b>						–
Yes vs No	–	–	–	–	–	–
<b>Total white blood cell counts</b>						0.0306*
Low vs normal	1.5973	0.5564	0.8070	3.1614	1.8100	0.1788
High vs normal	3.0335	1.3038	1.3065	7.0434	6.6700	0.0098*
<b>Lymphocyte counts</b>						0.0018*
Low vs normal	0.9706	0.3323	0.4962	1.8988	0.0100	0.9306
High vs normal	5.9754	3.2830	2.0356	17.5400	10.5900	0.0011
<b>Lactate dehydrogenase counts</b>						
Low vs normal	–	–	–	–	–	–
High vs normal	–	–	–	–	–	–
<b>Absolute neutrophil counts</b>						0.0945
Low vs normal	2.2558	0.8488	1.0790	4.7163	4.6700	0.0306*
High vs normal	1.0917	0.5837	0.3828	3.1134	0.0300	0.8697

\*p value is significant at 0.05

## Multivariate Analysis Model Occurrence of Adverse drug events

Number of cycles and lymphocyte counts' predictors were chosen for the multivariate model. The total white blood cells were excluded from the model of potential multicollinearity effect. In the multivariate model occurrence of adverse drug events, only lymphocyte counts remained statistically significant,  $p = 0.00$ . However, when examining the subgroup, only high lymphocyte counts were able to predict when an adverse drug event occurred,  $p = 0.00$ . Patients with high lymphocyte counts were 6.94 times more likely to experience adverse drug events compared to those with normal lymphocyte counts. As for increased number of cycles, patients were less likely to experience an adverse drug event. The odds were 0.45 for patients who received more than 7 cycles compared to those who only received 1 or 2 cycles. (Table 14) The fit criteria of Quasi likelihood under the Independence Model Criterion (QIC) was equal to 390.5975. It is used for comparing models based on the likelihood method. The model with the smaller statistical range will be chosen as the best model.

Table 14. Multivariate analysis for occurrence of adverse drug events

Predictors	L'Beta Estimate	Standard Error	L'Beta Confidence Limit		Chi-square	Pr>Chi Sq
<b>Lymphocyte counts</b>						0.0039*
Low vs normal	1.3827	0.4461	0.7347	2.6024	1.0100	0.3152
High vs normal	6.9382	4.0327	2.2207	3.0762	11.1100	0.0009
<b>Cycle</b>						0.2847
3-4 vs 1-2	0.6222	0.2579	0.2761	1.4020	1.3100	0.2523
5-6 vs 1-2	0.4851	0.2261	0.1946	1.2096	2.4100	0.1207
>7 vs 1-2	0.4458	0.2115	0.1760	1.1296	2.9000	0.0886

## Multivariate Analysis Model Count of Adverse drug events

In the multivariate model number of adverse drug events, only lymphocyte counts remained statistically significant, ( $p = 0.00$ ). The number of cycles was not significant in the multivariate model,  $p = 0.28$ . Like the previous model, it was demonstrated that only high lymphocyte counts were able to predict the occurrence of an adverse drug event,  $p = 0.00$ . Patients with high lymphocyte counts were 5.29 times more likely to experience more adverse drug events. Although the number of cycles was not statistically significant, patients who received increasing numbers of cycles of more than 7 were 0.5 less likely to experience more adverse drug events (Table 15). The fit criteria of Quasi likelihood under the Independence model Criterion (QIC) was equal to 347.8804. It is used for comparing models based on the likelihood method. The model with the smaller statistical range will be chosen as the best model

Table 15. Multivariate analysis for the number of adverse drug events

Predictors	L'Beta Estimate	Standard Error	L'Beta Confidence Limit		Chi-square	Pr>Chi Sq
<b>Lymphocyte counts</b>						0.0089*
Low vs normal	1.0463	0.3395	0.5540	1.9763	0.0200	0.8890
High vs normal	5.2927	3.0295	1.7237	16.2515	8.4700	0.0036
<b>Cycle</b>						0.2826
3-4 vs 1-2	0.5540	0.2381	0.2386	1.2865	1.8900	0.1695
5-6 vs 1-2	0.4214	0.1959	0.1694	1.0480	3.4600	0.0630
>7 vs 1-2	0.4996	0.2527	0.1854	1.3463	1.8800	0.1701

## **Univariate Analysis of Severity of Adverse Drug Events**

Using log binomial generalised estimating equations, univariate analysis was performed for the individual independent variable of adverse drug events. Adverse drug events were graded as either 1, 2 and 3 which equate with mild, moderate and severe respectively. The results are presented at significance level and odds ratio.

### **Age**

The data was not converged during the analysis because there were too few occurrences of adverse drug events in any age group (Table 16).

### **Gender**

Male patients had odds of 2.26 (95%CI 0.7, 7.26) of experiencing more severe adverse drug event as compared to the female patients,  $p = 0.17$  (Table 16).

### **Diagnosis**

The data was not converged during the analysis because there were too few occurrences of adverse drug events concerning the diagnosis (Table 16).

### **Stage of disease**

The data was not converged during the analysis because there were too few occurrences of adverse drug events related to stage of disease (Table 16).

### **Presence of cardiac or lung morbidity**

Patients who had cardiac or lung morbidity had odds of 1.88 (95%CI 0.55, 6.45) of experiencing more severe adverse drug events compared to those without,  $p = 0.32$  (Table 16).

Table 16. Association of patients' characteristics (Predictors) with the severity of adverse drug events

Predictors	L'Beta Estimate	Standard Error	L'Beta Confidence Limit		Chi-square	Pr>Chi Sq
<b>Age</b>						
51-60 vs ≤ 50	–	–	–	–	–	–
61-70 vs ≤ 50	–	–	–	–	–	–
71-80 vs ≤ 50	–	–	–	–	–	–
81-90 vs ≤ 50	–	–	–	–	–	–
<b>Gender</b>						
Male vs female	2.2556	1.3455	0.7006	7.2614	1.8600	0.1727
<b>Diagnosis</b>						
A/CLL vs NHL	–	–	–	–	–	–
Autoimmune disease vs NHL	–	–	–	–	–	–
LPD vs NHL	–	–	–	–	–	–
MGUS vs NHL	–	–	–	–	–	–
<b>Stage of disease</b>						
No stage vs Stage I-II	–	–	–	–	–	–
Stage III-IV vs Stage I-II	–	–	–	–	–	–
<b>Comorbidity (lung &amp; cardiac disease)</b>						
Yes vs No	1.8750	1.1813	0.5454	6.4460	1.0000	0.3184

### **Number of courses**

Patients who received more than one course of treatment had odds of 1.62 (95%CI 0.4, 6.65) of experiencing more severe adverse drug events compared to those who only received one course of treatment,  $p = 0.51$  (Table 17).

### **Number of cycles**

The data was not converged during the analysis because there were too few occurrences of adverse drug events related to the number of cycles (Table 17).

### **Type of treatment**

Patients received rituximab alone were 1.83 (95%CI 0.42, 8.05) more likely to develop more severe adverse drug events as compared to patients who received rituximab in combination with chemotherapy,  $p = 0.42$ . (Table 17)

### **Dosage prescription based on body surface area**

Patients who had their prescribed dosage rounded down from their original calculated body surface area had odds of 1.5 (95% CI 0.12, 19.18) of experiencing a more severe adverse drug event compared to those where their exact calculated dosage based on body surface area was administered. Those with their body surface area rounded up from their original calculated body surface area had odds of 5.25 (95%CI 1.14, 24.14) of developing more severe adverse drug events,  $p = 0.1$  (Table 17).

### **Use of corticosteroids as premedication**

Patients who received corticosteroids as premedication prior to rapid rituximab infusion had odds of 2.11 (95% CI 0.66, 6.73) of experiencing more severe adverse drug event compared to those who not receiving corticosteroids,  $p = 0.21$  (Table 17).

### **Use of antipyretics as premedication**

The data was not converged during the analysis because there were too few occurrences of adverse drug events in relation to the use of antipyretics (Table 17).

### **Use of antihistamines as premedication**

The data was not converged during the analysis because there were too few occurrences of adverse drug events related to this variable (Table 17).

### **Total white blood cell counts**

Patients with low total white blood cell counts had odds of 2.63 (95%CI 0.45, 15.22) of developing more severe adverse drug events compared to those with normal total white blood cell counts. Conversely, patients with high total white blood cell counts were 0.7 (95%CI 0.14, 3.45) less likely to experience more severe adverse drug events,  $p = 0.42$  (Table 17).

### **Lymphocyte counts**

Patients with low and high lymphocytes counts had odds of 0.15 (95%CI 0.03, 0.8) and 0.36 (0.03, 4.74) respectively of developing adverse drug events when compared to those with normal total white blood cells counts. This difference was statistically significant,  $p = 0.08$  (Table 17).

### **Lactate dehydrogenase level**

The data was not converged during the analysis because there were too few occurrences of adverse drug events at any level of LDH (Table 17).

In summary, none of the predictors that were included in the study demonstrated any association with the severity of the adverse drug events since only 57 episodes of adverse drug events were reported



Table 17. Association of patients' treatment characteristics (Predictors) with the severity of adverse drug events

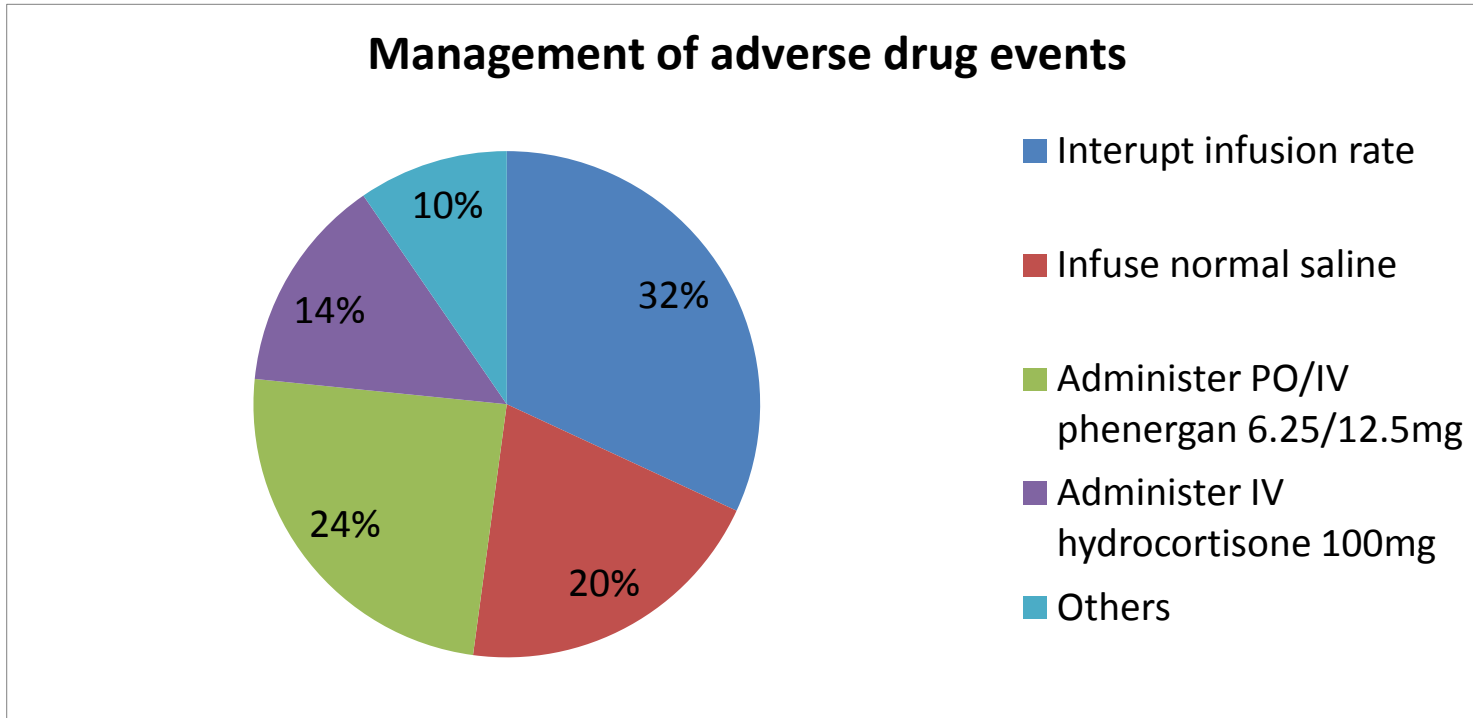
Predictors	L'Beta Estimate	Standard Error	L'Beta Confidence Limit		Chi-square	Pr>Chi Sq
<b>Course</b>						0.5050
2 > 1	1.6176	1.1671	0.3933	6.6529	0.4400	0.5050
<b>Cycle</b>						
3-4 vs 1-2	–	–	–	–	–	–
5-6 vs 1-2	–	–	–	–	–	–
>7 vs 1-2	–	–	–	–	–	–
<b>Type of treatment</b>						0.4220
Rituximb alone vs combination chemotherapy	1.8333	1.3839	0.4176	8.0494	0.6400	0.4220
<b>BSA</b>						0.1032
Round down vs exact	1.5000	1.9503	0.1173	19.1794	0.1000	0.7552
Round up vs exact	5.2500	4.0853	1.1423	24.1282	4.5400	0.0331
<b>Premedication: steroid</b>						0.2096
Yes vs No	2.1053	1.2491	0.6581	6.7349	1.5700	0.2096
<b>Premedication: Antipyretic</b>						–
Yes vs No	–	–	–	–	–	–
<b>Premedication: Antihistamine</b>						–
Yes vs No	–	–	–	–	–	–
<b>Total white blood cells counts</b>						0.4151
Subnormal vs normal	2.6250	2.3536	0.4528	15.2165	1.1600	0.2818
Abnormal vs normal	0.7000	0.5698	0.1420	3.4513	0.1900	0.6613
<b>Lymphocyte counts</b>						0.0806
Subnormal vs normal	0.1515	0.1282	0.0288	0.7958	4.9700	0.0258*
Abnormal vs normal	0.3636	0.4765	0.0279	4.7426	0.6000	0.4401
<b>Lactate dehydrogenase counts</b>						–
Subnormal vs normal	–	–	–	–	–	–
Abnormal vs normal	–	–	–	–	–	–

\*p value is significant at 0.05

## **Management of adverse drug events**

An adverse drug event could occur at any time during or immediately after infusion. For grade 1 adverse drug events, no medical intervention is needed. Staff would generally carry on with vital signs monitoring. For patients who experienced a grade 2 adverse drug event regardless of its type, the most common intervention was temporarily interrupting the rituximab infusion rate (32%) and keeping the vein open with normal saline infusion or administration of a bolus infusion (24%). Drug therapy was the second step and administered according to the symptoms and their severity. Generic drugs used include IV/PO Phenergen 6.25/12.5 mg (20%) and IV Hydrocortisone 100mg (14%). Other drugs may be used for targeted symptoms, for example: IV/PO Maxalon and Stemetil for nausea; and nebulised Ventolin for breathlessness. Non-pharmacological interventions included administration of oxygen for breathlessness and elevation of the legs to promote venous blood return. Additional tests such as ECG may be performed for patients complaining of chest pain. When the symptoms subsided, the rituximab infusion was restarted at half the rate of the previous infusion. Most patients went on to complete the treatment program without further adverse reactions. For those patients who developed adverse drug events again, the infusions were stopped and a further drug was administered for targeted signs or symptoms. Such a cyclical process was repeated until the completion of rituximab infusion. Rapid rituximab infusion was administered at an ambulatory setting, therefore for grade 3 adverse drug events; patients were admitted to an in-patient hospital for further observation and medical treatment. In these patients, rapid rituximab infusions were abandoned for all future treatment cycles (Figure 11).

Figure 11. Management of adverse drug events



## **Chapter 6. Discussion of the Phase 1 and Phase 2 Findings**

### **Phase 1 Study: Systematic Review**

#### **Meta-analysis of adverse drug events among non-Hodgkin Lymphoma patients**

The pooled meta-analysis strongly suggests that rapid rituximab infusion is relatively safe for NHL patients especially with reference to a 90-minute regimen. Patients tolerate rapid infusions well with 4.2% of mild acute adverse drug events reported among 572 patients in contrast to 33% in the standard rate at the second and subsequent infusion as per previous clinical studies reported in FDA label (package insert) .<sup>14</sup> Although only two studies included in the review evaluated a 60-minute regimen, the findings also suggest that this regimen is safe for patients, with only 5 grade 1 adverse drug events recorded among 94 patients. A possible contributor to such outcomes could be the use of steroids before starting the rapid infusion. The absence of bulky disease and leucocytosis may also result in lesser adverse drug events. However, there is no increase in acute adverse drug events in the patients who did not receive corticosteroids as part of the premedication. Furthermore, there is no analysis available from the primary studies to segregate patients who developed acute adverse drug events based on their disease's characteristics. Therefore, the exact reasons for the low incidence of adverse drug events are unclear in 90-minute regimen.

#### **Diagnoses included in the systematic review**

Of the initial 653 patients who were included in the NHL arm (11 studies), 12 (1.8%) patients were not clearly classified into a diagnosis of NHL. Some were Hodgkin Disease (HD), Post transplant Lymphoproliferative Disorder (PTLD), Immune Mediated

Thrombocytopenias and Immune Cytopenia. However, 1.8% of variation in diagnosis does not appear to contribute to the heterogeneity of the population. Initially, heterogeneity was detected in combination with 90- and 60-minute regimens in the eleven studies. Population characteristics were checked for any heterogeneity such as age, diagnosis, presence of bulky disease or leucocytosis but none of these appear to have contributed to the heterogeneity across the studies. The studies became homogenous when two studies using a 60-minute regimen were removed. However, when an additional study was added to the nine, the non-combinability test reported heterogeneity in the studies. Although this study<sup>94</sup> was the cause of heterogeneity, the final pooled result remained as low as 4.2% using a random effects model. Therefore, no further adjustment was made to the meta-analysis.

### **Assessment of publication bias**

There are three bias indicators available in Stat Directs for assessing publication bias. In this meta-analysis, the Harbord test was preferred to Begg-Mazumdar (Kendall's tau) and Egger to assess publication bias. This is because Harbord is able to maintain the same power as Egger when assessing bias yet reduce any false positive rates.<sup>123</sup> Examples of false positive rates are studies with large treatment effects or fewer events.<sup>123</sup> In this systematic review, the frequency of acute adverse drug events was considered as a rare event. Begg-Mazumar (Kendall's tau) has less assumptions to fulfill and is inferior to Egger in its sensitivity.<sup>123</sup> Similar to Egger, it has low power for detecting publication bias with a small number of studies.<sup>123</sup> Therefore, Harbord was more suitable for detecting publication bias than Begg-Mazumar (Kendall's tau) and Egger. In this review, no publication bias was detected.

## **Narrative Summary for Chronic Lymphocytic Leukemia**

The evidence for using rapid rituximab infusion in CLL patients is to be interpreted with caution. The review seems to suggest that rapid rituximab infusion is safe for CLL patients with only 6 Grade 1 adverse drug events reported. However, 2 primary studies included diagnoses other than CLL. In fact, the 73 patients who included in the analysis, only 15 were CLL patients. Therefore, the evidence is weak in relation to rapid rituximab infusion in CLL patients because of the small sample size and unspecified results in the studies.

## **Premedication used prior to rapid Rituximab infusion**

Choices of premedication are fairly consistent across the studies with some variation in the trade name, dosage and route of administration. All the studies followed the pharmaceutical manufacturer's guidelines for the administration of premedication to counteract any possible adverse drug events such as fever. However, it is uncertain if any type of premedication is particularly helpful in preventing or reducing adverse drug events.

## **Instrument for assessing adverse drug events**

In this review, the majority of acute adverse drug events were grade 1 and self-limiting. Therefore, according to NCI CTC or CTCAE, no specific interventions are needed except that patients continue to be monitored closely. However, one study<sup>72</sup> used a grade of 1 for a patient's symptoms where treatment was provided. Therefore, the reviewer amended the grading to 2 before doing a meta-analysis. Although many studies stated that NCI CTC or NCI CTCAE instruments were used to measure adverse drug events, inconsistency among the raters was apparent. Of the acute adverse drug events reported

in the studies, not all were serious. Rash, nausea and vomiting are not life-threatening. They can be managed sufficiently with additional antihistamine or anti-nausea and anti-vomiting agents. Other adverse drug events such as fever and chills can lead to a medical emergency if IV Pethedine is used. This is because a side effect of IV Pethedine is hypotension which can become a serious issue if the patient does not respond to the interruption of the infusion or fluid challenge. Adrenaline and Dopamine may be used in such cases. Chest pain may lead to cardiac arrest. A series of investigations will usually be carried out to establish the cause of chest pain. In the clinical setting, whenever patients develop a sign or symptom of an adverse reaction, they are generally closely monitored to ensure their safety and the early detection of complications. All of these acute adverse drug events occur mostly within a 30 minute to 90 minute infusion, and produce similar results to the standard rate of infusion.

### **Methodological quality of included studies**

Although all of the studies involved case series design, the description of the methodology and methods was consistent and almost identical for all studies. They all defined the patients' characteristics and administered two or more premeditations followed by rapid rituximab infusion. During and after the infusion, they recorded any adverse drug events related to the rapid infusion based on either vital signs or patient self-report. Despite the high quality of these case series studies, an inherent risk of bias moderates the degree to which the findings can be applied. Therefore, three clinical trials currently in progress will add significantly to the validity of the conclusions drawn in this review. One of the clinical trials has reported preliminary results for using rapid rituximab infusion.<sup>150</sup> One hundred and seventy-four patients received 656 cycles of

rapid rituximab infusion at 90-minute intervals and 3 episodes of adverse drug event were reported. This study was not included in this review because it is merely preliminary in nature.

In the process of undertaking this systematic review, the reviewer observed frequent duplication of studies<sup>73, 126, 146</sup> published in different journals. Such a situation reinforces the importance of systematic reviews that involve clear and specific inclusion and exclusion criteria, a comprehensive search strategy, rigorous critical appraisal processes, standardised data coding and extraction, and the generation of conclusions that draw directly from analysis of the results of included studies. This makes it possible to identify valid evidence to guide clinical practice.

### **The Limitations of the Phase 1 Systematic Review**

There were a small number of observational studies identified in the search (Appendix V) that aimed to establish the safety of rapid rituximab infusion. The findings of these studies suggest that rapid rituximab infusion is safe. However, they were excluded due to inconsistency or incongruence with the review's inclusion criteria or because the primary investigators could not be contacted for further details. Furthermore most of the included studies did not specify at which cycle the adverse drug events occurred. The lack of this information on cycle specification could limit the application of findings to any cycle of rapid infusion as it strongly suggested that adverse drug events have an inverse relationship with the number of cycles.



### **Implications for Practice from the Phase 1 Systematic Review**

Following an uncomplicated first cycle of rituximab, 90-minute rapid rituximab infusion with or without corticosteroids premedication is recommended for NHL patients at the second and subsequent infusion. No recommendations can be made concerning the suitability of the rapid regimen in relation to the stage of disease or the presence of bulky disease or leukocytosis.

It is not recommended, based on the current evidence, to use rapid rituximab on CLL patients. Currently, there is no indication of changing the guidelines on the administration of rituximab regarding infusion rates from the manufacturer (Roche). However, Roche has indicated that the company is aware that many hospitals around the globe have been using rapid rituximab infusion.

### **Implications for Research from the Phase 1 Systematic Review**

Further research is needed on the role of monoclonal antibodies development in rapid infusion, especially in the second and subsequent cycles. Currently, this review broadly establishes that rapid rituximab infusion over 90 minutes is safe for NHL patients. However, more research and detailed analysis is needed to develop more specific guidelines for administering rituximab rapidly such as age specification, stage of disease, presence of leukocytosis and others

## **Phase 2 study: Retrospective Cohort Study**

### **Using binary versus count data in outcome measures**

One of the challenges in this study was to analyse the results at the patient; course and cycle level. A patient can receive more than one course of rituximab therapy; and various numbers of cycles that make up a course of therapy. The second challenge was to quantify the number of adverse drug events. A patient can develop multiple adverse drug events at different times within a cycle and in subsequent cycles within a treatment course or a multiple of courses.

The purpose of this study, using both dichotomous and count data to determine the adverse drug event, was to elicit any differences between the two results. It also sought to generate recommendations for future study.

When the adverse drug events were reported in binary form (i.e. yes versus no), two predictors were included in the multivariate model, and only one (high lymphocyte counts) was found to be statistically significant. Similarly, when the adverse drug events were represented as a count event (number of adverse drug event), the two predictors that were included in the multivariate model were the same as those in the analysis of binary format data. Nonetheless, only one of the predictors was found to be statistically significant.

The lack of statistical power to determine the significance of other variables could be due to only 4 patients having experienced multiple episodes of adverse drug events within a cycle. It is suggested that using the binary form to report adverse drug events related to the safe usage of the drug is preferred. Technically, it is easier to tabulate and analyse the results based on binary data. Hence, the study was successful in using the

statistical test related to the generalized estimating equation, which considered repeated measures on subjects and the analysis of the outcomes at both binary and count levels.

Additionally, with the advancement of statistical analysis, more robust statistical tests such as the zero-inflated Poisson and hurdle Poisson models<sup>151</sup> can address adverse drug event that were reported in counts, rare events with expecting of high frequency of 0 and repeated measure on the subjects. Therefore, in reporting the safety profile of a drug, it is recommended to report results both in binary and count format.

### **High lymphocyte counts as a predictor of occurrence of adverse drug events from rapid Rituximab infusion**

In the univariate analysis, although both total white blood cell and lymphocyte counts were statistically and significantly related to the occurrence of adverse drug events. Only lymphocyte counts were chosen for the multivariate model because lymphocytes were part of the total white blood cell counts. Avoiding these two variables in the final model was done to prevent multicollinearity of variables. Patients in the study sample with abnormally high lymphocyte counts were 6.94 times more likely to experience adverse drug events in contrast to those with normal lymphocyte counts in a multivariate analysis that modeled the adverse drug event as binary response. In comparison to the multivariate analysis that modeled adverse drug event as count data, the odds of developing adverse drug events were 5.29 times greater. The difference between the two models was 1.65 which was fairly similar, it suggests that modeling adverse drug events as binary or count responses are both acceptable in reporting adverse drug events resulting from drug therapy. As mentioned earlier, the researchers in this area are encouraged to report adverse drug events in number form if the subjects are receiving

multiple cycles of drug therapy and being repeatedly measured. The usefulness of absolute lymphocyte count is not only useful in predicting adverse drug events; it also predicts the survival of patients with DLBCL and their relapsed rate.<sup>152</sup>

### **Applicability of identifying high lymphocyte count as a predictor of occurrence of adverse drug events**

Based on Australian statistics for the incidence of cancer in 2007,<sup>153</sup> lymphoid cancer is ranked in the top six. Judging by the trends of cancer diagnosis, it is observed that the number of new cases is increasing. Therefore, this study has generated evidence with regard to rapid rituximab infusion for people who require it. The identification of high lymphocyte counts as the only independent predictor of the occurrence of adverse drug events optimises patients' safety in receiving rapid rituximab infusion.

### **Frequency and type of adverse drug event**

The most commonly occurring adverse drug event was hypotension. This finding was similar to a current ongoing clinical trial<sup>150</sup> which also reports hypotension as the most often reported event among patients who receive rituximab regimen. The study involves a total of 534 patients who received 4923 cycles of standard rituximab infusion and 656 cycles of rapid infusion. Hypotension is identified as the most frequently occurring event in both groups of patients. As the number of adverse drug event is calculated based on cycle, hypotension rates of 0.9% and 0.5% are reported in standard and rapid infusion arms respectively. Thus, <1% of the adverse drug events is to be interpreted with caution. One could easily underestimate the harm when the number of events is calculated based on cycle instead of the number of patients. In this research study, 14 (32.6%) out of 43 patients experienced hypotension as an adverse drug event resulting from rapid rituximab infusion. Reporting adverse drug events based on the number of

patients is more accurate than using cycles in reflecting how safe a drug is in this study. On this theme, hypotension occurred more frequently in rapid rituximab infusion, however, fever and chills were more pronounced with slow infusion.<sup>52</sup> The likely explanation was rapid infusion causes even more rapid killing of B-lymphocytes leading to the earlier release of cytokine which in turn cause vasodilation.

Hypotension can be easily detected using a sphygmomanometer and stethoscope or a digital blood pressure set even before the patient exhibits any symptoms such as giddiness. Although hypotension was the most commonly reported adverse drug event, one third of this event was graded as 1 and did not require any medical intervention in this study. Although hypotension is not serious, it is recommended to continue monitoring patients' blood pressure at baseline prior to initiating infusion, and at 30 minutes before escalating to the last infusion rate which will complete the remaining infusion and the last blood pressure monitoring after the patient completes the entire infusion (depending on his or her toleration of it). Other vital signs, namely temperature, pulse saturation, heart and respiratory rate should also be monitored along with blood pressure.

### **Pattern of occurrence of adverse drug events**

The study demonstrates that there is a pattern of occurrence of adverse drug events which peak at the 30-, 60- and/or 90- minute mark of an infusion. Therefore, it is justifiable to monitor vital signs at 0, 30, 60 and 90 minute intervals. As this coincides with current clinical practice, the findings confirm that the current practice reflects the best available evidence and it is recommended that such practice continues.

## **Management of adverse drug events according to the severity of adverse drug events**

The severity of the adverse drug events was graded based on how they were managed. For a grade 1 adverse drug event, no medical or other intervention is required. Staff therefore continues with the existing infusion rate and a fixed frequency of monitoring. For grade 2 adverse drug events, the management of events was divided into 2 lines of treatment. The first line of treatment was generally interrupting the infusion rate temporarily (with or without a maintenance infusion of normal saline) until the symptoms subside. The second line of treatment was highly specific - targeted interventions - depending on patients' signs and symptoms. Patients with grade 3 adverse drug events often require hospitalisation for further monitoring if the first two lines of intervention failed to reverse a patient's condition.

The impact of adverse drug events on patient safety can be examined from the perspective of its frequency and severity. It is still considered safe to continue to administer the infusion if there are more grade 1 adverse drug events since drugs are bound to create some side effects. Conversely, if the adverse drug event is rare yet serious when it occurs, it will be acceptable for clinical use. A published study<sup>154</sup> has suggested that cancer patients continue to accept treatment (chemotherapy) despite knowing that the treatment might not be effective. From the researcher's personal clinical observation, many patients are willing to accept intensive treatment even though the chances of being cured are projected as low as 1%. As long as there is still treatment, they remain hopeful. In that study,<sup>154</sup> 78.75% and 5% of reported adverse drug events were graded as 2 and 3 respectively according to NCI CTCAE grading. The authors

conclude that using the drug in patients is safe despite the high incidence of a moderate adverse drug event (78.75%).

## **Age**

The patients in this study were allocated into 5 groups marked by 10 year spans which were applied largely to fulfill the statistical requirements of having at least an expected minimal number of adverse drug events reported in each group to facilitate a meaningful analysis. Although the literature<sup>155-157</sup> has suggested age can affect a patient's prognosis, response to treatment and readiness to receive treatment, this study did not find any statistical significance, suggesting that any age group was at a higher risk of experiencing adverse drug events. However, when closely examining the results, the findings suggest that the possibility of developing adverse drug events peaks in those aged between 61-70. The risk decreased in those aged 71-80 and increased again in those aged 81-90. Other studies<sup>105, 120</sup> that report a correlation between increasing age and adverse drug events did not break down those studies into age groups spanning 10 years; doing so in the present study suggests that some older patients should not be disqualified from receiving a potential curative treatment.

## **Gender**

This study suggests that the odds of experiencing an adverse drug event are 1.4 times greater in men as compare to women. Although no statistical significance was found in this study, gender was found to be a significant variable in a similar study with a much smaller study population.<sup>158</sup> However, the number of men and women was not equally distributed across groups. Men experienced slightly more events (5%) than women. As the sample of this study was taken from an urban hospital in South Australia, the

Australian cancer database<sup>153</sup> reported 57% of newly diagnosed cancers in 2007 occurred in men. Therefore, the ratio between male and female could be merely an artifact of a broader gender distribution in Australia.

## **Diagnosis**

Rapid rituximab infusion is a form of “off label use” which is commonly used worldwide. Twenty-two percent of the oncology population in Australia received “off label” drugs in 2004.<sup>159</sup> Under certain circumstances, the off label administration of a drug is acceptable and appropriate. Medical clinicians in Australia have developed a consensus over three scenarios to accept off label drug administration. The criteria are: the usage is highly recommended by high quality evidence; approval for the purposes of research; or justification by an individual’s clinical condition.<sup>160</sup> In this study, besides the FDA-approved NHL and CLL for rituximab treatment, other diagnoses such as ALL, autoimmune diseases, LPD and MGUS also received rapid rituximab infusion.

The literature supports off label use of rituximab for various clinical conditions. A study<sup>161</sup> published by the Princess Alexandra Hospital in Queensland in 2010 further confirms several other diagnoses which may benefit from rituximab (Lupus Nephritis and Thrombotic Thrombocytopenic Purpura had excellent response to the rituximab therapy). Furthermore, a recently published study<sup>118</sup> reports on the use of rapid rituximab infusion in treating Rheumatoid Arthritis since 2008. It concludes that no severe adverse drug events were linked to the regimen as they were mostly allergic or angio-odematic in nature.

The use of rituximab has extended to other diagnoses that are yet to be approved by the FDA. In a case report,<sup>162</sup> a patient with Hodgkin disease which had the expression of



CD 20 responded well to rituximab monotherapy therapy and remained in remission for the next 6 months. Another case report<sup>163</sup> also demonstrated a similar outcome for Waldenstrom's macroglobulinaemia (WM). A case report on AIHA (Autoimmune Haemolytic Anaemia) also reported a good response to rituximab treatment<sup>164</sup> and another report stated that 13 patients responded well to HyperCVAD-R.<sup>165</sup> Although the literature reports on the feasibility of using rapid and/or standard infusion rituximab in non-cancer diagnosis, this study did not support the use of rapid rituximab infusion in autoimmune disorder. Furthermore, patients diagnosed with autoimmune disorder such as ITP were 2.36 times more likely to develop adverse drug events, relative to NHL. A systematic review<sup>166</sup> also supports this finding. It examined the efficacy and safety of rituximab use among adult patients with Idiopathic Thrombocytopenia Purpura (ITP) from 1966 to 2006 across a number of reputable databases. The pooled results show that 62.5% (52.6-72.5) of patients have an overall response to platelet counts. However, while measured by NCI CTAE version 3, 66 (21.5%) out of 306 patients developed grade 1-2 adverse drug events and 10 (3%) patients developed grade 3-4 adverse drug events. Seven out of 10 of the grade 3-4 events were related to long-long-term toxicities. Nine (2.9%) patients died but a direct causal relationship between rituximab and death could not be established. As the studies included in this systematic review were of poor methodological design, the advice was not to use rituximab for ITP.

### **Stage of disease**

Stage III or IV disease in NHL is also known as advanced disease because the lymph node regions on both sides of the diaphragm are affected and the bone marrow is invaded by the disease in stage IV.<sup>102</sup> NHL is a disease that starts in the lymph node and

is embedded deeply underneath the surface of the skin. As a result, its abnormality cannot be easily seen by a layperson and, as a result, the disease is often only diagnosed at an advanced stage. Therefore, a stage III/IV diseases also implies that the disease is extensive. One study suggests that an advanced disease is associated with more infusion-related adverse drug events than stage I/II.<sup>105</sup> In this study, slightly more than 50% of the patients were diagnosed with advanced diseases. The adverse drug events were double those reported in stage III/IV compared to stage I/II disease. Nonetheless, statistically this was not significant.

### **Presence of cardiac or lung disease**

Only 15 (5.1%) out of the 294 patients who had an existing cardiac or/and lung disease experienced adverse drug events. These results provide greater confidence for the clinician to not exclude patients with cardiac or/and lung disease from rituximab treatment even at a rapid rate. This is because according to the current drug manufacturer's guideline,<sup>14</sup> special warnings and precautionary measures are recommended for patients who have existing cardiac and/or lung disease even while receiving slow rituximab infusion. Physiologically, rapid infusion is associated with fluid overload leading to pulmonary congestion causing respiratory and/or heart failure especially in the elderly population.<sup>167</sup>

### **Type of treatment**

rituximab is more commonly administered in combination with other chemotherapy in cancer patients whereas rituximab as monotherapy is typically administered as a maintenance therapy and/or for a non-cancer diagnosis. Although statistical significance between groups was not evident, patients in the rituximab combination group reported

experiencing more adverse drug events. This could be simply due more drugs being used in the combination group leading to a higher risk of side effects or adverse drug events.

### **Prescription dosage based on body surface area**

The hypothesis that a higher dosage could lead to more adverse drug events is evidenced in the cancer drug trial.<sup>168</sup> Therefore, the question of whether or not the adjusted body surface area (BSA) predicts higher frequency of adverse drug events was of the interest of this study if. The dosage of rituximab is based on the calculation of BSA presented in  $m^2$ . Although there is more than one way to calculate BSA, this depends on a person's height and weight. Clinically, BSA may be adjusted for: convenience of dilution; reduced toxicity as evidenced from previous dosage; or in obese patients. In this study, there was no significant difference between the groups with exact or adjusted BSA. This could be because the adjustment of the BSA was only minutely different to the original BSA.

### **Premedication**

Antipyretics, antihistamines and corticosteroids were given to almost all patients receiving rapid rituximab infusion. The corticosteroids were administered intravenously prior to each cycle of rapid rituximab infusion or orally as part of the chemotherapy regimen for 5 days. Adverse drug events remained prominent in 57 cycles of rapid infusion. This suggests that corticosteroids as premedication are not necessary and univariate analysis highlighted that corticosteroids could cause more harm than good because the odds of experiencing adverse drug events with corticosteroids was 1.48, relative to those without. A similar finding was also reported in another study.<sup>72</sup> Furthermore, the prolonged use of steroids may also cause steroid-induced diabetes.<sup>169</sup>

Although it is usual to use steroids as part of the chemotherapy regimen in order to cause apoptosis,<sup>170</sup> it should not be routinely prescribed to prevent or reduce the occurrence of adverse drug events associated with rapid rituximab infusion.

### **Blood counts**

In this study, it was not feasible to measure the size of the tumour if that correlated with the occurrence of an adverse drug event because CT (Computer Tomography) or PET (Positron Emission Tomography) scans were not routinely performed before each cycle of rapid rituximab infusion. However, the high level of lactate dehydrogenase (LDH) in the serum could be associated with a large tumour in the body.<sup>171</sup> Therefore, the measurement of serum LDH could possibly have been useful in the study to predict the occurrence of adverse drug events. As discussed earlier, a large tumour in the body could also indicate an advanced stage of disease that leads to more occurrences of adverse drug events.

### **Course and cycle**

It is safe for some patients to receive up to 21<sup>th</sup> cycles of rapid rituximab infusion. In view of the complex data involved in this study, it was categorised into 3 levels: patient (274); course (376); and cycle (1571). The rate of adverse drug events was 14.6% and 3.6% at the patient and cycle level respectively. Therefore, the risk of adverse drug events will be underestimated if the clinician only focuses on the cycle level. Conversely, only reporting the rate of adverse drug events at the patient level may overestimate the risk. The key principles are that researchers need to be transparent in data reporting and to present the results in ways that enable the clinician to make objective and informed decisions that do not jeopardise patients' safety. This study has

identified the possible bias that could occur in a research study by only reporting results at the cycle level.

The number of courses as an independent variable in this study was the only variable that gave rise to conflicting results when presented in binary format as compared to count data. It was found that patients who received more than one course of treatment were less likely to experience adverse drug events and vice versa when the outcome was measured as a count. To understand which is more accurate in reporting, another variable number of cycles will help to identify risk. Patients who received more than 7 cycles of rapid rituximab infusion were significantly less likely to experience adverse drug events in both binary and count data. More cycles of infusion were also associated with more courses of therapy; thus, patients who received more courses of therapy are less likely to experience an adverse drug event.

This study also identified that adverse drug events occurred more frequently in course 1. This information will help clinicians to anticipate the pattern of adverse drug events resulting from rapid rituximab infusion and to increase patients' safety.

### **Severity of adverse drug events**

Some of the data were not converged statistically because only 57 episodes of adverse drug events were reported. It was observed that some independent variables coincided with the occurrence of adverse drug events and some did not necessarily cause more severe adverse drug events to emerge. For example, male patients with cardiac or lung co-morbidities received more than one course of therapy; had their dosage adjusted based on body surface area; received corticosteroids as premedication; had low total

white blood cells and high lymphocyte counts; and were more likely to develop adverse drug events that were mostly more severe when the events occurred. Conversely, patients with high total white blood cells were more likely to experience adverse drug events but were less likely to experience severe adverse drug events when they occurred. In addition, patients who received rituximab as monotherapy were less likely to experience adverse drug events but more severe adverse drug events when they happened. The results in regard to the severity of the adverse drug events were interpreted with caution because this could be due to a lack of power to determine the significant predictors.

### **Management of adverse drug events**

The treatment of rituximab induced adverse drug events can be treated by simply stopping the infusion until all symptoms subside.<sup>68</sup> In the phase 2 study, the normal saline 0.9% solution, PO/IV Phenergan and IV Hydrocortisone were administered. Other drug of choice could be Pethidine/Meperidine that is effective for patients who develop chills and rigors. Other supportive treatments which were not reported in this study include oxygen support and the application of a heated blanket. When all the adverse drug events subside, rituximab is restarted at the slower rate or half of the previous rate. In the event where patients experience a cytokine storm, which is considered to be an oncology emergency, advanced treatment such as epinephrine, bronchodilator, vasopressin<sup>68, 103</sup> will be used and patients may be sent to the intensive care unit for close monitoring.

## **Chapter 7: Development of Clinical Practice Guidance**

After the Phase 1 and 2 studies, the evidence are consolidated and transferred into a clinical practice guideline (CPG). Evidence transfer is necessary to bring evidence from science to the bedside, and clinical practice guidelines represent one of the most effective ways to transfer the knowledge in this way. The Institute of Medicine (IOM) has defined clinical practice guidelines as "... systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances".<sup>172</sup> IOM has also developed eight standards<sup>173</sup> to guide development of CPG: (1) establishing transparency; (2) management of conflict of interest; (3) guideline development group composition; (4) systematic review intersection; (5) establishing evidence foundations for and rating strength and recommendation (6) articulation of recommendation; (7) external review; and (8) updating. How standards are applied is presented in more detail below.

### **Standard 1 Establishing transparency**

The development of the CPG on rapid rituximab infusion at 90 minutes would be the work of a PhD researcher with no external party funding except the scholarship awarded to the researcher from Health Manpower Development Programme (HMDP), Singapore.

### **Standard 2 Management of conflict of interest**

The researcher would invite other members of the hospital such as physicians, pharmacists, nurses and patients to provide their opinions on this CPG. We declared no conflict of interest in developing the CPG.

### **Standard 3 Guideline development group composition**

The CPG group's members were diversified and included the physician who prescribes, pharmacist who dilutes the drug, nurse who administers the drug, the patient who receives the drug and the finance officer who determines the fees.

### **Standard 4 Systematic review intersection**

This CPG would be guided from the recommendation and findings of the systematic review and primary retrospective study as mentioned in previous chapters. The group members would meet and discuss the outcomes of the review and study on a regular basis.

### **Standard 5 Establishing evidence foundations and rating strength and recommendation**

Each statement of the guideline would be assigned a level of evidence and grade of recommendation according to the Joanna Briggs Institute (JBI) levels of evidence and JBI grades of recommendations.<sup>174</sup>

### **Standard 6 Articulation of recommendation**

The statement of recommendation would be precise, clear and specific to the context.

### **Standard 7 External review**

The final draft of the CPG would be sent for external expert to review.

### **Standard 8 Updating**

The CPG would be updated when there is new evidence being generated and it would be reviewed on a 2-year basis.



# **Draft Administration guideline of rapid Rituximab infusion at 90 minutes and management of its infusion-related adverse drug events**

## **Scope of guideline:**

This draft guideline consists of the targeted population, infusion regimen and rate, premedication used prior to infusion, patterns of vital signs monitoring and the management of infusion-related adverse drug events.

## **Targeted population:**

This guideline is only applicable to adults with non-Hodgkin lymphoma who have previously received rituximab infusion without grade 3 or 4 adverse drug events and who have no known allergy to rituximab. (1A)

## **Recommended practice**

1. Patients with high lymphocyte counts are not suitable for rapid Rituximab infusion because they are five times more likely to experience adverse drug events compared to those with normal lymphocyte counts. (3A)
2. Antipyrexia and antihistamines are recommended prior to rapid rituximab infusion. Corticosteroids are not recommended as premedication. However, oral steroids as part of the chemotherapy regimen may be given as per chemotherapy protocol. (3A)
3. In the first cycle of rituximab infusion the recommended rate is 50mg/hour for 30 mins, escalating in increments of 50mg/hour increment at every 30 mins until a maximum rate of 400mg/hour is achieved. In the second cycle of rituximab

infusion the recommended rate is 100mg/hour, escalating in increments of 100mg/hour every 30 mins until a maximum rate of 400mg/hr. In the third and subsequent cycles 20% of the total dose may be administered over 30 mins followed by the remaining 80% at 60 mins. (Table 18) (3A)

*Table 18. Administration Rate of Rapid Rituximab Infusion*

BSA (m <sup>2</sup> )	Actual dose (mg)	Rituximab volume (ml)	Concentration (mg/ml)	Dosage rate	
				20% of total dose over 30 mins	80% of total dose over 60 mins
				Infusion rate (ml/hr)	
375mg/m <sup>2</sup> (rituximab diluted in 500mls infusion bag to yield a final concentration of 1-4mg/ml)					
1.4	525	53	1.05	210	443
1.5	563	56	1.13	211	454
1.6	600	60	1.2	212	448
1.7	638	64	1.28	213	451
1.8	675	68	1.35	213.6	454.4
1.9	713	71	1.43	214	457
2	750	75	1.5	215	460
2.1	788	79	1.58	215.8	463.2
2.2	825	83	1.65	216.6	466.4

- The monitoring of vital signs (including temperature, blood pressure, heart rate and respiratory rate) should occur at 0 min (baseline), and then every 30 mins in the first and second cycles; and, in the third and subsequent cycles, at 0 min (baseline), 30 mins and 90 mins. (3A)
- When a patient experiences any infusion-related adverse drug event, the infusion should be stopped and IV normal saline administered to keep the vein open. Depending on the signs and symptoms, medication should be administered for symptomatic relief: (3A)

- a. IV hydrocortisone 100mg for generic symptoms, e.g. facial flushing, itchiness
  - b. IV antihistamine (e.g. IV Diphenhydramine 25-50mg, IV ranitidine 50mg, IV Phenergan 25mg) for generic symptoms, e.g. facial flushing, itchiness
  - c. IV antiemetic (e.g. IV Metaclophramide 10-20mg, IV Ondansteron 8mg) for nausea and vomiting
  - d. IV Pethidine 25mg for chills and rigors
  - e. Oxygen depending on the level of oxygen saturation for breathlessness.
6. Additional investigations such as electrocardiography (ECG) may be ordered for symptoms related to heart, e.g. palpitation, tachycardia (4A)
  7. When the signs and symptoms subside, the infusion rate should restart at half of the previous rate and maintained at the same rate until completion of the rituximab infusion. (3A)
  8. Document the patient's tolerance of rituximab infusion in the medical notes. (4A)

## **Draft Patient information pamphlet for Rituximab infusion**

### **Who this is for**

This information is for patients who were planning to receive rituximab infusion as single therapy or in combination with other cancer treatment. rituximab is approved by

the Food and Drug Administration (FDA) in the United States for the following conditions:

- CD 20 positive, previously untreated, stage III/IV follicular, B-cell non-Hodgkin lymphoma;
- CD 20 positive, relapsed or refractory low grade or follicular, B-cell non-Hodgkin lymphoma;
- CD 20 positive, diffuse large B-cell non-Hodgkin lymphoma in combination with chemotherapy;
- CD 20 positive chronic lymphocytic leukemia (CLL) in combination with chemotherapy; and
- Severe rheumatoid arthritis intolerance to at least one tumour necrosis factor (TNF) antagonist therapy in combination with methotrexate.

## **What we know about the rate of Rituximab infusion**

### ***First cycle***

In the first cycle of rituximab infusion the rate of administration is 50mg/hour for 30 mins, and then escalates by 50mg per hour every 30 mins until it reaches the maximum rate of 400mg/hour.

### ***Second cycle***

When you tolerated the first cycle well without severe adverse drug events, in the second cycle of rituximab infusion the rate is 100mg/hour, and then escalated by 100mg/hour every 30 mins until it reaches the maximum rate of 400mg/hour.

### ***Third and subsequent cycle***

When you tolerated the previous cycles without severe adverse drug events and without high absolute lymphocyte counts, the third and subsequent cycle is given at 20% of the total dose over 30 mins followed by the remaining 80% in 60 mins.

### **Premedication prior to Rituximab infusion**

You would be given oral Paracetamol 1 g and intravenous Diphenhydramine 25/50mg at least 30 minutes before all cycles of rituximab infusion commence. Do not consume antihypertensive medicine on the morning you were going to receive a rituximab infusion.

### **Side effects you might experience during the Rituximab infusion**

The most common side effects associated with *standard infusion* are:

- Fever, chills and severe shivering
- Swelling of the tongue, face, lips, mouth or throat
- Itchiness
- Breathlessness
- Wheezing or coughing
- Dizziness or lightheadedness
- Nausea or vomiting
- Headache
- Fatigue
- Runny nose
- Flushing
- Fast heart beat
- Chest pain may spread to the neck and shoulders
- Pain where the cancer is located
- Muscle and joint pain

- Stomach pain or discomfort
- Throat irritation

The **most** common side effects associated with **rapid infusion** are:

- Low blood pressure
- Feeling hot and facial flushing
- Itchiness

The **less** common side effects associated with rapid rituximab infusion are:

- Chest tightness
- Rash or hives
- Nausea and/or vomiting
- Pain
- Breathlessness
- Dry throat
- Fast heart beat
- Headache
- Restless legs
- Rigors
- High blood pressure
- Fever
- Indigestion

### **Vital signs monitoring**

Your temperature, blood pressure, heart rate and respiratory rate will be monitored by the nurses closely at regular intervals.

Figure 12. Draft prescription and monitoring chart

Patient sticky label		Diagnosis:		Height: cm	Cycle:			
		Drug Allergy:		Weight: kg	Lymphocytes count:			
		<input type="checkbox"/> NKDA		BSA: m <sup>2</sup>				
Date Given:								
Route	Premedication	Dose	Diluent	Time Given	Given By	Checked by		
PO	Antiprexyia							
PO / IV	Antihistamine							
Route	Drug	Dosage (mg/m <sup>2</sup> )	Total dose (mg)					
IV	Rituximab							
	Rate(mg/hr)	Given By	Vital signs monitoring				Adverse drug event	Management
			T	BP	HR	RR		
1st infusion	0							
	50 x 30mins							<input type="checkbox"/> Stop rituximab <input type="checkbox"/> Give medication <input type="checkbox"/> Give IV N/S <input type="checkbox"/> Continue observation
	100 x 30mins							<input type="checkbox"/> Stop rituximab <input type="checkbox"/> Give medication <input type="checkbox"/> Give IV N/S <input type="checkbox"/> Continue observation
	150 x 30mins							<input type="checkbox"/> Stop rituximab <input type="checkbox"/> Give medication <input type="checkbox"/> Give IV N/S <input type="checkbox"/> Continue observation
	200 x 30mins							<input type="checkbox"/> Stop rituximab <input type="checkbox"/> Give medication <input type="checkbox"/> Give IV N/S <input type="checkbox"/> Continue observation
	250 x 30mins							<input type="checkbox"/> Stop rituximab <input type="checkbox"/> Give medication <input type="checkbox"/> Give IV N/S <input type="checkbox"/> Continue observation
	300 x 30mins							<input type="checkbox"/> Stop rituximab <input type="checkbox"/> Give medication <input type="checkbox"/> Give IV N/S <input type="checkbox"/> Continue observation
	350 x 30mins							<input type="checkbox"/> Stop rituximab <input type="checkbox"/> Give medication <input type="checkbox"/> Give IV N/S <input type="checkbox"/> Continue observation
	400 x 30mins							<input type="checkbox"/> Stop rituximab <input type="checkbox"/> Give medication <input type="checkbox"/> Give IV N/S <input type="checkbox"/> Continue observation
	400 for remainder							<input type="checkbox"/> Stop rituximab <input type="checkbox"/> Give medication <input type="checkbox"/> Give IV N/S <input type="checkbox"/> Continue observation
2 nd infusion	0							
	100 x 30mins							<input type="checkbox"/> Stop rituximab <input type="checkbox"/> Give medication <input type="checkbox"/> Give IV N/S <input type="checkbox"/> Continue observation
	200 x 30mins							<input type="checkbox"/> Stop rituximab <input type="checkbox"/> Give medication <input type="checkbox"/> Give IV N/S <input type="checkbox"/> Continue observation
	300 x 30mins							<input type="checkbox"/> Stop rituximab <input type="checkbox"/> Give medication <input type="checkbox"/> Give IV N/S <input type="checkbox"/> Continue observation
3rd & subsequent infusion	0							
	20% x 30mins							<input type="checkbox"/> Stop rituximab <input type="checkbox"/> Give medication <input type="checkbox"/> Give IV N/S <input type="checkbox"/> Continue observation
	80% x 60mins							<input type="checkbox"/> Stop rituximab <input type="checkbox"/> Give medication <input type="checkbox"/> Give IV N/S <input type="checkbox"/> Continue observation
Patient Outcome <input type="radio"/> Patient discharge home <input type="radio"/> Patient admitted to Ward						Doctor's name, MCR and signature		
Additional notes								
Staff name/ signature:						Date/Time:		

## **Chapter 8. Conclusion**

### **Restatement of problem and research outcome**

Patient safety is the core value of this project. The rapid administration of rituximab for cancer patients is practiced worldwide. As no published papers emerged that critically appraised the methodological quality of studies supporting the use of rapid rituximab infusion, in Phase 1 of this project, a systematic review was conducted to synthesise the best available evidence. The findings of the systematic review strongly support the view that rapid rituximab infusion is safe for patients with non-Hodgkin Lymphoma but not for those with chronic lymphocytic leukemia. This significant finding was further researched in Phase 2 in order to improve patient safety by identifying any predictors that could predict the occurrence and severity of adverse drug event. The findings of the retrospective cohort study show that patients with high lymphocyte counts are more likely to experience an adverse drug event in comparison to those with low or normal lymphocytes counts. Other variables such as the type of premedication, patients' characteristics, and the pattern of nursing monitoring were addressed in this study. In Phase 3, the study findings were used to develop a draft clinical practice guideline for the safe and rapid administration of rituximab.

### **Summary description of procedures**

The researcher's interest in rituximab as a monoclonal antibody is discussed in Chapter 1. Chapter 2 sets out the theoretical framework for the study and presents three contextualised literature reviews addressing different aspects of rituximab. Chapter 3 describes the methodological underpinning of the Phase 1 comprehensive systematic review and Phase 2 primary research study. In Chapters 4 and 5 the findings of the



systematic review and primary research study are reported respectively and Chapter 6 discusses the findings of the systematic review and the primary research study. A draft Clinical Practice Guideline and Patient Information Sheet constitutes Chapter 7. The final chapter presents the conclusion for the safe administration of rapid rituximab infusion based on the best available evidence.

## **Implications for clinical practice**

The emergence of monoclonal antibodies such as rituximab has provided a new modality of treatment for patients whose diseases originate from plasma B-cell with CD-20 antigen positive. This was a positive development for some cancer patients who used to have minimal hope in their treatment at best. The introduction of rituximab has minimised many long-term side effects that used to occur in chemotherapy. Although rituximab infusion does cause adverse drug events that could be potentially fatal, our understanding of the drug's mechanisms has improved in recent years. Clinicians (doctors and nurses) are increasingly more experienced and prepared in the prevention and management of adverse drug events.

This study has successfully contributed to knowledge related to the administration of rituximab and the findings support the current off-label practice of the rapid infusion of rituximab at 90-minutes and affirmed that only a high lymphocyte count can be recognised as a reliable independent factor in predicting the occurrence and frequency of adverse drug events. No predictors were found in relation to the severity of adverse drug events. The study findings also support the clinical observation that the occurrence of adverse drug events is in inverse relationship to an increased number of cycles.

Apart from the focus on patients, this study in context of oncology provides guidance to nurses on when to monitor the vital signs. Clinically, there is much debate over patterns of nursing monitoring that could be considered excessive and more than necessary. This is the first study to recommend that monitoring vital signs at 30 minute intervals is sufficient to detect and minimise adverse drug events.

Steroids as premedication are not recommended because there is a lack of evidence supporting their use. Furthermore findings suggest that the use of steroids as premedication may cause more harm in relation to the occurrence of adverse drug events.

## **Conclusion**

Rapid rituximab infusion over 90 minutes is safe for any patients diagnosed with non-Hodgkin Lymphoma except those with abnormally high lymphocyte counts.

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# Appendixes

## Appendix I. Example of NCI CTC & CTCAE

Adverse drug event	Grade				
	0	1	2	3	4
Hypotension	0	1	2	3	4
	None	Changes, but no therapy required	Requiring brief fluids replacement or other therapy but not hospitalisation; no physiological consequences	Requiring therapy and sustained medical attention, but resolved without persisting physiological consequences	Shock (associated with <u>academia</u> <b><u>[is this correct word?]</u></b> and impaired vital organs' function due to tissue hypo perfusion

Adverse drug event	Grade				
	0	1	2	3	4
Hypotension	0	1	2	3	4
	None	Changes, but no therapy required	Requiring brief fluids replacement or other therapy but not hospitalisation; no physiological consequences	Requiring therapy and sustained medical attention, but resolved without persisting physiological consequences	Shock (associated with <u>academia</u> <b><u>[is this correct word?]</u></b> and impairing vital organs function due to tissue hypo perfusion

*Appendix II. Search Strategy*

Databases	Block Building
1. PubMed/Medline	(rituximab[nm] OR rituximab[tw] OR mabthera[tw] OR rituxan[tw]) AND (infusions, intra-arterial[mh] OR infusion*[tw])
2. Web of Science	(rituximab OR mabthera OR rituxan) AND ( rapid infus*)
3. Scopus	Title-Abs-Key(rituximab OR mabthera OR rituxan) AND ("rapid infus*")
4. Cochrane Central Register of Controlled Trials	(rituximab OR mabthera OR rituxan) AND (infus*)
5. Science Direct	(rituximab OR mabthera OR rituxan) AND ('rapid infusion')
6. CINAHL	(TX rituximab OR TX mabthera OR TX rituxan) AND TX (infusions, intra-arterial) or TX infus*
7. Scifinder	Rituximab rapid
8. Mednar	(rituximab OR mabthera OR rituxan) AND ( rapid infus*)

*Appendix III. Critical Appraisal Instrument*  
**JBI Critical Appraisal Checklist for Descriptive/ Case Series**

NOTE:

This appendix is included on page 187 of the print copy  
of the thesis held in the University of Adelaide Library.

*Appendix IV. Data Extraction Instrument*

NOTE:

This appendix is included on pages 188-189 of the print copy of the thesis held in the University of Adelaide Library.



*Appendix V. Included studies*

Author	Year	Study Method	Setting	Participants							Intervention	Instrument
				# of patients	Age	Diagnosis	Chemotherapy	Stage of Disease	Bulky Disease (>7cm)	Leucocytosis		
Al Zahrani et al.	2009	Observational	Outpatient Chemotherapy Day Unit in Riyadh Military Hospital in Saudi Arabia	21	Mean 48 (28-68)	DLBCL, Low Grade Lymphoma, unspecified lymphoma	RCHOP, Monotherapy, Mod-FCN-R, other	NS	Yes	Yes	(90min) 20% in first 30min, 80% for the remaining over 60min	CTC CTAE Version 3
Chiang et al.	2010	Observational	Ambulatory Cancer Center in National Cancer Center Singapore	79	Median 56	DLBCL, FL, BL, MCL, unspecified lymphoma	RCHOP, RCVP, RCEOP, R alone	NS	NS	NS	(90min) 20% in first 30min, 80% for the remaining over 60min	NS
Corey et al.	2007	Observational	Community Based Cancer Center at Gundersen Lutheran Health in United States	46	Median 69(32-91)	NHL	RP, RCHOP, RCVP, RCEP, RCFP, RCP	I-IV	NS	No	(90min) 20% in first 30min, 80% for the remaining over 60min	CTC CTAE Version 3
El-Aganf et al.	2007	Observational	Outpatient Day Therapy Unit at Ulster Hospital, Northern Ireland	17	Median 75(44-87)	DLBCL, FL, NHL	RCHOP, RCVP	I-IV	NS	No	(90min) 20% in first 30min, 80% for the remaining over 60min	NS
Gibbs et al.	2007	Observational	Haematology Unit of Norfolk and Norwich University Hospital, United Kingdom	61	Range (18-80)	DLBCL	RCHOP	NS	NS	NS	90 min	CTC CTAE

Abbreviation: NS-Not Stated; DLBCL-Diffuse Large B Cell Lymphoma; FL-Follicular Lymphoma; BL-Burkitts Lymphoma; MCL-Mantle Cell Lymphoma; NHL-Non Hodgkin Lymphoma; MALT-Mucosa-Associated Lymphatic Tissue; PTLD-Post Translant Lymphoproliferative Disorder.

R-Rituximab, CHOP-Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone; CVP-Cyclophosphamide, Vincristine, Prednisolone; CEOP-Cyclophosphamide, Etoposide, Vincristine, Prednisolone; P-Prednisolone; CEP-Cyclophosphamide, Etoposide, Prednisolone; CFP-Cyclophosphamide, Fludarabine, Prednisolone; CP-Cyclophosphamide, Prednisolone;

Author	Year	Study Method	Setting	Participants							Intervention	Instrument
				Number of patients	Age	Diagnosis	Chemotherapy	Stage of Disease	Bulky Disease (>7cm)	Leucocytosis		
Salar et al.	2006	Observational	In and outpatient of Department of Clinical Haematology in the Hospital Del Mar in Spain	70	Median 64(28-87)	DLBCL, FL, MALT, MCL, unspecified lymphoma, PTLD, Immune cytopenia	RCHOP, REPOCH, Monotherapy, R-f,ludarabine, R-Gemcitabine, R-Chlorambucil	NS	NS	No	(90min) 20% in first 30min, 80% for the remaining over 60min	NS
Sehn et al.	2007	Observational	Ambulatory Chemotherapy Unit in British Columbia Cancer Agency, Canada	205	Median 60(19-92)	NHL	RCHOP, RCVP, R alone.	NS	NS	No	(90min) 20% in first 30min, 80% for the remaining over 60min	NS
Statham et al.	2006	Observational	Ambulatory Haematology Unit within the North London Cancer Network United Kingdom	23	Median 56(36-82)	DLBCL, FL, MCL, Waldenstrom's Macroglobulinemia, HD, PTLD	RCHOP, RCVP, R alone, RPMLiCEBO, RIVE, RIVAC	NS	NS	Ns	(90min) 20% in first 30min, 80% for the remaining over 60min	NCI CTC Version 2
Milone et al.	2007	Observational	Argentina	31	NS	NHL, CLL	RCHOP, R	NS	NS	NS	(90min) 20% in first 30min, 80% for the remaining over 60min	NS

Abbreviation: NS-Not Stated; DLBCL-Diffuse Large B Cell Lymphoma; FL-Follicular Lymphoma; BL-Burkitts Lymphoma; MCL-Mantle Cell Lymphoma; NHL-Non Hodgkin Lymphoma; HD-Hodgkin Disease; CLL-Chronic Lymphocytic Leukemia; MZL-Marginal zone Lymphoma  
R-Rituximab, CHOP-Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone; CVP-Cyclophosphamide, Vincristine, Prednisolone; CEOP-Cyclophosphamide, Etoposide, Vincristine, Prednisolone; P-Prednisolone; CEP-Cyclophosphamide, Etoposide, Prednisolone; CFP-Cyclophosphamide, Fludarabine, Prednisolone; CP-Cyclophosphamide, Prednisolone; EPOCH-Etoposide, Vincristine, Doxorubicin, Cyclophosphamide, Prednisolone;PMLiCEBO-Mitoxantrone, Cyclophosphamide, Etoposide, Vincristine, Bloemycin, Prednisolone;; EPOCH-Etoposide, Vincristine, Doxorubicin, Cyclophosphamide, Prednisolone;

Author	Year	Study Method	Setting	Participants							Intervention	Instrument
				Number of patient	Age	Diagnosis	Chemotherapy	Stage of Disease	Bulky Disease (>7cm)	Leucocytosis		
Soria et al.	2008	Observational	Outpatient at Zaragoza, Spain	37	Mean 55.3(24-77)	FL	RCHOP,RFCM, RFC	I-IV	Yes	Yes	(90min) 20% in first 30min, 80% for the remaining over 60min	NS
Swan et al.	2010	Observational	Outpatient and inpatient oncology unit in The Methodist Hospital, Houston, United State	13	62(24-89)	FL, DLBCL, NHL, WM	RCHOP, R, FCR, high dose MTX, RCC	NS	NS	NS	(90min) 20% in first 30min, 80% for the remaining over 60min	NCI CTCAE Version 4
Provencio et al.	200	Observational	Outpatient in Spain	40	Median 60(29-87)	DLBCL, Low Grade Lymphoma, HD	RCHOP, RCOMP, RCVP, other	I-V	Yes	Yes	60 min	NCI CTC Version 3
Tuthill et al.	2009	Observational	United Kingdom	54	Median 60(20-86)	DLBCL, FL, MCL, Maltoma, Immune Mediated Thrombocytopenias	NS	NS	NS	No	60min	NS
Aurran et al.	2005	Observational	Outpatient Unit in Marseille, France	69	Median 61(26-85)	DLBCL, FL, MCL, MZL, CLL, Lymphoplasmocytic, Castelman Disease, ITP	RCHOP, R	NS	NS	NS	60min	NS

Abbreviation: NS-Not Stated;DLBCL-Diffuse Large B Cell Lymphoma;FL-Follicular Lymphoma; MCL-Mantle Cell Lymphoma HD-Hodgkin Disease;CLL-Chronic Lymphocytic Leukemia;MZL-Marginal zone Lymphoma;ITP-Idopathic Thrombocytopenia Purpura;NHL- Non-Hodgkin Lymphoma;WM-Waldenstrom'sMacroglobulinemia;MZL-Mantle Zone Lymphoma.R-Rituximab, CHOP-Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone; CVP-Cyclophosphamide, Vincristine, Prednisolone; R-Rituximab; FC-Fludarabine, Cyclophosphamide; FCM-Fludarabine, Cyclophosphamide, Mitoxantrone; MTX-Methotrexate; RCC- Rituximab, Cladribine, Cyclophosphamide



## *Appendix VI. Excluded Studies*

Rapid-infusion rituximab helps meet cancer targets. Pharm J. 2005; 275(7356).

**Reason for exclusion:** Discussion paper

Focus on oncology nursing. Nurses can administer rituximab safely by rapid infusion. Oncology News International. 2007; 16(9): 15.

**Reason for exclusion:** Discussion paper

Brice P, Franchi-Rezgui P, Derni C, Nocton V, Hascouet I, Kadia C, et al. Rituximab rapid infusion (90 minutes) is feasible after the first dose in an outpatient setting, a single center prospective study of 80 courses. Haematologica. 2007 Jun;92:0605.

**Reason for exclusion:** Incongruent with review inclusion criteria for intervention, the median duration of rituximab infusion was at 90 minutes.

Byrd J, Peterson B, Morrison V, Park K, Jacobson R, Hoke E, et al. Randomized phase 2 study of fludarabine with concurrent versus sequential treatment with rituximab in symptomatic, untreated patients with B-cell chronic lymphocytic leukemia: results from Cancer and Leukemia Group B 9712 (CALGB 9712). Blood. 2003;101(1):6.

**Reason for exclusion:** Incongruent with review inclusion criteria for intervention, different infusion rate were used within the same arm.

Byrd JC, Murphy T, Howard RS, Lucas MS, Goodrich A, Park K, et al. Rituximab using a thrice weekly dosing schedule in B-Cell chronic lymphocytic leukemia and small lymphocytic lymphoma demonstrates clinical activity and acceptable toxicity. J Clin Oncol. 2001 Apr;19(8):2153-64.

**Reason for exclusion:** The analysis of results were unclear, not able to extract outcome measures as stated in the review

Byrd JC, Waselenko JK, Maneatis TJ, Murphy T, Ward FT, Monahan BP, et al. Rituximab therapy in hematologic malignancy patients with circulating blood tumor cells: Association with increased infusion-related side effects and rapid blood tumor clearance. J Clin Oncol. 1999 Mar;17(3):791-5.

**Reason for exclusion:** Discussion paper

Filewich A, Fitzgerald C, Gill K. Brief report rapid infusion rituximab in combination with steroid containing chemotherapy or as maintenance therapy is well tolerated and can safely be delivered in the community setting. Blood. 2007.

**Reason for exclusion:** Duplicated paper

Filewich A, Fitzgerald CK, Gill D. Rapid infusion rituximab in combination with steroid containing chemotherapy can be given safely and substantially reduces resource utilization. Blood. 2004.

**Reason for exclusion:** Duplicated paper

Graham AH. Administering rituximab: infusion-related reactions and nursing implications. Cancer Nurs Pract. 2009;8(2):30-5.

**Reason for exclusion:** Discussion paper

Gundogdu F, Akgedik K, Atay S, Arpaci A, Yilmaz F, Korucuoglu Z, et al. P36 Rapid infusion of rituximab in lymphoma treatment as maintenance therapy is well tolerated. Eur J Oncol Nurs. 2010;14(Supplement 1):S33-S.

**Reason for exclusion:** The analysis of the results from the study was vague.

Kanelli S, Ansell SM, Habermann TM, Inwards DJ, Tuinstra N, Witzig TE. Rituximab toxicity in patients with peripheral blood malignant B-cell lymphocytosis. *Leuk Lymphoma*. 2001 Nov-Dec;42(6):1329-37.

**Reason for exclusion:** Discussion paper

Kramers AMG, Zijlstra-Baalbergen JM. Rapid infusion rituximab, an evidence based-practice approach. *Bone Marrow Transplant*. 2008 Mar;41:S369-S.

**Reason for exclusion:** Incongruent with review inclusion criteria for population, 29.4% patients were AIHA and ITP patients

McCoy C, Watterson P, Martin N, Ong YL, Moore A, Black B, et al. Rapid infusion of Rituximab can be given safely and has a significant impact on capacity. *Br J Haematol*. 2006 Apr;133:8-

**Reason for exclusion:** Duplicated paper

Middleton H, Mollee P, Bird R, Mills A, Marlton P, Gill D. Accelerated Delivery of Rituximab Is Safe on an Out-Patient Basis. *Am Soc Hematology*; 2005. p. 4777-

**Reason for exclusion:** Incongruent with review inclusion criteria for intervention, infusion rate of 400mg/hr was used with median infusion time was 1 hour 55 minutes.

Peinert S, Moloney M, Prince HM, Wolf M, Ritchie D, Westerman D, et al. Rapid infusion of rituximab is well tolerated and enables more efficient use of haematology aday ward resources. *Haematologica*. 2009 Jun;94:0424.

**Reason for exclusion:** Incongruent with review inclusion criteria for population, patients aged 16 years old were included in the study.

Provencio M, Sanchez A, Maximiano C, Cantos B, Mendez M, Bonilla F. A prospective study of left ventricle function after treatment with rapid-infusion Rituximab in patients with non-Hodgkin lymphoma. *Leuk Lymphoma*. 2009;50(10):1642-6.

**Reason for exclusion:** Incongruent with review inclusion criteria for outcome measures, the study examined long term complication of rapid rituximab infusion.

Ramadan K, McCoy C, Ong YL, Eswedi AH, El-Agnaf MR. Rapid infusion of rituximab over 90-minutes from second infusion onwards on an out-patient basis is safe and improves resource utilization. *Haematologica*. 2007 Jun;92:0938.

**Reason for exclusion:** Duplicated paper

Romejko-Jarosinska J, Borawska AB. Rituximab rapid compared to standard infusion rate in a busy oncology practice. *Jarosinska*. 2010.

**Reason for exclusion:** Duplicated paper

Sehn L, Donaldson J, Filewich A, Fitzgerald C, Gill K, Runzer N, et al. Rapid infusion rituximab can be safely administered and has a positive impact on resource utilization. *Ann Oncol*. 2005 Jun;16:107.

**Reason for exclusion:** Duplicated paper

Sehn LH, Donaldson J, Filewich A, Fitzgerald C, Gill KK, Runzer N, et al. Rapid infusion rituximab in combination with steroid containing chemotherapy can be given safely and substantially reduces resource utilization. *Blood*. 2004 Nov;104(11):1407.

**Reason for exclusion:** Duplicated paper

Siano M, Lerch E, Negretti L, Zucca E, Rodriguez-Abreu D, Oberson M, et al. A Phase I-II Study to Determine the Maximum Tolerated Infusion Rate of Rituximab with Special Emphasis on Monitoring the Effect of Rituximab on Cardiac Function. Clin Cancer Res. 2008 Dec;14(23):7935-9.

**Reason for exclusion:** Incongruent with review inclusion criteria for intervention, infusion rate ranged from 50-700mg/h were used.

Uresandi A, Guinea J, Menchaca C, Hernandez R, Mendizabal A, Ardanaz MT, et al. Rituximab fast infusion tolerance. Ann Oncol. 2008;19(Supp 4).

**Reason for exclusion:** Incongruent with review inclusion criteria for intervention, infusion rate of 400mg/hr was used with no specification on the duration of completion.

Wenger M, De Marco E, Vitolo U, Poddubnaya I, Chamone D, Warburton P, et al. Rituximab maintenance therapy can be safely administered via a rapid infusion protocol: results from the maxima study. Haematologica. 2008 Jun;93:0272.

**Reason for exclusion:** Duplicated paper

*Appendix VII. Example of Codes from SAS*

Stat:

```
proc genmod data=statdemo descending;
  class id recourse;
  model ar = recourse /link=logit dist=binomial type3 wald;
  repeated subject=id /type=ind;
  estimate 'recourse 2 vs. 1' recourse -1 1 /exp;
run;
proc genmod data=statdemo descending;
  class id age;
  model ar = age /link=logit dist=binomial type3 wald;
  repeated subject=id /type=ind;
  estimate 'age 2 vs. 1' age -1 1 0 0 0 /exp;
  estimate 'age 3 vs. 1' age -1 0 1 0 0 /exp;
  estimate 'age 4 vs. 1' age -1 0 0 1 0 /exp;
  estimate 'age 5 vs. 1' age -1 0 0 0 1 /exp;
run;
proc genmod data=statdemo descending;
  class id gender;
  model ar = gender /link=logit dist=binomial type3 wald;
  repeated subject=id /type=ind;
  estimate 'Gender male vs. female' gender 1 -1 /exp;
run;
proc genmod data=statdemo descending;
  class id diganosis;
  model ar = diganosis /link=logit dist=binomial type3 wald;
  repeated subject=id /type=ind;
  estimate 'Diganosis 2 vs. 1' diganosis -1 1 0 0 0 /exp;
  estimate 'Diganosis 3 vs. 1' diganosis -1 0 1 0 0 /exp;
  estimate 'Diganosis 4 vs. 1' diganosis -1 0 0 1 0 /exp;
  estimate 'Diganosis 5 vs. 1' diganosis -1 0 0 0 1 /exp;
run;
proc genmod data=statdemo descending;
  class id stage;
  model ar = stage /link=logit dist=binomial type3 wald;
  repeated subject=id /type=ind;
  estimate 'stage 0 vs. 1' stage 1 -1 0 /exp;
  estimate 'stage 2 vs. 1' stage 0 -1 1 /exp;
run;
proc genmod data=statdemo descending;
  class id comorbid;
  model ar = comorbid /link=logit dist=binomial type3 wald;
```

```

    estimate 'fLD 3 vs. 2' fld 0 -1 1 /exp;
run;

proc genmod data=statdemo descending;
    class id dosage fwbc flymphocyte course_group;
    model ar = dosage fwbc flymphocyte course_group /link=logit
dist=binomial type3 wald;
    repeated subject=id /type=ind;
    estimate 'Dosage 2 vs. 1' dosage -1 1 0 0 /exp;
    estimate 'Dosage 3 vs. 1' dosage -1 0 1 0 /exp;
    estimate 'Dosage 4 vs. 1' dosage -1 0 0 1 /exp;
    estimate 'FWBC 1 vs. 2' fwbc 1 -1 0 /exp;
    estimate 'FWBC 3 vs. 2' fwbc 0 -1 1 /exp;
    estimate 'FLymphocyte 1 vs. 2' flymphocyte 1 -1 0 /exp;
    estimate 'FLymphocyte 3 vs. 2' flymphocyte 0 -1 1 /exp;
    estimate 'Courses 3-4 vs. 1-2' course_group -1 1 0 0 /exp;
    estimate 'Courses 5-6 vs. 1-2' course_group -1 0 1 0 /exp;
    estimate 'Courses 7+ vs. 1-2' course_group -1 0 0 1 /exp;
run;

proc genmod data=statdemo;
    class id fwbc flymphocyte course_group;
    model count_ar = fwbc flymphocyte course_group /link=log dist=poisson
type3 wald;
    repeated subject=id /type=ind;
    estimate 'FWBC 1 vs. 2' fwbc 1 -1 0 /exp;
    estimate 'FWBC 3 vs. 2' fwbc 0 -1 1 /exp;
    estimate 'FLymphocyte 1 vs. 2' flymphocyte 1 -1 0 /exp;
    estimate 'FLymphocyte 3 vs. 2' flymphocyte 0 -1 1 /exp;
    estimate 'Courses 3-4 vs. 1-2' course_group -1 1 0 0 /exp;
    estimate 'Courses 5-6 vs. 1-2' course_group -1 0 1 0 /exp;
    estimate 'Courses 7+ vs. 1-2' course_group -1 0 0 1 /exp;
run;

```

## **Publication**

**Article 1:** Lang SP, George C. Acute Adverse Reactions Of Rapid Rituximab Infusion Among Adult Patients With Non-Hodgkin Lymphoma and Chronic Lymphocytic Leukemia JBI Library of Systematic Reviews. 2011;9(1):1-37.

**Article 2:** Safety of rapid rituximab infusion in adult cancer patients: A systematic review. International Journal of Nursing Practice. 2011;17(4):357-69.

**Article 3:** Evaluation of safety and feasibility of rapid rituximab infusion. Asia-Pacific Journal of Clinical oncology. 2012;8 (1):71-5.

# Acute adverse reactions of rapid Rituximab infusion among adult patients with Non-Hodgkin Lymphoma and Chronic Lymphocytic Leukemia

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## Executive summary

**Background** Rapid Rituximab infusion has become increasingly popular globally. Although pharmaceutical manufacturers recommend second and subsequent infusions to run over 2-3 hours, many cancer centres have changed their clinical practice based on their own research and the results from other primary studies. Such research studies claim that it is safe to administer Rituximab rapidly among cancer patients especially in Non Hodgkin Lymphoma (NHL) and Chronic Lymphocytic Leukemia (CLL). In addition, the studies suggest that the rapid infusion of Rituximab also results in benefits of cost saving and better resource utilisation. However, these studies have not been critically appraised for their validity and application to the global population. No previous systematic reviews on this topic have been identified.

**Objective** The objective of this review was to critically appraise, synthesise and present the best available evidence related to the safety of rapid Rituximab infusion among adult patients with NHL and CLL.

### Inclusion criteria

*Type of participants* The participants of interest were adults aged 18 years old and above who had a diagnosis of NHL or CLL at any stage, have had prior exposure to Rituximab and received Rituximab with or without combination of any chemotherapy.

*Type of intervention* The intervention of interest was rapid Rituximab infusion to be completed at less than or equal to 120 minutes.

*Type of studies* The studies of interest were both experimental and non-experimental studies.

*Type of outcomes* The primary outcomes of interest were the presence of acute adverse reactions and their severity. The secondary outcomes of interest were the management of the acute adverse reactions and patient mortality rate resulting from adverse reactions.

*Search strategy* The search sought to identify published and unpublished studies from 1997 till 2010. A three-step search strategy was used for electronic databases, grey literature and reference lists.

*Methodological quality* Two independent reviewers used the standard critical appraisal tool from JBI-MASStARI to assess the methodological qualities of the studies that matched with inclusion criteria.

*Data collection* A standard data form from JBI-MASStARI was used to extract the data across all included studies.

*Data synthesis* Proportional Meta-analysis based on DerSimonian-Laird weights for the random effects model was used for statistical pooling through Stats Direct. Heterogeneity was assessed using Cochran Q. When statistical pooling is not possible, the findings are presented in narrative summary.

**Results** A total of 753 patients were included in this review. All except one patient completed 2298 cycles of rapid Rituximab infusions. Seventeen and one acute adverse reactions were reported among NHL and CLL patients respectively. There were five reactions were not cleared if they were occurring in NHL or CLL patients. All were all mild to moderate reactions except one patient developed severe reaction and withdrew from the study.

**Conclusions** Rapid Rituximab infusion is safe for NHL patients especially in a 90-minute regimen. However, it is not recommended for CLL patients due to lack of evidence.

**Implications for practice** 90-minute rapid Rituximab infusion with or without steroid premedication is recommended for NHL patient at second and subsequently infusions. No recommendations can be made in relation to stage of disease or the presence of bulky disease or leucocytosis particularly suitable for above regimen. It is not recommended, based on the current evidence, to use rapid Rituximab for CLL patients.

**Implications for research** Further research is needed on the role of monoclonal antibodies development in rapid infusion, especially in the second and subsequent cycles. Currently, this review broadly establishes that rapid Rituximab infusion over 90 minutes is safe for NHL patients. However, more research and detailed analysis is needed to develop more specific guidelines.

**Keywords** Rituximab, rapid infusion, Non-Hodgkin Lymphoma, Chronic Lymphocytic Leukemia, systematic review

## Background

Rituximab (Rituxan/Mabthera) is a chimerical monoclonal antibody that acts directly against the CD-20 antigen, a hydrophobic transmembrane protein located on the surface of normal and malignant B cells.<sup>1</sup> It was the first monoclonal antibody approved for cancer treatment by the Food and Drug Administration (FDA) in the United States (US) in 1997.<sup>2</sup> The FDA approved the use of Rituximab for 4 types of cancer patients<sup>3</sup> - patients with CD-20 positive, previously untreated, stage III/IV Follicular, B cell Non Hodgkin Lymphoma; patients with CD-20 positive, relapsed or refractory low grade or Follicular, B cell Non Hodgkin Lymphoma; patients with CD-20 positive, Diffuse Large B cell Lymphoma in combination chemotherapy; and patients with CD-20 positive, Chronic Lymphocytic Leukemia in combination chemotherapy. However, the use of Rituximab is rapidly expanding to other



diseases in addition to its application in cancer patients. There are ongoing clinical trials and research studies of Rituximab in non cancer conditions such as Multiple Sclerosis,<sup>4</sup> Refractory Thrombotic Thrombocytopenic Purpura,<sup>5</sup> Systemic Lupus Erythematosus,<sup>6</sup> Epidermolysis Bullosa Acquisita<sup>7</sup> and Rheumatoid Arthritis.<sup>8</sup>

The population of interest in this review was adult cancer patients with Non Hodgkin Lymphoma and Chronic Lymphocytic Leukemia. This is because these are the cancer populations approved by FDA to date. The other characteristics of the population such as performance status, presence of any co-morbidity and disease staging were also included in the review. The results from the review were treated separately with individual analysis for NHL and CLL.

There are 3 mechanisms commonly used to describe how Rituximab triggers binding between human's antibodies and tumour cells leading to cell death. Zhou et al<sup>9</sup> describes them as follows. The first mechanism is called antibody-Dependent Cellular Cytotoxicity (ADCC). When Rituximab's fragment antigen binding (Fab) domain binds to antigens on the surface of CD-20 cells, the human (fragment crystallisable) Fc domain of the drug is able to attract human immune effector cells, natural killer cells, monocytes and macrophages causing either cell lysis or phagocytosis. The second mechanism is called Complement-Dependent Cytotoxicity (CDC). The Fc domain of Rituximab activates the complement system leading to cell lysis. The third mechanism is called apoptosis (programmed cell death). Rituximab causes a direct effect against tumor activity through intracellular signaling pathways without activating the host immune system. The pharmacodynamics of Rituximab is described as follows: when Rituximab is infused at conventional rates intravenously, it is absorbed immediately, resulting in a rapid depletion of circulating B-lymphocytes. The drug is detected in the blood after completion of treatment 3-6 months later.<sup>10</sup> However, pharmacodynamics of rapid Rituximab infusion is as yet unknown, as there are no published studies examining the absorption, distribution and excretion of the drug to date.

Monoclonal antibodies, such as Rituximab, are known to cause infusion related adverse reactions.<sup>11</sup> Dillman<sup>12</sup> suggests that monoclonal antibodies react with circulating tumour cells which can lead to a reaction called cytokine release syndrome, or in more severe cases, cytokine storm. Cytokines are a group of polypeptide proteins<sup>13</sup> which are small cell signaling protein molecules that are secreted by the glial cells of the nervous system and by numerous cells of the immune system and are a category of signaling molecules used extensively in intercellular communication. Cytokines are produced and secreted by many cell types, especially macrophages and whenever cells are removed by the spleen or liver.<sup>12</sup> Examples of cytokines include; interleukins (IL), interferons (IFNs), tumour necrosis factors (TNF) and colony-stimulating factors (CSFs). The clinical presentation of cytokine release syndrome can include; fever, nausea, chills, hypotension, tachycardia, asthenia, headache, rash, scratchy throat, tongue and throat swelling and dyspnea.<sup>13</sup> A study<sup>14</sup> reported that the level of some cytokines (IL-6, IL-8, TNF- $\alpha$  and IFN- $\gamma$ ) can be correlated with adverse reactions in patients who have developed hypotension, hypoxemia or dyspnea. However, only the correlation for IL-8 was found to be statistically significant, with a p value = 0.02.<sup>14</sup> In contrast, levels of complement activation products such as CH50 and C3 have not shown any correlation with adverse reactions. Van Der Kolk et al<sup>15</sup> disagree with this finding as their study concludes that high levels of C3b/c can be associated with severe side effects. They reason that Rituximab causes rapid complement activation which is part of the immune system, leading to further activation of macrophages and mast cells, resulting in further release of C3b/c and C4b/c. These results should be treated with caution however, as the results are unpublished and the sample size is limited to 5 patients.

There are numerous risk factors contributing to cytokine release syndrome. High numbers of circulating CD-20 positive blood tumor cells are believed to be one of the major risk factors associate

with significant adverse reactions namely severe rigors, fever, bronchospasm, hypoxemia and thrombocytopenia.<sup>14</sup> Winkler et al<sup>16</sup> supports this finding as their study records peaks of TNF- $\alpha$  and IL-6 at 90 minutes in a cytokine release syndrome among patients with lymphocyte counts exceeding  $50.0 \times 10^9/L$ ,  $p=0.049$ . However, another study<sup>14</sup> shows contradictory findings and suggests that disease type, prior therapy, absolute tumor blood count number, extensive nodal involvement and tumor CD-20 expression may not be correlate with adverse reactions except increasing age,  $p=0.02$ .

In the literature, different terminologies are used to describe drug related reactions. For instance, adverse event,<sup>17, 18</sup> adverse reaction,<sup>19, 20</sup> and toxicity.<sup>21, 22</sup> Despite the variety of terms used, drug inserts<sup>1</sup> have adopted the National Cancer Institute (NCI) severity grading system in order to standardise reporting for adverse reactions. The most commonly used NCI severity grading scales are Common Toxicity Criteria (CTC)<sup>23</sup> or Common Terminology Criteria for Adverse Events (CTCAE)<sup>24</sup> using a scale of 0-4 for CTC or 1-5 for CTCAE. An example of CTC and CTCAE can be found in Appendix I. CTCAE is the revised version of CTC. In these tools, an adverse event is defined by any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medical treatment or procedure that may or may not be considered related to the medical treatment or procedure.<sup>24</sup> In this review, the term adverse reaction is most frequently used. However, other terms namely adverse event or toxicity is used where appropriate.

Rituximab related infusion reactions are very common. The incidence of first cycle of infusion related reactions has been reported as high as 77%, with 7% of being Grade 3 and 4 adverse events, and 33% with 2% Grade 3 and 4 adverse events at subsequent infusions.<sup>1</sup> In clinical trials, where Rituximab was infused at a standard rate (discussed later), the most common adverse reactions were infusion reactions such as; fever, lymphopenia, chills, infection, and asthenia for lymphoid malignancies. In treatment for CLL the most common adverse reactions are infusion reactions and neutropenia.<sup>3</sup> The infusion reactions have been described as hypotension, fever, chills, rigors, urticaria, bronchospasm, angioedema (sensation of tongue and throat swelling), nausea, fatigue, headache, pruritus, dyspnoea, rhinitis, vomiting, flushing and pain at the disease site.<sup>1</sup> Adverse reactions usually occur at the beginning of the first infusion within 30 minutes to 2 hours.<sup>1, 3, 11</sup> Other possible and more serious adverse reactions are tumour lysis syndrome (TLS), mucocutaneous reaction, progressive multifocal leukoencephalopathy, hepatitis B reactivation with fulminant hepatitis, infection, cardiac arrhythmias, renal toxicity, bowel obstruction and perforation.<sup>1, 3</sup>

Different types of acute adverse reactions and long term complications have been identified from the Rituximab standard rate infusion. However, very few studies have examined the long-term effect of rapid Rituximab infusion on patients' health. One study<sup>25</sup> monitored patients' cardiac function following a rapid Rituximab infusion starting at 50mg/hr and increasing gradually to 700mg/hr as a maximum rate. Thirty-two patients participated in the study and none showed any clinically relevant Electrocardiogram (ECG) alterations. Furthermore, there was no significant change in other measures of cardiac health (Troponin I levels or mean Left Ventricular Ejection Fraction (LVEF). However, mean levels of Brain Natriuretic Peptide (BNP - a polypeptide secreted by the ventricles of the heart in response to excessive stretching of heart muscle cells) were increased significantly after 24 hours of rapid Rituximab infusion. Although BNP increased significantly, they remained within the normal range with an exception of one patient. Therefore, the investigators concluded that the rise of the BNP was non-specific but fluid overload could not be ruled out. Another study<sup>25</sup> showed that 13 patients who received Rituximab in combination with Adriamycin-based chemotherapy had a decrease in LVEF >10% compared to their pre-treatment baseline 3 months later. These patients recovered normally,

but another 6 patients who had LVEF that decreased >15% compared to baseline levels, did not recover to an acceptable range. Adriamycin is known to cause cardiac toxicity.<sup>26</sup> The patients who had not received Adriamycin did not show a decrease in LVEF. The patients in the study were followed for up to two years. Patients who had the shown the decrease in LVEF following Rituximab treatment, did not show any episode of cardiac failure or signs and symptoms of cardiomyopathy after two years. Therefore, the investigators suggest that Rituximab may increase the risk of cardiac toxicity when combined with other drugs but otherwise had no severe clinical implication to patient's long term overall health.

For the purpose of this review, the primary outcome was the measurement of the presence or absence of acute adverse reactions, and their severity, on different scales or ranking frameworks proposed by the investigators of the primary studies. Examples of these adverse reactions include hypotension, fever, chills, rigors, urticaria, bronchospasm, angioedema (sensation of tongue and throat swelling), nausea, fatigue, headache, pruritus, dyspnoea, rhinitis, vomiting, flushing and pain at the disease site.

Rituximab can cause possible fatal adverse reactions. A very strict administration regimen<sup>3</sup> has been recommended by the pharmaceutical's manufacturers (Roche). The recommended initial rate for infusion is at 50mg/hr. If patients are able to tolerate the drug without any severe acute adverse reactions and vital signs are stable, the infusion rate can be gradually increased at 50mg/hr every 30 minutes to a maximum of 400mg/hr. When patients tolerate well for the first infusion, the subsequent infusion rate can be started at 100mg/hr and gradually increased at 100mg/hr every 30 minutes interval to a maximum rate of 400mg/hr. The dosage of Rituximab is calculated based on the patient's body surface area. The recommended dosage for the treatment of Lymphoma is 375mg/m<sup>2</sup> on Day 1 for each cycle up to 6-8 cycles.<sup>1</sup> The interval between cycles usually takes approximately 3 weeks. The recommended dosage for CLL is slightly different from NHL that 375mg/m<sup>2</sup> is prescribed on Day 1 at first cycle and followed by 500mg/m<sup>2</sup> for subsequent 5 cycles.<sup>1</sup> Therefore, with the regimen recommended by the pharmaceutical manufacturers, the initial and the subsequent duration for completion of the infusion in each cycle will take 5-6 hours and 3-4 hours respectively.<sup>3</sup>

The reason for the variation in the administration rate between the initial and subsequent infusion is because at the initial infusion, there is a rapid breaking down of the circulating B lymphocytes causing more adverse reactions to occur. In subsequent cycles, when the number of B lymphocytes has decreased in the blood stream, lesser adverse reactions arise.<sup>13</sup> As a result, it is safer for the subsequent infusion to run at a rapid rate. This also explains why patients may react to the first infusion, and have no severe adverse reactions to subsequent infusions.

For the purpose of this review, rapid Rituximab infusion is defined as Rituximab infusion completed in equal or to less than 120 minutes in the second or subsequent cycles of infusion. The most common rapid infusion rate is to complete in either 60<sup>17, 27</sup> or 90<sup>20, 25</sup> minutes.

In addition to the precautionary measures of closely monitoring the rate of infusion and vital signs monitoring, Paracetamol, Diphenhydramine<sup>13, 14, 17, 22</sup> and Corticosteroids<sup>20, 28</sup> are usually administered 30 minutes before Rituximab infusion with the aim of minimising infusion reactions. The treatment of Rituximab induced adverse reactions can be treated by simply stopping the infusion until all symptoms subside.<sup>11</sup> When patients develop chills and rigors, Corticosteroids and Pethidine/Meperidine are frequently administered to them. Other supportive treatments include oxygen support and the application of a heater blanket. When all the adverse reactions subside, Rituximab is restarted at the slower rate or half of the previous rate. In the event of patients experiencing a cytokine storm, which is considered as an oncology emergency, advanced therapy

such as epinephrine, bronchodilator, vasopressin<sup>11, 29</sup> is used and patients may be sent to the intensive care unit for close monitoring.

In 2009, statistics from the US showed that the number of people being diagnosed and living with NHL and CLL were 452,723 and 85,713 respectively.<sup>30</sup> So far, 1.5million of patients worldwide have been treated with Rituximab.<sup>20</sup> In 2004, a report showed that more than 1200 patients have received rapid infusions of Rituximab in Canada.<sup>31</sup> In addition, 20 independent NHS trusts from the United Kingdom (UK) were interviewed about their Rituximab administration policy and it was reported that 70% of second and subsequent Rituximab infusions were administered over 90 minutes and 5% over 60 minutes.<sup>20</sup> The diagnosis of NHL and CLL is continuously rising, partially due to increased life expectancy. Ageing is considered as one of the major risk factors for CLL.<sup>32</sup> Therefore, it is anticipated that many will require Rituximab as part of their treatment regimen. As a result, lengthy infusion has a great impact on health care providers; it challenges them to work within limited resources such as space constraints, human resources and long waiting times for patients to receive their treatment on schedule. In addition patients or insurance companies have to pay more for the long infusion hours as some medical centres charge treatment fees based on the duration of the infusion.<sup>17</sup>

As a result, many medical centres from different regions across the world including the US and Canada, Europe, the Middle East and Asia have conducted research studies<sup>18-20, 22, 25, 27, 31, 33-42</sup> to evaluate the feasibility and safety of rapid Rituximab infusion. All these studies are related to the safety of infusion rates with the assumption that the effectiveness of Rituximab is not compromised by the rate of infusion. Only one study examined both the effectiveness and safety of rapid Rituximab infusion concurrently.<sup>28</sup> The results suggest that rapid infusion is as effective as conventional rate infusion in patients with Diffuse Large B Cell Lymphoma, a subtype of NHL. The benefits of rapid Rituximab infusion are clearly evidenced in some of these studies.<sup>17, 19</sup> They demonstrate that rapid Rituximab infusion is safe and able to translate into cost saving, better resource utilisation and increased patients' satisfaction. However, one study<sup>43</sup> highlights the down side of the cost issue where the occurrence of the infusion reactions can require more staff time (33%) resulting in higher human resource costs. Nonetheless, the benefit of rapid Rituximab infusions has been well articulated in terms of cost savings and better resource utilisation without compromising effectiveness.

Randomised controlled trials (RCT) have been considered the gold standard to study harm.<sup>44</sup> However, the majority studies<sup>17, 19, 20, 22, 27, 28, 34, 35</sup> examining the tolerability and safety of rapid Rituximab infusion are case series. For the purpose of this review, the reviewer has considered both experimental and non-experimental studies that report on the definition, number, seriousness and severity of adverse reactions to rapid Rituximab infusion. Other factors considered include a clear description of the scale of measurement and the mode and timing of data collection on adverse reactions. The mode of data collection can be either active such as measurement of vital signs or passive through self-reporting from patients or both.<sup>44</sup>

Currently, there are no systematic reviews that examine how safe it is to administer Rituximab rapidly. This systematic review was undertaken in a timely manner to present the best available evidence to inform clinical practice. This is because overestimating a risk may inhibit an effective treatment that can potentially provide a cure and improve quality of life. Conversely, underestimating a risk may cause health care providers especially doctors and nurses to be caught unprepared with potential adverse reactions that endanger patients' lives.

## Review objective

The objective of this review is to critically appraise, synthesise and present the best available evidence related to the safety of rapid Rituximab infusion among adult patients with NHL and CLL.

### Review questions

The specific review questions to be addressed were:

1. What is the frequency of acute adverse reactions from rapid Rituximab infusion?
2. How severe are the acute adverse reactions from rapid Rituximab infusion?
3. What are the treatments for patients if they develop acute adverse reactions from rapid Rituximab infusion?
4. What is the mortality rate of patients who develop acute adverse reactions from rapid Rituximab infusion?
5. What are the types, dosages and routes of administration of premedication given to patients prior to rapid Rituximab infusion?

## Criteria for considering studies for this review

### Types of studies

This systematic review considered experimental, quasi-experimental and observational studies that report on the definition, number, seriousness and severity of adverse reactions of Rituximab at rapid infusion rates.

### Types of participants

The participants of interest included adults 18 years old and above, scoring between 0-4 in the Eastern Cooperative Oncology Group Performance Status (ECOG), with any co-morbidity including but not limited to cardiac and respiratory diseases and one of the following diagnosis:

- 1) Non-Hodgkin lymphoma
  - a. Based on histology findings of any stage from I to IV based on Ann-Arbor staging<sup>45</sup>
  - b. Any subtypes including but not limited to Diffuse Large B Cell Lymphoma (DLBCL), Follicular Lymphoma, Mantle Cell Lymphoma (MCL) and Burkitt's Lymphoma
  - c. Who receive Rituximab as monotherapy or combination with any types of chemotherapy including but not limited to CHOP (Cyclophosphamide, Doxorubicin, Vincristine and Prednisone), and CVP (Cyclophosphamide, Vincristine and Prednisone)
  - d. Prior exposure to Rituximab infusion
- 2) Chronic Lymphocytic Leukemia
  - a. Based on cytology or phenotype findings
  - b. Any stage from O-IV based on Rai classification or any stage from A-C based on Binet staging<sup>46</sup>
  - c. Who receive Rituximab as monotherapy or combination with any types of chemotherapy including but not limited to Fludarabine, and FC (Fludarabine, Cyclophosphamide)
  - d. Prior exposure to Rituximab infusion

Patients who were diagnosed with autoimmune diseases such as Thrombotic Thrombocytopenic Purpura (TTP), Autoimmune Haemolytic Anaemia (AIHA), Systemic Lupus Erythematosus, Epidermolysis Bullosa Acquisita(EBA) and Rheumatoid Arthritis(RA) were excluded from this review as they are autoimmune diseases, and their pathogenesis is different from cancer.

### ***Types of interventions***

The intervention of interest was rapid Rituximab infusion to be completed in equal or to less than 120 minutes, not limited to 60 or 90 minutes at the second and subsequent cycles with a range of 4-8 cycles of treatment.

### ***Comparators***

The comparator group was any Rituximab infusion rates of more than 120 minutes or without a comparison group.

### ***Types of outcome measures***

The primary outcomes measures of interest were:

- a. Frequency, type and severity of acute adverse reactions
- b. Cycles of infusion completed by the number of patients without acute adverse reactions
- c. Types, dosages and route of administration of premedication including but not limited to PO Paracetamol 1g, IV Diphenhydramine 25mg and IV Hydrocortisone 100mg

The secondary outcomes measures of interest were:

- a. Number of patients who continue the rapid Rituximab infusion regardless of acute adverse reactions
- b. Number of patients who discontinue from the study due to adverse reactions
- c. Type of treatment rendered to patients after acute adverse reactions
- d. All causes of mortality including death caused by the underlying diseases or treatment related

## **Review methods**

### **Search strategy**

Before undertaking this systematic review, the Cochrane Library, Joanna Briggs Institute Library of Systematic Review, MEDLINE and the Database of Abstracts and Review were searched and no systematic reviews on this topic were found.

The search strategy aimed to find both published and unpublished studies. A three step search strategy was developed to guide the systematic review. MESH terms from Pubmed were used to determine the words used to search in MEDLINE and CINAHL. The first search from MEDLINE and CINAHL was undertaken followed by analysis of the text words contained in the title and abstract, and the text terms used to describe the article. A second search used all the identified keywords and index terms to search across all accessible databases and websites. As some databases are different in their search features, search terms were slightly different between the databases. The search strategy focused only on the inclusion of the intervention "rapid Rituximab infusion" appearing in the title or abstract. Thirdly, the relevant lists of all identified reports and articles were searched for

additional studies. (Appendix II)

Rituximab was approved for therapeutic use by the FDA in 1997. Therefore, the search started from 1997 until October 2010 with no language restrictions. For the studies that were published in other languages such as Dutch, reviewers from Joanna Briggs Institute Collaborating Centers in Belgium were asked to assist in critical appraisal and data extraction.

The primary authors were contacted for further details of studies when abstracts were found in conference proceedings.

Databases searched included the following:

- a. Pubmed
- b. Web of science
- c. Scopus
- d. Cochrane Central Register of Controlled Trials
- e. Science Direct
- f. CINAHL
- g. Scifinder
- h. Mednar

In addition, Loke et al<sup>47</sup> from Cochrane Adverse Effects Methods Group recommend an exhaustive search for adverse affects which includes the following resources.

- a. FDA post market drug safety information  
<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/default.htm>
- b. European Public Assessment Reports from the European Medicines Evaluation Agency  
[http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar\\_search.jsp&jse-enabled=true](http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&jse-enabled=true)
- c. Current Problems in Pharmacovigilance  
<http://www.mhra.gov.uk/Publications/Safetyguidance/CurrentProblemsinPharmacovigilance/index.htm>
- d. Australian Adverse Drug Reactions Bulletin <http://www.tga.gov.au/adr/aadrb.htm>
- e. Roche <http://www.roche-australia.com/portal/eipf/australia/au/corporate>
- f. Agency for Healthcare Research and Quality (AHRQ) <http://www.ahrq.gov>
- g. Health Technology Assessment Programme (HTA) <http://www.hta.ac.uk>
- h. US National Institutes of Health, ClinicalTrials.gov <http://www.clinicaltrials.gov>

The key words used in the initial search were Rituximab, Rituxan, Mabthera, rapid and infusion. Endnote was used to manage the returned results.

## Method of the review

After detailed examination, those articles that appeared to match the inclusion criteria were appraised by 2 reviewers independently. They assessed the methodological validity of the articles prior to inclusion in the review using the standardised critical appraisal instruments from the Joanna Briggs Institute Meta Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI). (Appendix III ) Any disagreements that arose between the reviewers were resolved through discussion with a third reviewer.

## Data collection

Data were extracted from the non-experimental studies that “passed” critical appraisal using standardised data extraction tools from the JBI-MAStARI. (Appendix IV)

## Data synthesis

The included primary studies were case series studies with only a single group in each study. Therefore, for the purposes of this review, the effect size from the pooled results was presented using proportional meta-analysis using Stats Direct (statistical software).<sup>48</sup> In this analysis, the software transforms proportions to logits, which can take any numerical value.<sup>49</sup> The pooled proportion is calculated based on Der Simonian and Laird weights for the random effects model.<sup>48</sup> Statistical heterogeneity was assessed using Cochran Q.<sup>48</sup> When statistical pooling was not possible, the findings are presented in a narrative summary.

## Results

### Description of studies

A total of 2079 and 294 studies were retrieved from 8 commercially published and Grey literature electronic databases respectively. An additional study was found through the reference lists to give a total of 2374 studies. Of these, 672 duplicated studies were removed. The remaining 1702 study titles and abstracts were examined for a match with the inclusion criteria and it was found that 1663 studies were either irrelevant or incongruent with the inclusion criteria. Only 39 studies appeared to match the inclusion criteria and full texts were retrieved for further examination. After detailed examination, 13 studies qualified for inclusion based on methodological quality assessment and 23 studies were excluded. A further three clinical trials<sup>50-52</sup> appeared to match the inclusion criteria but they were not included in this review as the results will not be published until the end of 2010 or early 2011. One study was available in Dutch. Therefore, this report was sent to the Joanna Briggs Institute's Collaborating Centre in Belgium for critical appraisal. The Dutch study<sup>53</sup> was excluded because approximately one third, 29.4% out of 17 patients, were treated for either AIHA or Idiopathic Thrombocytopenic Purpura (ITP). These are autoimmune diseases and were not included in the review inclusion criteria. The remaining 22 studies were published in the English language and were excluded after detailed examination. They were discussion papers,<sup>21, 54-57</sup> duplicated studies<sup>58-65</sup> and incongruent with the review inclusion criteria related to population,<sup>40, 53</sup> intervention<sup>14, 33, 35, 41, 42, 66</sup> or outcome measures<sup>25, 34</sup>. Figure I details the process of study selection for this review. All 13 included studies scored at least 5 out of 9 criteria during methodological assessment using the JBI-MAStARI appraisal instrument. Therefore, 13 studies were included in this review for analysis. Details of the studies included in the review are presented in Appendix V. Studies excluded from the review and reasons for their exclusion are detailed in Appendix VI.



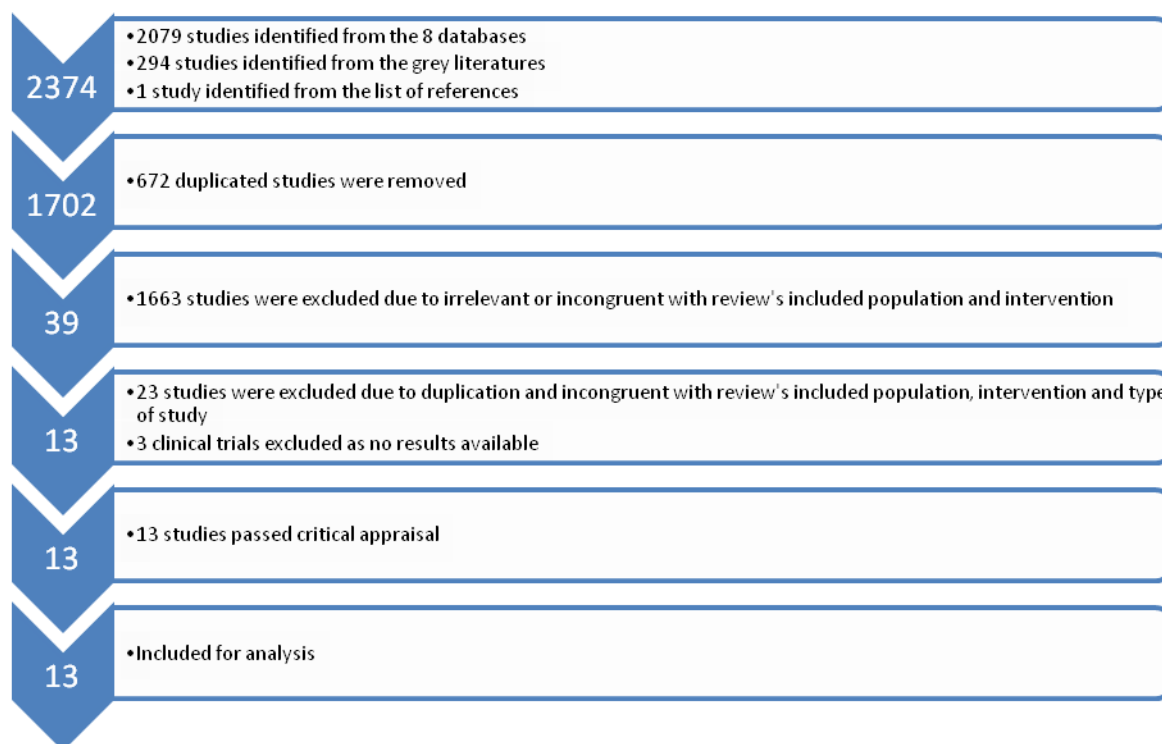


Figure I Process of study selection

**Methodological quality**

All the 13 included studies in the analysis were observational studies. Each study design was case series without a comparison group. Each used convenience sampling depending on the availability of the patients that sought treatment at the study site. The sample definition was reported based on age, diagnosis and treatment regimen. The other characteristics of patients were identified including type of premedication, especially steroids usage, presence of bulky disease (>7cm) or advance stage III & IV diseases and presence of leucocytosis (Total White Blood Cells of >25,000). Although some of the studies did not mention the name of the instrument used to measure the outcomes, they reported adverse reactions using Grades, which could imply the use of NCI CTC or NCI CTAE. These are standard tools used globally for grading adverse events.

This review focused on the acute adverse reaction of rapid Rituximab infusion, therefore, studies that reported adverse reactions during the infusion and the subsequent 1-2 hours following completion were included. Only one patient withdrew from the rapid infusion regimen but was included in the analysis due to a Grade 3 adverse reaction. Some of the outcome measures were determined objectively using a thermometer or a manual or digital sphygmomanometer. However, the majority of these outcomes were measured subjectively and depended on patients' self-reporting and observations made by the nurses in charge of the Rituximab infusion. Descriptive analyses were used to describe patient characteristics, numbers of patients and numbers of cycles of rapid Rituximab infusion completed by the patients. Reports on the type of adverse reaction, description of the treatment rendered to patients who developed adverse reaction and the outcome after the treatment were also included.

Patient diagnosis was clearly reported by the included studies (Appendix VII). 753 patients were included in the analysis with the majority being NHL, n= 722 (96%), followed by CLL, n= 15 (2%) and other diagnoses n= 16 (2%) that were not stated in the inclusion criteria. However, these 16 patients

with other diagnoses were decided to be included in the review because the result of frequency of adverse reactions was not reported based on individual diagnosis. Only 2 studies<sup>17, 39</sup> reported patient Eastern Cooperative Oncology Group (ECOG) scoring and one study<sup>17</sup> presented patients' co morbidities such as hypertension and diabetes. Four studies<sup>19, 25, 37, 39</sup> described the stage of the patients diseases. Three studies<sup>25, 27, 39</sup> reported the presence of bulky disease and 6 studies<sup>18, 19, 25, 27, 31, 37</sup> identified if the patients were in a stage of leucocytosis during rapid Rituximab infusion. Most studies<sup>17-19, 22, 25, 27, 28, 31, 36-39</sup> stated the type of chemotherapy regimens used except in one study<sup>20</sup> which did not mention it in the report.

Two common rapid Rituximab infusion regimens were reported by the majority of the included studies. The first rapid Rituximab infusion regimen was infused over 30 minutes for 20% of the total dose at the beginning. When the patients tolerated the infusion well, the remaining 80% was infused over 60 minutes. Therefore, the total duration of infusion was in 90 minutes. Ten studies<sup>17-19, 22, 27, 28, 31, 37-39</sup> used a 90-minute regimen and the remaining 3 studies used 60-minute regimen. There were two methods of rapid Rituximab infusion over 60 minutes. The first study<sup>25</sup> used a constant rate throughout 60 minutes. The second study<sup>36</sup> used the rate of 100mg/hr for the first 15 minutes. When patients tolerated the infusion well, the rate was increased to 500mg/hr. The third study<sup>20</sup> did not explain how the Rituximab was administered rapidly over 60 minutes.

The adverse reactions were measured by NCI CTC version 2<sup>22</sup> or 3<sup>25</sup> or CTCAE version 3<sup>19, 37</sup> in 5 studies and one study<sup>28</sup> did not specify the version used. The type of adverse reactions were clearly described in 6 studies<sup>17, 18, 22, 25, 38, 39</sup>. Among those studies that reported adverse reactions, 5<sup>17, 18, 25, 37, 39</sup> specified the exact time of the occurrence of the adverse reactions and 4<sup>17, 18, 22, 37</sup> clearly described the management of the adverse reactions.

All the studies<sup>17-20, 22, 25, 27, 28, 31, 36-39</sup> reported the use of antipyretic and antihistamine as part of the premedication regimen before rapid Rituximab infusion. A slight variation was noted across all these studies in term of their route of administration and dosage. Seven studies<sup>18-20, 28, 38, 39</sup> also included administered steroids.

The majority of the studies<sup>17, 19, 22, 25, 27, 28, 31, 36, 37, 39</sup> were conducted in outpatient or ambulatory settings in different countries including Saudi Arabia, Singapore, the United States, Ireland, the United Kingdom, Spain, Argentina, France and Denmark. Only one study<sup>18</sup> was conducted in both inpatient and outpatient settings. Two studies<sup>20, 38</sup> did not state the research setting in their reports.

## Results

A total 753 patients were included in the review. They completed a total of 2298 cycles of rapid Rituximab infusion. A total of 23 acute adverse reactions were reported in the studies. Of these 23 reactions, 12 were Grade 1 and 5 were Grade 2 adverse reactions occurred in NHL patients. Seven of the Grade 1 adverse reactions were reported in 90-minute regimen and the remaining 5 were reported for the 60-minute regimen in NHL group. No Grade 3 or 4 acute adverse reactions were reported in the NHL population. There was only one Grade 1 adverse reaction occurred in 60-minute regimen in one CLL patients. There were 5 occurrence of adverse reactions were not clearly reported in either NHL or CLL group. Of these 5 adverse reactions, 4 were Grade 1 and 1 was Grade 3 adverse reactions in 90-minute regimen. (Table I)

**Table I Frequency and severity of acute adverse reactions in Non Hodgkin Lymphoma (NHL) and (Chronic Lymphocytic Leukemia (CLL) patients in 90 and 60 minute- regimen**

Population	Regimen	Study	Grade				Total number of adverse reactions	Total number of patients	Total number of cycles
			1	2	3	4			
NHL	90 min	Al Zahrani 2009					0	21	126
		Chiang 2010	2	2			4	79	269
		Corey 2007		1			1	46	135
		El Agnaf 2007					0	17	73
		Gibbs 2007					0	61	250
		Salar 2006	1	1			2	70	319
		Sehn 2007	1				1	205	565
		Statham 2006	1	1			2	23	62
		Soria 2008	2				2	37	-
		NHL	60 min	Provencio 2006	5				5
Tuthill 2009							0	54	105
CLL	90 min	Milone 2007	4		1		¥ 31	67	
	60 min	Aurran 2005	1				1	69	94
		Total	17	5	1		23	753	2298

¥ Among 31 patients, 4 were CLL and 27 were NHL. It was not stated in which group of patients that the 5 adverse reactions occurred. Several attempts were made to contact primary authors, but they were not contactable.

Grade 1: Intervention not indicated

Grade 2: Non-urgent medical intervention indicated

Grade 3: Hospitalisation indicated

Grade 4: Life threatening and urgent medical intervention indicated

The most commonly reported acute adverse reactions were rash (5 patients) followed by fever and chills (4 patients); abdominal pain (4 patients); nausea and vomiting (3 patients); sore throat (1 patient) and hypotension (1 patient). However, 1 study did not specify the type of reaction. Rash, fever and chills were more prominent among NHL patients. (See Table II). It was unclear either CLL or NHL patients complained more of abdominal pain. The onset of acute adverse reactions ranged from 30 minutes into the infusion to immediately post rapid Rituximab infusion. Treatments were not needed for Grade 1 adverse reactions as they were usually self-limiting. For Grade 2 adverse reactions, interruption of the rapid infusion temporarily and supplement of additional drugs namely antiemetic, antihistamine and opioid eased the symptoms. Only one patient withdrew from the 90-minute rapid Rituximab regimen because of abdominal pain. (Table III) No deaths were reported in any of the studies.

**Table II Type, time of event and treatment of adverse reactions in Non Hodgkin Lymphoma (NHL patients)**

	Study	Grade of Adverse Reaction	Type of Adverse Reaction	Time of Event	Treatment of Adverse Reactions	Withdraw from Study		
						Death		
NHL	Chiang 2010	1	Nausea & vomiting	Immediately post rapid infusion	Not stated	No		
		1	Nausea & vomiting	Immediately post rapid infusion	Not stated	No		
		2	Nausea & vomiting	70 min into the infusion	IV Metoclopramide given	No		
		2	Chills & rigors	45 min into infusion	IV Diphenhydramine 25mg given and restarted infuse at a slower rate	No		
	Corey 2007	2	Rigors & back pain	5 min post rapid infusion	Meperidine 12.5mg given	No		
	Salar 2006	1	Abdominal discomfort	30 min into infusion	No intervention, the symptoms resolved spontaneously	No		
		2	Sore throat	30 min into infusion	Infusion rate was reduced	No		
	Sehn 2007	1	Unclear	Unclear	Unclear	No		
	Statham 2006	1	Hypotension	Unclear	No intervention	No		
		2	Rash	Unclear	Rapid infusion was discontinued temporary and antihistamine was given	No		
	Soria 2008	1	Skin erythema	During rapid infusion	Not stated	No		
		1	Skin erythema	During rapid infusion	Not stated	No		
	60 min	Provencio 2006	1	Fever	During rapid infusion	Not stated	No	
			1	Chills	During rapid infusion	Not stated	No	
			1	Chills	During rapid infusion	Not stated	No	
			1	Rash	During rapid infusion	Not stated	No	
			1	Rash	During rapid infusion	Not stated	No	

**Table III Type, time of event and treatment of adverse reactions in Chronic Lymphocytic Leukemia (CLL) patients**

Population	Regimen	Study	Grade of Adverse Reaction	Type of Adverse Reaction	Time of Event	Treatment of Adverse Reactions	Withdraw from Study Death
CLL	90 min	Milone 2007 <sup>∞</sup>	1	Hypotension	Not stated	Not stated	No
			1	Chest pain	Not stated	Not stated	No
			1	Abdominal pain	Not stated	Not stated	No
			1	Abdominal pain	Not stated	Not stated	No
			3	Abdominal pain	Not stated	Not stated	Yes
	60 min	Aurran 2005	1	Not stated	Not stated	Not stated	No

<sup>∞</sup> This study consisted of both NHL and CLL patients. It was not stated which group of patients developed acute adverse reactions

All the studies used antipyretics, namely Acetaminophen/Paracetamol as a premedication for rapid Rituximab infusion. The dosage of the medication ranged from 375 mg to 1000mg either in the form of tablet(s) or injection. The most common antihistamine was either oral or parenteral Diphenhydramin 25-50mg followed by parenteral Chlorphenamine 10mg, oral Dexchlorpheniramine 5mg and oral Hydroxyzine 20mg. The common choice of steroids was parenteral Hydrocortisone 100mg, Prednisolone 100mg and Metylprednisolone. (See Table IV)

**Table IV Type, name, route and dosage of premedication used in the Non Hodgkin Lymphoma (NHL) and Chronic Lymphocytic Leukemia (CLL) patients**

Population	Regimen	Study	Antipyretic			Antihistamine			Steroids		
			Route	Name	Dosage (mg)	Route	Name	Dosage (mg)	Route	Name	Dosage (mg)
NHL	90 min	Al Zahrani 2009	PO	Paracetamol	1000	PO	Hydroxyzine	20	NS	NS	NS
		Chiang 2010	PO	Paracetamol	1000	IV	Diphenhydramine	25	NS	NS	NS
		Corey 2007	PO	Acetaminophen	625	IV	Diphenhydramine	25-50	NS	NS	NS
		El Agnaf 2007	PO	Acetaminophen	1000	IV	Chlorphenamine	10	IV	Hydrocortisone	100
		Gibbs 2007	PO	Paracetamol	1000	NS	Chlorphenamine	8	NS	Prednisolone	100
		Salar 2006	NS	Acetaminophen	NS	NS	Diphenhydramine	NS	NS	Methylprednisolone	NS
		Sehn 2007	PO	Acetaminophen	375	PO	Diphenhydramine	50	NS	NS	NS
		Statham 2006	NS	Paracetamol	NS	NS	Chlorphenamine	NS	NS	NS	NS
		Soria 2008	IV	Paracetamol	1000	PO	Dexchlorpheniramine	5	PO	Steroid	40
		Provencio 2006	IV	Paracetamol	1000	PO	Dexchlorpheniramine	5	NS	NS	NS
CLL	90 min	Tuthill 2009	PO	Paracetamol	1000	IV	Chlorphenamine	10	IV	Hydrocortisone	100
		Milone 2007	PO	Paracetamol	NS	IV	Diphenhydramine	NS	IV	Hydrocortisone	NS
CLL	60 min	Aurran 2005	NS	Paracetamol	NS	NS	Diphenhydramine	NS	NS	Steroids	NS

Abbreviations: PO - Per Oral; IV - Parenteral; NS - Not Stated

### Meta-analysis of NHL patients in 90-minute regimen

The aim of this review was to examine the incidence and severity of acute adverse reactions from rapid rituximab infusion. To account for possible heterogeneity present due to variations within the interventions, a random effects model was used. Meta-analysis of proportions was performed using random effects model (DerSimonian-Laird) showed a pooled proportion of (95%CI, 0.012-0.055) among 11 studies of 653 NHL patients. In other words, 3% of acute adverse reactions were reported among 653 NHL patients in 2137 cycles of rapid Rituximab infusions. (Figure II) Significant heterogeneity was detected in the 11 studies,  $p=0.01, I^2=56.9%$  (95%CI, 0%-76%) (Box I) In account of this heterogeneity, 2 studies that utilised a 60-minute regimen were removed. The subsequent analysis that used random effects model, the non-combinability test shows homogenous of studies,  $p=0.0955$  and  $I^2=40.8%$  (95%CI, 0%-71.3%) (Box II) Therefore, the pooled proportion in the 9 studies of a 90- minute rapid Rituximab infusion regimen among 559 patients in 1855 cycles is 0.026, equilibrium of 2.6%. (Figure III).

Bias assessment plot is performed to detect any publication bias among the studies that could possibly skew the results. In both analyses that performed in the 11 and 9 studies, the studies were symmetrically distributed under the funnel plots. The statistical test, Harbord bias further confirmed the absence of publication bias,  $p=0.25$  in Plot I and  $p=0.30$  in Plot II respectively.

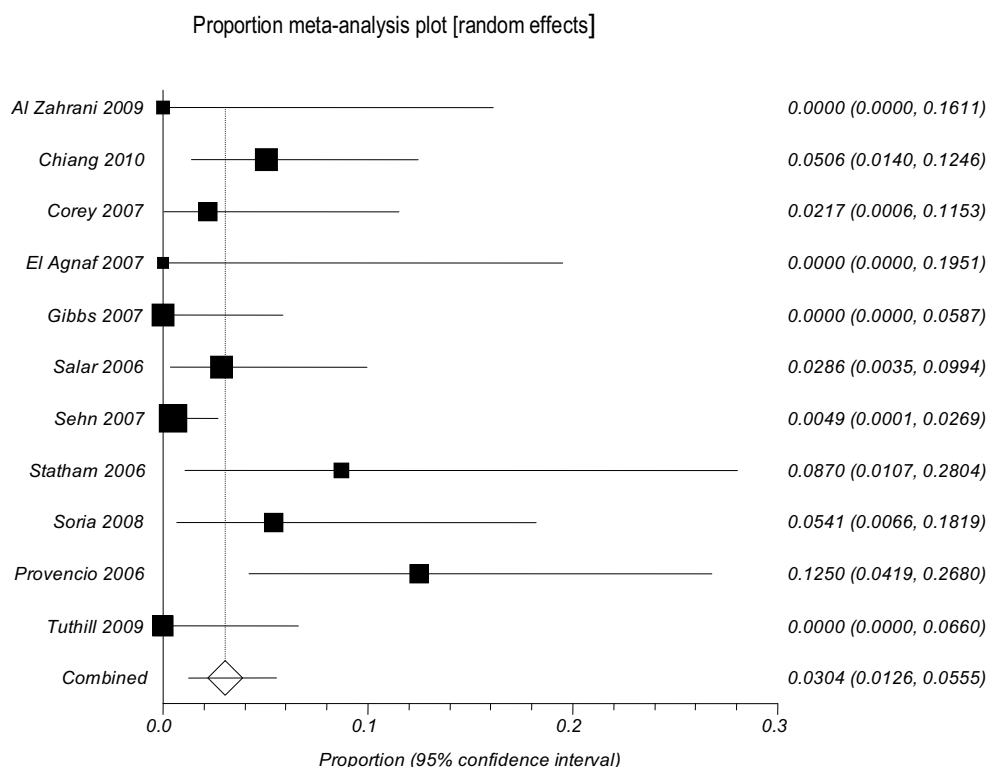
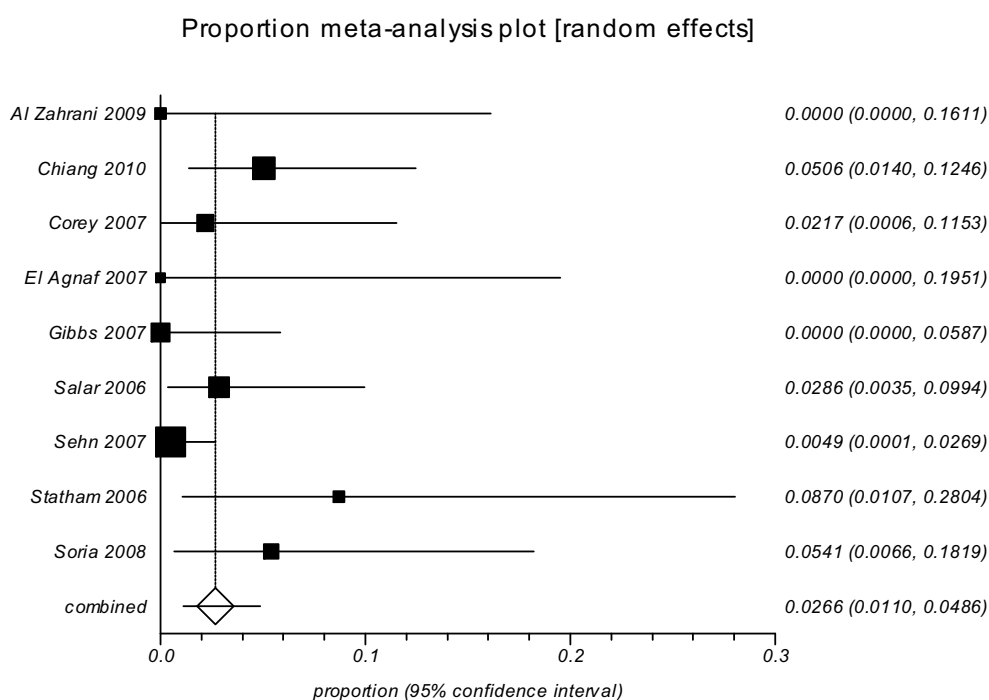


Figure II Proportion meta-analysis of acute adverse reactions in 11 studies (combination of both 90 and 60 minute- regimen) among Non Hodgkin Lymphoma patients

Cochran Q = 23.202124 (df = 10) P = 0.01  
 Moment-based estimate of between studies variance = 0.023475  
 I<sup>2</sup> (inconsistency) = 56.9% (95% CI = 0% to 76.4%)

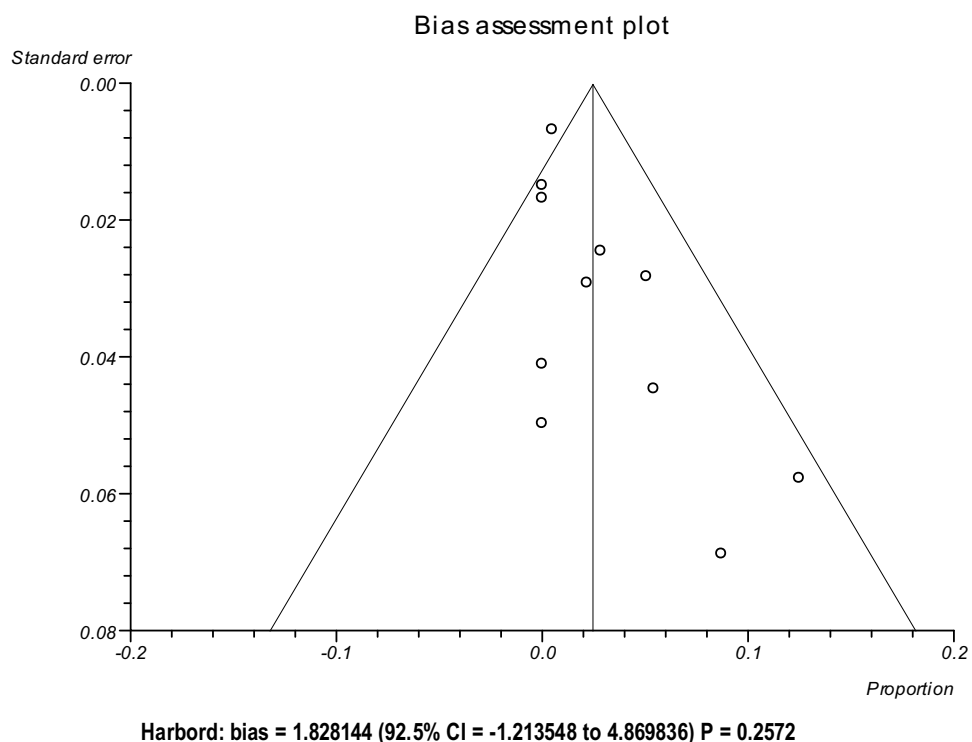
**Box I Non-combinability of studies for 11 studies (combination of 90 and 60-minute regimen)**



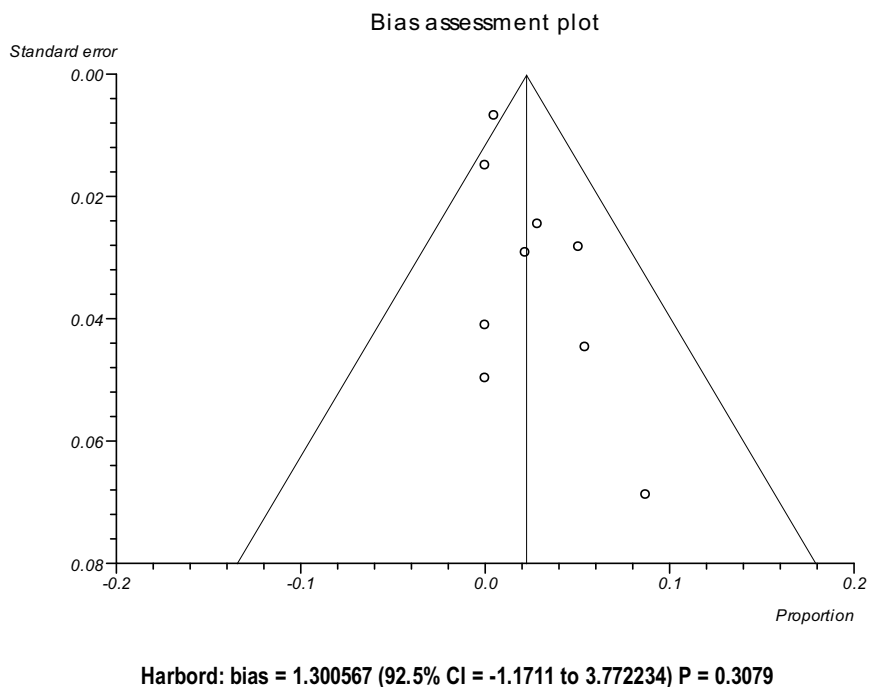
**Figure III Proportion meta-analysis of acute adverse reactions in 9 studies (90-minute regimen) in Non Hodgkin Lymphoma patients**

Cochran Q = 13.510486 (df = 8) P = 0.0955  
 Moment-based estimate of between studies variance = 0.012044  
 I<sup>2</sup> (inconsistency) = 40.8% (95% CI = 0% to 71.3%)

**Box III Non-combinability of 9 studies (90-minute regimen)**



**Plot I Bias assessment plot and indicator for 11 studies (combination of 90 and 60-minute regimen) in Non Hodgkin Lymphoma patients**



**Plot II Bias assessment plot and indicator for 9 studies (combination of 90-regimen) in Non Hodgkin Lymphoma patients**



## Summary of Non Hodgkin Lymphoma patients in 60-minute rapid Rituximab regimen

Two studies were included in this review for NHL patients undergoing a 60-minute rapid Rituximab regimen. In the Provencio et al study,<sup>25</sup> 5 of the 40 patients who completed 233 cycles of rapid Rituximab infusions developed Grade 1 adverse reactions. The adverse reactions were fever, chills and rash that occurred during the rapid Rituximab infusions. The treatment for these reactions was not stated. No patients withdrew from the study. No steroids were used as part of the premedication regimen. In the Tuthill et al study,<sup>20</sup> no adverse reaction was reported among 69 patients who completed 94 cycles of rapid Rituximab infusions. In this study, parenteral Hydrocortisone 100mg was used as part of the premedication.

## Summary of Chronic Lymphocytic Leukemia patients in 90 and 60-minute rapid Rituximab regimen

Only 2 studies included CLL patients and meta-analysis was not possible for the studies as 1 study used a 90 and the other a 60-minute regimen. In Milone et al study,<sup>38</sup> 4 patients were CLL and 27 patients were NHL who completed 67 cycles of rapid Rituximab infusion. 4 Grade 1 acute adverse reactions were reported, although it was unclear which patients developed the adverse reactions. One patient from this study developed a Grade 3 adverse reaction in a 90-minute regimen. It was unclear that which group of patients developed adverse reactions. Several attempts were done to contact primary authors for more details but to no available. The treatment for these adverse reactions was not stated in the study. Parenteral Hydrocortisone 100mg was used in the premedication.

In Aurran et al study,<sup>36</sup> there were total number of 69 patients completed 94 cycles of rapid Rituximab infusions. 11 patients were CLL, the rest were 27 DLBCL, 22 FL, 2 Mantle Cell Lymphoma (MCL), 3 Marginal Zone Lymphoma (MZL), 2 Lymphoplasmocytic, 1 Castelman Disease and 1 Idiopathic Thrombocytopenia Purpura. In this study, it was clearly stated that the only one patient who developed Grade 1 acute adverse reaction was CLL patients. The type and treatment of the adverse reaction was not stated in the study. A steroid was used in the study but there was no mention of its specification.

## Discussion

The pooled meta-analysis strongly suggests that rapid Rituximab infusion is safe for NHL patients especially in relation to a 90-minute regimen. Patients tolerated rapid infusions well with 2.6% of mild acute adverse reactions reported as compared to 33% in the standard rate at the second and subsequent infusion.<sup>1</sup> Although only 2 studies included in the review for a 60-minute regimen, the findings also suggests this regimen is safe for patients, with only 5 Grade 1 adverse reactions recorded. A possible contributor to such outcomes could be the use of steroids before starting the rapid infusion. The absence of bulky disease and leucocytosis may also result in lesser adverse reactions. However, there is no increase in acute adverse reactions in the patients who did not receive steroids as part of the premedication. Furthermore, there is no analysis available from the primary studies to segregate patients who developed acute adverse reactions based on their disease's characteristics. Therefore, the exact reasons for the low incidence of adverse reactions are unclear.

Of the 653 patients that were included in the NHL arm (11 studies), 12 (1.8%) patients were not clearly classified into a diagnosis of NHL. Some were Hodgkin Disease (HD), Post transplant

Lymphoproliferative Disorder (PTLD), Immune Mediated Thrombocytopenias and Immune Cytopenia. However, 1.8 % of variation in diagnosis does not appear to contribute to the heterogeneity of the population. Initially, heterogeneity was detected in combination with 90 and 60-minute regimens in the 11 studies. Population characteristics were checked for any heterogeneity such as age, diagnosis, presence of bulky disease or leucocytosis but none of these appear to have contributed to the heterogeneity across the studies. The studies became homogenous when 2 of the studies using a 60-minute regimen were removed.

There are three bias indicators available in Stat Directs for the assessment of publication bias. In this meta-analysis, Harbord was chosen over Begg-Mazumdar (Kendall's tau) and Egger to assess publication bias. This is because Harbord is able to maintain the same power as Egger to assess bias yet reducing any false positive rates.<sup>48</sup> Examples of false positive rates are studies with large treatment effects or fewer events.<sup>48</sup> In this systematic review, the frequency of acute adverse reactions was considered as a rare event. Begg-Mazumdar (Kendall's tau) has lesser assumptions to fulfill and is inferior to Egger in its sensitivity.<sup>48</sup> Similar to Egger, it has low power to detect publication bias with small number of studies.<sup>48</sup> Therefore, Harbord was more suitable for detecting publication bias than Begg-Mazumdar (Kendall's tau) and Egger. In this review, no publication bias detected that offered greater objectivity of the results published from the included studies.

The evidence for the use of rapid Rituximab infusion among CLL patients is to be interpreted with caution. The review seems to suggest that rapid Rituximab infusion is safe for CLL patients with only 6 Grade 1 adverse reactions reported. However, 2 primary studies had included other diagnosis other than CLL. Furthermore, the total patients for analysis were 73 with only 15 were CLL patients. Therefore, the evidence is weak to support rapid Rituximab infusion in CLL patients especially due to small sample size and unspecific results.

Choices of premedication are fairly consistent across the studies with some variation on the trade name, dosage and route of administration. All the studies followed the pharmaceutical manufacturer's guidelines for the administration of premedication to counteract any possibly adverse reactions such as fever. However, it is uncertain if any type of premedication particularly helps in preventing or reducing adverse reactions.

From this review, the majority of acute adverse reactions were Grade 1 and self-limiting. Therefore, according to NCI CTC or CTCAE, no specific interventions are needed except that patients continue to be monitored closely. However, there was one study<sup>18</sup> which graded 1 on patient's symptoms where treatment was provided. Therefore, the reviewer has amended the grading to 2 before performing meta-analysis. Although many studies stated that NCI CTC or NCI CTCAE instruments were used to measure adverse reactions, inconsistency among the raters was apparent. Of the acute adverse reactions reported in the studies, not all were serious. Rash, nausea and vomiting are not life threatening. They can be managed sufficiently with additional antihistamine or anti nausea and anti vomiting. Other adverse reactions such as fever and chills can lead to medical emergency if IV Pethidine was used. This is because the side effect of IV Pethidine is hypotension which can become a serious issue if the patient does not respond to the interruption of the infusion or to fluids challenge. Adrenaline and Dopamine may be used in such cases. Chest pain may lead to cardiac arrest. A series of investigations will usually be carried out to establish the cause of chest pain. In the clinical setting, whenever a patient develops a sign or symptom of adverse reaction, they are generally closely monitored to ensure patients' safety and early detection of complications. All of these acute adverse reactions occurred mostly within a 30 minute to 90-minute infusion, which produced similar results from to the standard rate of infusion.

Although all of the studies' involved case series design, the description of the methodologies was consistent and almost identical across the studies. They all defined the patients' characteristics and administered two or more premeditations followed by rapid Rituximab infusion. During and after the infusion, they recorded any adverse reactions related to the rapid infusion based on either vital signs or patient self-report. Despite the high quality of case series studies, an inherent risk of bias moderates the degree to which the findings can be applied. Therefore, the 3 clinical trials currently in progress will add significantly to the validity of the conclusions drawn in this review from case series studies.

In the process of undertaking this systematic review, the reviewer observed frequent duplication of studies<sup>19, 60, 61</sup> published in different journals with the same authors in the team. Such a situation reinforces the importance of systematic reviews that involve clear and specific inclusion and exclusion criteria, a comprehensive search strategy, vigorous critical appraisal processes, standardised data coding and extraction, and the generation of conclusions that draw directly from analysis of the results of included studies to identify valid evidence to guide clinical practice.

### **Limitation**

There were a small number of observational studies identified in the search (Appendix V) that aimed to establish the safety of rapid Rituximab infusion. The findings of these studies have suggested that rapid Rituximab infusion is safe. However, they were excluded because of incongruence with the review's inclusion criteria or because the primary investigators were not contactable for further details. Most of the included studies did not specify at which cycle the adverse reactions occurred. The lack of this information on cycle specification could limit the application of findings to any cycle of rapid infusion as it has been suggested that adverse reactions have an inverse relationship with the number of cycles.

### **Implications for practice**

90-minute rapid Rituximab infusion with or without steroids premedication is recommended for NHL patient at second and subsequently infusion. No recommendations can be made in relation to stage of disease or the presence of bulky disease or leucocytosis particularly suitable for above regimen. It is not recommended, based on the current evidence, to use rapid Rituximab on CLL patients. Currently, there is no suggestion of changing the guidelines on the administration of Rituximab regarding infusion rates from the Manufacturer (Roche). However, Roche has indicated that the company is aware that at least one hospital in New South Wales has formulated a new protocol to run Rituximab rapidly.

### **Implications for research**

Further research is needed on the role of monoclonal antibodies development in rapid infusion, especially in the second and subsequent cycles. Currently, this review broadly establishes that rapid Rituximab infusion over 90-minute is safe for NHL patients. However, more research and detailed analysis is needed to develop more specific guidelines.

### **Conclusion**

The best available evidence from this systematic review strongly suggests that 90-minute rapid Rituximab infusion is safe for NHL patients. However, the evidence is very weak in regard to CLL patients.

## Conflict of interest

None.

## Acknowledgement

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  53. Kramers AMG, Zijlstra-Baalbergen JM. Rapid infusion rituximab, an evidence based-practice approach. *Bone Marrow Transplant*. 2008 Mar;41:S369-S.
  54. Rapid-infusion rituximab helps meet cancer targets. *Pharm J*. 2005;275(7356):9.
  55. Focus on oncology nursing. Nurses can administer rituximab safely by rapid infusion. *Oncology News International*. 2007;16(9):15-.
  56. Byrd JC, Waselenko JK, Maneatis TJ, Murphy T, Ward FT, Monahan BP, et al. Rituximab therapy in hematologic malignancy patients with circulating blood tumor cells: association with increased infusion-related side effects and rapid blood tumor clearance. *J Clin Oncol*. 1999 Mar;17(3):791-5.

57. Graham AH. Administering rituximab: infusion-related reactions and nursing implications. *Cancer Nurs Pract.* 2009;8(2):30-5.
58. Filewich A, Fitzgerald CK, Gill D. Rapid infusion Rituximab in combination with steroid containing chemotherapy can be given safely and substantially reduces resource utilization. *Blood.* 2004.
59. Filewich AC, K F, Gill K. Brief report rapid infusion Rituximab in combination with corticosteroid-containing chemotherapy or as maintenance therapy is well tolerated and can safely be delivered in the community setting. *Blood.* 2007.
60. McCoy C, Watterson P, Martin N, Ong YL, Moore A, Black B, et al. Rapid infusion of Rituximab can be given safely and has a significant impact on capacity. *Br J Haematol.* 2006 Apr;133:8-.
61. Ramadan K, McCoy C, Ong YL, Eswedi AH, El-Agnaf MR. Rapid infusion of rituximab over 90-minutes from second infusion onwards on an out-patient basis is safe and improves resource utilization. *Haematologica.* 2007 Jun;92:0938.
62. Romejko-Jarosinska J, Borawska AB. Rituximab rapid compared to standard infusion rate in a busy oncology practice. *Jarosinska.* 2010.
63. Sehn L, Donaldson J, Filewich A, Fitzgerald C, Gill K, Runzer N, et al. Rapid infusion rituximab can be safely administered and has a positive impact on resource utilization. *Ann Oncol.* 2005 Jun;16:107.
64. Sehn LH, Donaldson J, Filewich A, Fitzgerald C, Gill KK, Runzer N, et al. Rapid infusion rituximab in combination with steroid containing chemotherapy can be given safely and substantially reduces resource utilization. *Blood.* 2004 Nov;104(11):1407.
65. Wenger M, De Marco E, Vitolo U, Poddubnaya I, Chamone D, Warburton P, et al. Rituximab maintenance therapy can be safely administered via a rapid infusion protocol: results from the maxima study. *Haematologica.* 2008 Jun;93:0272.
66. Byrd J, Peterson B, Morrison V, Park K, Jacobson R, Hoke E, et al. Randomized phase 2 study of fludarabine with concurrent versus sequential treatment with rituximab in symptomatic, untreated patients with B-cell chronic lymphocytic leukemia: results from Cancer and Leukemia Group B 9712 (CALGB 9712). *Blood.* 2003;101(1):6.



## Appendix I: Example of NCI CTC and CTCAE

Adverse event	Grade				
	0	1	2	3	4
Hypotension	None	Changes, but no required therapy	Requiring brief fluids replacement or other therapy but not hospitalisation; no physiologic consequences	Requiring therapy and sustained medical attention, but resolves without persisting physiologic consequences	Shock (associated with academia and impairing vital organs function due to tissue hypo perfusion

Adverse event	Grade				
	0	1	2	3	4
Hypotension	None	Changes, but no required therapy	Requiring brief fluids replacement or other therapy but not hospitalisation; no physiologic consequences	Requiring therapy and sustained medical attention, but resolves without persisting physiologic consequences	Shock (associated with academia and impairing vital organs function due to tissue hypo perfusion

## Appendix II: Search strategy

Databases	Block Building
1. Pubmed/Medline	(rituximab[nm] OR rituximab[tw] OR mabthera[tw] OR rituxan[tw]) AND (infusions, intra-arterial[mh] OR infusio[n]*[tw])
2. Web of Science	(rituximab OR mabthera OR rituxan) AND ( rapid infus*)
3. Scopus	Title-Abs-Key(rituximab OR mabthera OR rituxan) AND ("rapid infus*")
4. Cochrane Central Register of Controlled Trials	(rituximab OR mabthera OR rituxan) AND (infus*)
5. Science Direct	(rituximab OR mabthera OR rituxan) AND ('rapid infusion')
6. CINAHL	(TX rituximab OR TX mabthera OR TX rituxan) AND TX (infusions, intra-arterial) or TX infus*
7. Scifinder	Rituximab rapid
8. Mednar	(rituximab OR mabthera OR rituxan) AND ( rapid infus*)

## Appendix III: Critical appraisal instruments

NOTE:

This appendix is included in the print copy  
of the thesis held in the University of Adelaide Library.

## Appendix IV: Data extraction instrument

NOTE:

This appendix is included in the print copy  
of the thesis held in the University of Adelaide Library.

## Appendix V: Included studies

Author	Year	Study Method	Setting	Participants							Intervention	Instrument
				# of patients	Age	Diagnosis	Chemotherapy	Stage of Disease	Bulky Disease (>7cm)	Leucocytosis		
Al Zahrani et al.	2009	Observational	Outpatient Chemotherapy Day Unit in Riyadh Military Hospital in Saudi Arabia	21	Mean 48 (28-68)	DLBCL, Low Grade Lymphoma, unspecified lymphoma	RCHOP, Monotherapy, Mod-FCN-R, other	NS	Yes	Yes	(90min) 20% in first 30min, 80% for the remaining over 60min	CTC CTAE Version 3
Chiang et al.	2010	Observational	Ambulatory Cancer Center in National Cancer Center Singapore	79	Median 56	DLBCL, FL, BL, MCL, unspecified lymphoma	RCHOP, RCVP, RCEOP, R alone	NS	NS	NS	(90min) 20% in first 30min, 80% for the remaining over 60min	NS
Corey et al.	2007	Observational	Community Based Cancer Center at Gundersen Lutheran Health in United States	46	Median 69(32-91)	NHL	RP, RCHOP, RCVP, RCEP, RCFP, RCP	I-IV	NS	No	(90min) 20% in first 30min, 80% for the remaining over 60min	CTC CTAE Version 3
El-Aganf et al.	2007	Observational	Outpatient Day Therapy Unit at Ulster Hospital, Northen Ireland	17	Median 75(44-87)	DLBCL, FL, NHL	RCHOP, RCVP	I-IV	NS	No	(90min) 20% in first 30min, 80% for the remaining over 60min	NS
Gibbs et al.	2007	Observational	Haematology Unit of Norfolk and Norwich University Hospital, United Kingdom	61	Range (18-80)	DLBCL	RCHOP	NS	NS	NS	90 min	CTC CTAE

Abbreviation: NS-Not Stated; DLBCL-Diffuse Large B Cell Lymphoma; FL-Follicular Lymphoma; BL-Burkitts Lymphoma; MCL-Mantle Cell Lymphoma; NHL-Non Hodgkin Lymphoma; MALT-Mucosa-Associated Lymphatic Tissue; PTLD-Post Translant Lymphoproliferative Disorder.  
R-Rituximab, CHOP-Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone; CVP-Cyclophosphamide, Vincristine, Prednisolone; CEOP-Cyclophosphamide, Etoposide, Vincristine, Prednisolone; P-Prednisolone; CEP-Cyclophosphamide, Etoposide, Prednisolone; CFP-Cyclophosphamide, Fludarabine, Prednisolone; CP-Cyclophosphamide, Prednisolone;

Author	Year	Study Method	Setting	Participants							Intervention	Instrument
				Number of patients	Age	Diagnosis	Chemotherapy	Stage of Disease	Bulky Disease (>7cm)	Leucocytosis		
Salar et al.	2006	Observational	In and outpatient of Department of Clinical Haematology in the Hospital Del Mar in Spain	70	Median 64(28-87)	DLBCL, FL, MALT, MCL, unspecified lymphoma, PTLD, Immune cytopenia	RCHOP, REPOCH, Monotherapy, R-fludarabine, R-Gemcitabine, R-Chlorambucil	NS	NS	No	(90min) 20% in first 30min, 80% for the remaining over 60min	NS
Sehn et al.	2007	Observational	Ambulatory Chemotherapy Unit in British Columbia Cancer Agency, Canada	205	Median 60(19-92)	NHL	RCHOP, RCVP, R alone.	NS	NS	No	(90min) 20% in first 30min, 80% for the remaining over 60min	NS
Statham et al.	2006	Observational	Ambulatory Haematology Unit within the North London Cancer Network United Kingdom	23	Median 56(36-82)	DLBCL, FL, MCL, Waldenstrom's Macroglobulinemia, HD, PTLD	RCHOP, RCVP, R alone, RPMLICEBO, RIVE, RIVAC	NS	NS	Ns	(90min) 20% in first 30min, 80% for the remaining over 60min	NCI CTC Version 2
Milone et al.	2007	Observational	Argentina	31	NS	NHL, CLL	RCHOP, R	NS	NS	NS	(90min) 20% in first 30min, 80% for the remaining over 60min	NS

Abbreviation: NS-Not Stated; DLBCL-Diffuse Large B Cell Lymphoma; FL-Follicular Lymphoma; BL-Burkitts Lymphoma; MCL-Mantle Cell Lymphoma; NHL-Non Hodgkin Lymphoma; HD-Hodgkin Disease; CLL-Chronic Lymphocytic Leukemia; MZL-Marginal zone Lymphoma  
R-Rituximab, CHOP-Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone; CVP-Cyclophosphamide, Etoposide, Vincristine, Prednisolone; P-Prednisolone; CEP-Cyclophosphamide, Etoposide, Prednisolone; CFP-Cyclophosphamide, Fludarabine, Prednisolone; CP-Cyclophosphamide, Prednisolone; EPOCH-Etoposide, Vincristine, Doxorubicin, Cyclophosphamide, Prednisolone;PMLICEBO-Mitoxantrone, Cyclophosphamide, Etoposide, Vincristine, Bloemycin, Prednisolone;; EPOCH-Etoposide, Vincristine, Doxorubicin, Cyclophosphamide, Prednisolone;

Author	Year	Study Method	Setting	Participants							Intervention	Instrument
				Number of patient	Age	Diagnosis	Chemotherapy	Stage of Disease	Bulky Disease (>7cm)	Leucocytosis		
Soria et al.	2008	Observational	Outpatient at Zaragoza, Spain	37	Mean 55.3(24-77)	FL	RCHOP,RFCM, RFC	I-IV	Yes	Yes	(90min) 20% in first 30min, 80% for the remaining over 60min	NS
Provencio et al.	200	Observational	Outpatient in Spain	40	Median 60(29-87)	DLBCL, Low Grade Lymphoma, HD	RCHOP, RCOMP, RCVP, other	I-V	Yes	Yes	60 min	NCI CTC Version 3
Tuthill et al.	2009	Observational	United Kingdom	54	Median 60(20-86)	DLBCL, FL, MCL, Maltoma, Immune Mediated Thrombocytopenias	NS	NS	NS	No	60min	NS
Aurran et al.	2005	Observational	Outpatient Unit in Marseille, France	69	Median 61(26-85)	DLBCL, FL, MCL, MZL, CLL, Lymphoplasmocytic, Castelman Disease, ITP	RCHOP, R	NS	NS	NS	60min	NS

Abbreviation: NS-Not Stated; DLBCL-Diffuse Large B Cell Lymphoma; FL-Follicular Lymphoma; MCL-Mantle Cell Lymphoma HD-Hodgkin Disease; CLL-Chronic Lymphocytic Leukemia; MZL-Marginal zone Lymphoma; ITP-Idopathic Thrombocytopenia Purpura.  
R-Rituximab, CHOP-Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone; CVP-Cyclophosphamide, Vincristine, Prednisolone; R-Rituximab; FC-Fludarabine, Cyclophosphamide; FCM-Fludarabine, Cyclophosphamide, Mitoxantrone

## Appendix VI: Excluded studies

Rapid-infusion rituximab helps meet cancer targets. Pharm J. 2005; 275(7356).

**Reason for exclusion:** Discussion paper

Focus on oncology nursing. Nurses can administer rituximab safely by rapid infusion. Oncology News International. 2007; 16(9): 15.

**Reason for exclusion:** Discussion paper

Brice P, Franchi-Rezgui P, Derni C, Nocton V, Hascouet I, Kadia C, et al. Rituximab rapid infusion (90 minutes) is feasible after the first dose in an outpatient setting, a single center prospective study of 80 courses. Haematologica. 2007 Jun;92:0605.

**Reason for exclusion:** Incongruent with review inclusion criteria for intervention, the median duration of rituximab infusion was at 90 minutes.

Byrd J, Peterson B, Morrison V, Park K, Jacobson R, Hoke E, et al. Randomized phase 2 study of fludarabine with concurrent versus sequential treatment with rituximab in symptomatic, untreated patients with B-cell chronic lymphocytic leukemia: results from Cancer and Leukemia Group B 9712 (CALGB 9712). Blood. 2003;101(1):6.

**Reason for exclusion:** Incongruent with review inclusion criteria for intervention, different infusion rate were used within the same arm.

Byrd JC, Murphy T, Howard RS, Lucas MS, Goodrich A, Park K, et al. Rituximab using a thrice weekly dosing schedule in B-Cell chronic lymphocytic leukemia and small lymphocytic lymphoma demonstrates clinical activity and acceptable toxicity. J Clin Oncol. 2001 Apr;19(8):2153-64.

**Reason for exclusion:** The analysis of results were unclear, not able to extract outcome measures as stated in the review

Byrd JC, Waselenko JK, Maneatis TJ, Murphy T, Ward FT, Monahan BP, et al. Rituximab therapy in hematologic malignancy patients with circulating blood tumor cells: Association with increased infusion-related side effects and rapid blood tumor clearance. J Clin Oncol. 1999 Mar;17(3):791-5.

**Reason for exclusion:** Discussion paper

Filewich A, Fitzgerald C, Gill K. Brief report rapid infusion rituximab in combination with steroid containing chemotherapy or as maintenance therapy is well tolerated and can safely be delivered in the community setting. Blood. 2007.

**Reason for exclusion:** Duplicated paper

Filewich A, Fitzgerald CK, Gill D. Rapid infusion rituximab in combination with steroid containing chemotherapy can be given safely and substantially reduces resource utilization. Blood. 2004.

**Reason for exclusion:** Duplicated paper

Graham AH. Administering rituximab: infusion-related reactions and nursing implications. Cancer Nurs Pract. 2009;8(2):30-5.

**Reason for exclusion:** Discussion paper

Gundogdu F, Akgedik K, Atay S, Arpaci A, Yilmaz F, Korucuoglu Z, et al. P36 Rapid infusion of rituximab

- in lymphoma treatment as maintenance therapy is well tolerated. *Eur J Oncol Nurs.* 2010;14(Supplement 1):S33-S.
- Reason for exclusion:** The analysis of the results from the study was vague.
- Kanelli S, Ansell SM, Habermann TM, Inwards DJ, Tuinstra N, Witzig TE. Rituximab toxicity in patients with peripheral blood malignant B-cell lymphocytosis. *Leuk Lymphoma.* 2001 Nov-Dec;42(6):1329-37.
- Reason for exclusion:** Discussion paper
- Kramers AMG, Zijlstra-Baalbergen JM. Rapid infusion rituximab, an evidence based-practice approach. *Bone Marrow Transplant.* 2008 Mar;41:S369-S.
- Reason for exclusion:** Incongruent with review inclusion criteria for population, 29.4% patients were AIHA and ITP patients
- McCoy C, Watterson P, Martin N, Ong YL, Moore A, Black B, et al. Rapid infusion of Rituximab can be given safely and has a significant impact on capacity. *Br J Haematol.* 2006 Apr;133:8-.
- Reason for exclusion:** Duplicated paper
- Middleton H, Mollee P, Bird R, Mills A, Marlton P, Gill D. Accelerated Delivery of Rituximab Is Safe on an Out-Patient Basis. *Am Soc Hematology;* 2005. p. 4777-.
- Reason for exclusion:** Incongruent with review inclusion criteria for intervention, infusion rate of 400mg/hr was used with median infusion time was 1 hour 55 minutes.
- Peinert S, Moloney M, Prince HM, Wolf M, Ritchie D, Westerman D, et al. Rapid infusion of rituximab is well tolerated and enables more efficient use of haematology aday ward resources. *Haematologica.* 2009 Jun;94:0424.
- Reason for exclusion:** Incongruent with review inclusion criteria for population, patients aged 16 years old were included in the study.
- Provencio M, Sanchez A, Maximiano C, Cantos B, Mendez M, Bonilla F. A prospective study of left ventricle function after treatment with rapid-infusion Rituximab in patients with non-Hodgkin lymphoma. *Leuk Lymphoma.* 2009;50(10):1642-6.
- Reason for exclusion:** Incongruent with review inclusion criteria for outcome measures, the study examined long term complication of rapid rituximab infusion.
- Ramadan K, McCoy C, Ong YL, Eswedi AH, El-Agnaf MR. Rapid infusion of rituximab over 90-minutes from second infusion onwards on an out-patient basis is safe and improves resource utilization. *Haematologica.* 2007 Jun;92:0938.
- Reason for exclusion:** Duplicated paper
- Romejko-Jarosinska J, Borawska AB. Rituximab rapid compared to standard infusion rate in a busy oncology practice. *Jarosinska.* 2010.
- Reason for exclusion:** Duplicated paper



Sehn L, Donaldson J, Filewich A, Fitzgerald C, Gill K, Runzer N, et al. Rapid infusion rituximab can be safely administered and has a positive impact on resource utilization. *Ann Oncol*. 2005 Jun;16:107.

**Reason for exclusion:** Duplicated paper

Sehn LH, Donaldson J, Filewich A, Fitzgerald C, Gill KK, Runzer N, et al. Rapid infusion rituximab in combination with steroid containing chemotherapy can be given safely and substantially reduces resource utilization. *Blood*. 2004 Nov;104(11):1407.

**Reason for exclusion:** Duplicated paper

Siano M, Lerch E, Negretti L, Zucca E, Rodriguez-Abreu D, Oberson M, et al. A Phase I-II Study to Determine the Maximum Tolerated Infusion Rate of Rituximab with Special Emphasis on Monitoring the Effect of Rituximab on Cardiac Function. *Clin Cancer Res*. 2008 Dec;14(23):7935-9.

**Reason for exclusion:** Incongruent with review inclusion criteria for intervention, infusion rate ranged from 50-700mg/h were used.

Uresandi A, Guinea J, Menchaca C, Hernandez R, Mendizabal A, Ardanaz MT, et al. Rituximab fast infusion tolerance. *Ann Oncol*. 2008;19(Supp 4).

**Reason for exclusion:** Incongruent with review inclusion criteria for intervention, infusion rate of 400mg/hr was used with no specification on the duration of completion.

Wenger M, De Marco E, Vitolo U, Poddubnaya I, Chamone D, Warburton P, et al. Rituximab maintenance therapy can be safely administered via a rapid infusion protocol: results from the maxima study. *Haematologica*. 2008 Jun;93:0272.

**Reason for exclusion:** Duplicated paper

## Appendix VII: Patients' diagnoses in the 13 included studies

Study	AL Zahrani 2009	Chiang 2010	Corey 2007	EL Agnaf 2007	Gibbs 2007	Soria 2008	Salar 2006	Sehn 2007	Statham 2006	Tuthill 2009	Provencio 2006	Aurran 2005	Milone 2007
Diagnosis													
CLL												11	4
NHL			46	1				205					27
DLBCL	15	43		12	61		28		12	34	24	27	
FL		28		4		37	25		5	10		22	
MCL		1					4		1	4		2	
BL		3											
MZL												3	
MALT							8						
Low Grade Lymphoma	3										15		
Waldenstr om's Macroglob uliemia									2				
Maltoma										1			
Unspecifie d Lymphoma	3	4					2						
HD									1		1		
PTLD							2		1				
Immune Cytopenia							1						
Immune Mediated Thromobo cytopenias										5			
Lymphopla smocytic												2	
Castelman Disease												1	
ITP												1	
B-ALL									1				

Lang, S.P., Hagger, C. & Pearson, A. (2011) Safety of rapid rituximab infusion in adult cancer patients: A systematic review.  
*International Journal of Nursing Practice*, v. 17 (4), pp. 357-369.

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<http://dx.doi.org/10.1111/j.1440-172X.2011.01950.x>

Lang, S.P., Prouse, J., Barry, F., Catherwood, A., Chaplin, K., Elliott, L., Greco, K., McGahey, W. Nilsen, J. & Singhal, N. (2012) Evaluation of safety and feasibility of rapid rituximab infusion. *Asia-Pacific Journal of Clinical Oncology*, v. 8 (1), pp. 71-75.

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