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Medical Writer: Anna Christofides MSc, RD, New Evidence
Rituximab is a human/murine immunoglobulin G1 chimeric monoclonal antibody that binds to the B-cell CD20 antigen, causing rapid and targeted B-cell depletion. In Canada, rituximab is approved by Health Canada for the treatment of patients with non-Hodgkin’s lymphoma (NHL) and B-cell chronic lymphocytic leukemia (CLL). Rituximab is also indicated to reduce signs and symptoms in adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to one or more tumour necrosis factor (TNF) inhibitor therapies. Rituximab in combination with methotrexate (MTX) has been shown to reduce the rate of progression of joint damage as measured by X-ray in the RA setting.

The addition of rituximab to standard chemotherapy has been shown to improve outcomes in patients with NHL, CLL, and RA. In patients with NHL and untreated CLL, rituximab improves both progression-free survival (PFS) and overall survival (OS); maintenance and second-line rituximab also delays progression in these patients.

Rituximab is a good treatment alternative to patients with RA who have failed TNF inhibitors and has proven to be as or more effective than a second TNF inhibitor in this setting. Results of clinical trials in RA patients show that a significant number achieve ACR50 and low disease activity levels after treatment with rituximab. Ongoing clinical trials are also examining the use of rituximab in vasculitis, multiple sclerosis, refractory thrombotic thrombocytopenic purpura, systemic lupus erythematosus, and epidermolysis bullosa acquisita.

Although generally well tolerated, biologic treatments, including rituximab, are associated with infusion-related reactions. To minimize these reactions, the standard administration of rituximab has a long infusion time, resulting in a significant drain on health resources and patient time. For this reason, shorter infusion protocols have been tested in oncology settings and have proven to be safe and practical. Similarly, routine use of rapid infusion protocols in the RA setting should provide further benefits for these patients and their healthcare providers.

Background

Rituximab is a human/murine immunoglobulin G1 chimeric monoclonal antibody that binds to the B-cell CD20 antigen, causing rapid and targeted B-cell depletion. In Canada, rituximab is approved by Health Canada for the treatment of patients with non-Hodgkin’s lymphoma (NHL) and B-cell chronic lymphocytic leukemia (CLL). Rituximab is also indicated to reduce signs and symptoms in adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to one or more tumour necrosis factor (TNF) inhibitor therapies. Rituximab in combination with methotrexate (MTX) has been shown to reduce the rate of progression of joint damage as measured by X-ray in the RA setting.

The addition of rituximab to standard chemotherapy has been shown to improve outcomes in patients with NHL, CLL, and RA. In patients with NHL and untreated CLL, rituximab improves both progression-free survival (PFS) and overall survival (OS); maintenance and second-line rituximab also delays progression in these patients.

Standard administration protocol

One barrier to effective treatment with rituximab is its lengthy administration protocol, resulting in a time- and labour-intensive process. The standard administration protocol for rituximab takes approximately three or four hours for the first infusion and two or three hours for subsequent infusions in the oncology and RA settings, respectively. These long infusion times place a significant strain on health resources.

Patients are expected to arrive at the clinic early and wait afterwards to ensure there are no adverse reactions. A total of around four to six hours of patient time is therefore needed to complete one rituximab infusion, including waiting time. Because of the long infusion time, patients need to plan for a full day of treatment at the clinic, with a negative impact on their quality of life.

The burden of the standard infusion protocol to the healthcare system is also significant. Long infusion protocols increase required patient chair time, thus decreasing the ability to treat other patients. This results in increased nursing and administration staff workload, longer wait times for treatment, and less efficient delivery of services. The financial cost in terms of healthcare provider time and use of resources is also a concern. Ultimately, the burden of long infusion times may result in a lack of adherence or discontinuation of treatment, potentially reducing treatment efficacy. For these reasons, rapid infusion protocols have been developed in some infusion centres.
Figure 1. Standard administration of rituximab: initial infusion

Adapted from Hoffmann-La Roche Ltd. RITUXAN® Product Monograph, 2010.
Note: The rituximab solution for infusion should be administered intravenously at an initial rate of 50 mg/hr. If hypersensitivity or infusion-related events do not occur, the infusion rate may be escalated in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.

Figure 2. Standard administration of rituximab: subsequent infusions

Adapted from Hoffmann-La Roche Ltd. RITUXAN® Product Monograph, 2010.
Note: Subsequent infusions of rituximab can be administered at an initial rate of 100 mg/hr and increased by 100 mg/hr increments at 30 minute intervals, to a maximum of 400 mg/hr as tolerated.
**Infusion-related reactions**

Rituximab is generally well tolerated in both the oncology and rheumatology settings. However, infusion-related reactions may occur and typically manifest 30 to 120 minutes after rituximab administration. Although the mechanism is poorly understood, symptoms may develop as a result of the binding of rituximab to tumour cells and normal B cells, causing the release of inflammatory cytokines such as TNF-α and interleukin-6 (IL-6) and/or other chemical mediators.\(^1\)\(^-\)\(^3\)\(^,\)\(^11\)

Usually, symptoms of infusion reactions are less severe in the RA setting than in the oncology setting. Symptoms are generally mild to moderate in nature and may include fever, rash, and cardiovascular or respiratory insufficiency. Rarely, severe symptoms occur, which may result in urticaria, hypotension, angioedema, hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, or cardiogenic shock.\(^2\)\(^,\)\(^3\)\(^,\)\(^11\)

Infusion reactions are more frequent in the oncology setting than the RA setting due to the higher B-cell burden of these patients. In the oncology setting, older patients and those with increased tumour bulk are at highest risk.\(^2\)\(^,\)\(^3\)\(^,\)\(^13\)\(^,\)\(^14\) Typically, the risk of infusion-related toxicity is greatest with the first infusion, occurring in 77% and 29% of patients with NHL and RA, respectively.\(^5\)\(^,\)\(^10\) Infusion reaction rates decrease substantially after the first infusion, with approximately 30% of NHL patients and 12% of RA patients reporting reactions after subsequent infusions.\(^10\)\(^,\)\(^11\)

A similar trend is observed for severe (grade 3/4) reactions, which occur in around 7% of patients with NHL after the first infusion and decrease to 2% after the fourth infusion; severe reactions in RA patients are rare and occur in <1% of patients.\(^2\)\(^,\)\(^3\)\(^,\)\(^11\)

The risk for infusion reactions associated with the use of rituximab should be kept in perspective with the risk of reactions associated with other agents. In general, the incidence of infusion reactions associated with rituximab in the oncology setting is similar to that associated with other biologics, taxanes, and platinum agents.\(^14\) In the RA setting, the incidence of infusion reactions is similar to that of other biologics and some TNF inhibitors, such as infliximab.\(^15\) Discontinuation of rituximab rarely occurs as a result, and the majority of reactions are resolved by slowing or interrupting the infusion and giving supportive care.\(^14\) In addition, the clinical benefit of rituximab clearly outweighs the risk, with a favourable risk:benefit profile.

**Rapid infusion protocols in clinical trials**

**Oncology setting**

Routine use of rapid infusion protocols can result in significant reductions in healthcare costs and resources. Accelerated infusions of rituximab were first used in the oncology setting in patients diagnosed with NHL or CLL. A preliminary study by O’Brien, et al. (2001) in patients with CLL found that dose escalations of rituximab up to 2,250 mg/m\(^2\) given at infusion rates up to 400 mg/hr did not increase the rate of infusion reactions.\(^16\) Subsequently, 60- and 90-minute infusion protocols were developed and tested in a number of studies in the oncology setting; these protocols were found to be well tolerated with no increase in the rate of infusion-related reactions. (Appendix A) However, the standard infusion rate was given for the first infusion of all courses in both protocols to assess patient tolerability.

Overall, clinical studies in the oncology setting show that adverse events (AEs) with rapid infusions are rare and manageable, the majority being mild in nature (grade 1/2). The largest study to date included 206 patients receiving the 90-minute protocol and reported no serious infusion reactions and no increase in mild infusion reactions. After follow-up of more than 1,200 patients, only one patient experienced a more serious (grade 3) reaction.\(^11\) Based on the results of clinical trials, rapid infusion protocols are now routinely used in the majority of oncology centres across Canada.
Prevention of infusion-related reactions
Identification of patients at increased risk is of key importance in preventing infusion-related reactions. Prior to rituximab administration, individual patient risk factors for infusion reactions should be assessed. (Table 1) Other factors, such as whether rituximab is to be administered in combination or as a single agent and which (if any) other concomitant therapies will be used may also influence the risk of infusion reactions. Of particular importance is any history of previous allergic reactions. A detailed patient history, including baseline assessments of vital signs and cognition, is therefore an important first step before initiating treatment with rituximab.14

Infusion reactions may be higher in patients with Sjögren’s syndrome than in those with RA. In a small phase II study in patients with primary Sjögren’s syndrome, significant improvements in subjective symptoms and salivary gland function were observed. However, 4/15 patients developed human anti-chimeric antibodies (HACAs), which resulted in serum sickness–like disease in three patients.19

In the oncology setting, pre-medication consisting of an antihistamine and an anti-pyretic should be administered prior to each rituximab infusion. For patients with large tumour burden and therefore higher risk of infusion reactions, IV corticosteroids can be administered in addition to other supportive measures to prevent tumour lysis syndrome.

Rapid infusion protocols in clinical practice

Prevention of infusion-related reactions
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Table 1. Patient risk factors for hypersensitivity reactions

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Prevention Strategy</th>
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<tbody>
<tr>
<td>Female gender</td>
<td>Pre-existing cardiac or pulmonary dysfunction</td>
</tr>
<tr>
<td>Higher than standard drug doses</td>
<td>Previous exposure to the drug</td>
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<tr>
<td>Iodine or seafood allergies</td>
<td>Asthma diagnosis</td>
</tr>
<tr>
<td>Newly diagnosed, untreated patients</td>
<td>Atopic patients (i.e., patients who tend to react to specific allergens, such as hay fever, skin irritations, and asthma)</td>
</tr>
<tr>
<td>Older age</td>
<td>Circulating lymphocyte counts of 25,000 mm³ or higher</td>
</tr>
<tr>
<td>Hematologic malignancies</td>
<td>Concomitant β-adrenergic blocker therapy</td>
</tr>
<tr>
<td>Personal history of significant drug allergy or previous immediate reaction to a medication</td>
<td>Concurrent autoimmune disease</td>
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</table>

Adapted from Vogel, et al. 2010.
Stepwise or fractionated dosing, for example administering a 100 mg dose in 1,000 mL of normal saline on day 1 and the remainder on day 2, may also be considered in these high-risk patients. At Princess Margaret Hospital (PMH) in Toronto, Ontario, fractionated dosing is given to CLL patients with high white blood cell (WBC) counts. A similar approach is employed at the Juravinski Hospital and Cancer Centre (JHCC) in Hamilton, Ontario, where physicians may elect to give 50 mg/m² on day 1 and the remaining 325 mg/m² on day 2 for the first cycle. For high-risk patients, hospitalization may be necessary when stringent monitoring is required.

Many patients with RA are not given pre-medications, and the use of corticosteroids is not required before rituximab administration. However, in a study by Emery, et al. (2006), use of glucocorticoids reduced infusion reactions and did not alter the response to rituximab in patients with RA.

Prior to rituximab administration, patients should be educated about the potential for infusion reactions and instructed to report any adverse reactions immediately. Healthcare practitioners should reassure patients that appropriate measures will be taken to prevent infusion reactions. Patients should also be advised that these reactions are generally mild to moderate and are easily managed.

### Administration of the rapid infusion protocol

In the oncology setting, it is recommended that rituximab infusions be administered in an environment with full resuscitation facilities and under the close supervision of professionals capable of dealing with severe reactions. During infusions, healthcare practitioners should monitor patient vital signs, watching for any sign of infusion reactions. Constant visual observation is important during the first infusion, when patients are at the greatest risk; however, monitoring should continue with every subsequent infusion. The first infusion of rituximab should be delivered at the standard infusion rate to assess patient tolerability. If the first infusion is well tolerated, subsequent infusions may be given at an accelerated infusion rate over approximately 90 to 120 minutes in the oncology setting or 120 minutes in the RA setting. (Figure 3)

#### Figure 3. Rapid administration of rituximab

<table>
<thead>
<tr>
<th>Rate</th>
<th>Time</th>
<th>Quantity of rituximab</th>
<th>Total dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>200 mg/hr</td>
<td>0–30 min</td>
<td>100 mg</td>
<td>100 mg</td>
</tr>
<tr>
<td>400 mg/hr</td>
<td>30–60 min</td>
<td>200 mg</td>
<td>300 mg</td>
</tr>
<tr>
<td>600 mg/hr</td>
<td>60–90 min</td>
<td>300 mg</td>
<td>600 mg</td>
</tr>
<tr>
<td>800 mg/hr</td>
<td>90–120 min</td>
<td>400 mg</td>
<td>1000 mg</td>
</tr>
</tbody>
</table>

*Note: The rituximab solution for infusion should be administered intravenously at an initial rate of 200 mg/hr. If hypersensitivity or infusion-related events do not occur, the infusion rate may be escalated in 200 mg/hr increments every 30 minutes, to a maximum of 800 mg/hr.*
In the oncology setting, rapid infusion of rituximab has become the standard in the majority of centres across Canada. PMH began using the rapid infusion protocol shortly after data from the Sehn, et al. (2007) study in the NHL setting was released. The standard protocol at PMH therefore recommends administering 375 mg/m² at the 90-minute infusion rate if the patient tolerates the first infusion or has only a mild-to-moderate reaction. If there are significant pulmonary symptoms after the first infusion, the second infusion may be given using the standard infusion rate before moving to the rapid protocol. When patients show more severe reactions (grade 3/4), treatment may be stopped; however, severe reactions rarely occur.

The adoption of a rapid infusion protocol at PMH means that a total of 8 to 10 patients can be seen per day, compared to only 5 patients with the standard protocol. Patients are often able to concurrently book lab and infusion time on the same day, thereby reducing the number of days spent in the clinic. A detailed description of the rapid infusion protocol at PMH is presented in Appendix B.

Recent funding approval in Ontario for the use of rituximab in combination with fludarabine-based treatment for previously untreated CLL has required a slightly different approach to the management of rituximab infusions. First, CLL patients tend to have higher grade 1 and 2 reactions than patients with other lymphocytic subtypes. As previously mentioned, this risk is managed by optional fractionated first dosing. Second, the rituximab dose in cycles 2–6 for CLL is 500 mg/m². Early pharmacokinetic and dose-escalation studies observed that rituximab at standard 375 mg/m² was less effective in CLL than in other lymphoma subtypes. Reasons for this finding include generally lower CD20 expression and a shorter rituximab half-life in CLL, which can be overcome with higher doses.

The current practice at JHCC for rituximab infusions in CLL follows the PMH processes previously described, with cycle 1 at 375 mg/m² (with optional fractionation) and cycle 2 at 500 mg/m² at standard infusion rates. Assuming no clinically significant reactions are observed, cycles 3–6 are given at 500 mg/m² over approximately 90 minutes.

Given the success of rapid infusion protocols in the oncology setting and the growing evidence of their safety in patients with RA, the accelerated protocol should become the standard of care in the RA setting across Canada.

**Conclusion**

Rituximab has proven to be an invaluable treatment option, dramatically improving the outcome of patients with non-Hodgkin’s lymphoma, chronic lymphocytic leukemia, and rheumatoid arthritis. Despite the clear benefits of rituximab in the oncology and rheumatology settings, its standard administration is time consuming, resulting in a significant burden for patients and healthcare providers.

Studies using accelerated infusion protocols for rituximab in both oncology and RA settings have shown rapid administration to be safe and practical. Rapid infusion of rituximab can reduce healthcare costs, improve resource utilisation, and increase patient satisfaction and quality of life. Based on the positive results of studies in the oncology and RA settings, rapid infusion of rituximab should be recommended in all infusion clinics across Canada.
## Appendix A. Rapid infusion protocols used in clinical trials

<table>
<thead>
<tr>
<th>Study/Patient population</th>
<th>Rapid infusion protocol</th>
<th>Findings</th>
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</thead>
<tbody>
<tr>
<td>Oncology setting</td>
<td></td>
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</tbody>
</table>
| Byrd JC, et al. J Clin Oncol 2001 (CLL, SLL; R-monotherapy) | • 100 mg administered over 4 hours (25 mg/h) for first infusion  
• 375 mg/m\(^2\) using standard infusion rate for second infusion  
• 375 mg/m\(^2\) for infusions 3 to 12 administered at 50 mg/h rate for 15 minutes, then increased to administer entire dose over 60 minutes  
**Pre-medication:** diphenhydramine (50 mg IV), acetaminophen (650 mg orally) | • Rapid infusion data from cohort III of study: 23/33 patients  
• No IRRs noted beyond the second infusion in the 23 patients using rapid infusion on the third and subsequent infusions  
• No SAEs with rapid infusions |
| Aurran Scleinitz T, et al. ASH 2005: Abstract 4759 (NHL, CLL; 67 R-chemo; 2 R-monotherapy) | • 375 mg/m\(^2\) using standard infusion rate for first infusion  
• In cases where patients had circulating malignant CD20+ cells, first infusion administered over 2 days  
• Subsequent infusions given at 100 mg/h for 15 minutes, then at 500 mL/h for a total of 60 minutes  
**Pre-medication:** 1 mg/kg dose of steroids, diphenhydramine, acetaminophen given 20 minutes before | • Data from 69 patients for a total of 115 courses, including 21 first cycles  
• No grade 3/4 toxicity noted  
• During the first infusion, two patients developed grade 2 reactions and three developed grade 1 reactions  
• One CLL patient had a grade 1 reaction after the second cycle |
| Middleton Hj, et al. ASH 2005: Abstract 4777 (NHL, CLL; R-chemo, R-monotherapy) | • 375 mg/m\(^2\) using standard infusion rate for first infusion  
• In first four patients, infusion was administered at 100 mg/h, increasing to 400 mg/h after 15 minutes in the absence of reaction  
• All subsequent patients commenced the infusion at 400 mg/h  
**Pre-medication:** acetaminophen, promethazine, hydrocortisone | • Data from 23 patients and 62 infusions (median 3 infusions per patient)  
• Median infusion time was 1 hour and 55 minutes; 76% of infusions completed within 2 hours  
• Two AEs with no grade 3/4 IRRs |
| Salar A, et al. Eur J Haematol 2006 (CD20+ disease; R-chemo with or without steroids) | • 375 mg/m\(^2\) using standard infusion rate for first infusion  
• Subsequent infusions over 90 minutes (20% of the dose in the first 30 minutes, the remaining 80% over 60 minutes)  
**Pre-medication:** acetaminophen, diphenhydramine, methylprednisolone given only to patients receiving steroid-containing chemotherapy | • Data from 70 patients and 319 rapid infusions  
• No grade 3/4 AEs  
• Three patients developed symptoms, all were grade 1  
• Rapid infusion was well tolerated, both in patients who received steroids and in patients who did not |
| Provencio M, et al. Ann Oncol 2006 (DLBCL, low-grade lymphoma, Hodgkin’s lymphoma; R-chemo[R-CHOP, n = 27], R-monotherapy) | • 375 mg/m\(^2\) using standard infusion rate for first course  
• Subsequent courses using constant infusion rate over 60 minutes  
**Pre-medication:** acetaminophen (1g IV), dexchlorpheniramine (5 mg orally), steroids recommended by each therapeutic protocol | • Data on 40 patients given a total of 233 infusions  
• IRRs reported included fever (n = 1), chills (n = 2), and limited cutaneous reaction with rash (n = 2), all grade 1  
• Voluminous mass and advanced age was not associated with increased toxicity  
• Rituximab was well tolerated with no additional toxicity when added to CHOP |
| Sehn LH, et al. Blood 2007 (DLBCL, FL, other NHL; R-chemo, R-maintenance) | • 375 mg/m\(^2\) using standard infusion rate for first course  
• Subsequent courses over 90 minutes (20% of the dose in the first 30 minutes and the remaining 80% over 60 minutes)  
**Pre-medication:** corticosteroids for R-chemo and no pre-medication for R-maintenance | • Data from 150 patients receiving rituximab as a component of corticosteroid-containing chemotherapy and 56 patients receiving R-maintenance therapy  
• No grade 3/4 reactions  
• No increase in minor IRRs  
• Rituximab was well tolerated when added to chemotherapy or as maintenance therapy |
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<tr>
<td>Gibbs S, et al.</td>
<td>375 mg/m² using standard infusion rate for first infusion</td>
<td>Data from 61 patients given 250 rapid infusions</td>
</tr>
<tr>
<td>EHA 2007: Abstract 0708</td>
<td>Subsequent courses over 90 minutes</td>
<td>One patient had a grade 1 reaction during initial standard-rate infusion; all patients progressed to the accelerated protocol</td>
</tr>
<tr>
<td>(DLBCL; R-CHOP)</td>
<td><strong>Pre-medication:</strong> chlorphenamine (8 mg), prednisolone (100 mg), acetaminophen (1 g), and tropisetron (5 mg)</td>
<td>All rapid infusions were well tolerated with no IRRs</td>
</tr>
<tr>
<td>Milone J, et al.</td>
<td>All patients had previously received rituximab at standard infusion rate for ≥1 infusion without grade 3/4 toxicity</td>
<td>Data from 31 patients and 67 rapid infusions</td>
</tr>
<tr>
<td>ASH 2007: Abstract 4503</td>
<td>Subsequent courses over 90 minutes (20% of dose over first 30 minutes, remaining 80% over 60 minutes)</td>
<td>Four patients had grade 1 AEs and one patient developed a grade 3 AE and withdrew from rapid protocol</td>
</tr>
<tr>
<td>(NHL, CLL; R-CHOP or R-maintenance)</td>
<td><strong>Pre-medication:</strong> oral acetaminophen, hydrocortisone (IV), diphenhydramine</td>
<td>Rapid infusion was safe and well tolerated</td>
</tr>
<tr>
<td>El-Agnaf MR, et al.</td>
<td>375 mg/m² using standard infusion rate for first infusion</td>
<td>Data from 17 patients and 73 rapid infusions</td>
</tr>
<tr>
<td>Leuk Lymphoma 2007</td>
<td>Subsequent infusions over 90 minutes (20% of the dose in the first 30 minutes and the remaining 80% over 60 minutes)</td>
<td>No AEs reported</td>
</tr>
<tr>
<td>(DLBCL, FL; R-CHOP, R-CVP)</td>
<td><strong>Pre-medication:</strong> chlorphenamine (10 mg IV), corticosteroids (hydrocortisone, 100 mg IV), acetaminophen (1 g) 30 minutes prior</td>
<td>Rapid infusion was safe and well tolerated</td>
</tr>
<tr>
<td>Siano M, et al.</td>
<td>375 mg/m² at an initial infusion rate of 200 mg/h in the first cohort and increased by 100 mg/h in each subsequent cohort</td>
<td>Data from 32 patients and 128 cycles</td>
</tr>
<tr>
<td>ASH 2007: Abstract 3411</td>
<td>Rate increased by 100 mg/h every 30 minutes within each cycle to the prescribed total dose</td>
<td>All patients tolerated the increased infusion rate without major side effects</td>
</tr>
<tr>
<td>(DLBCL, FL, indolent and aggressive NHL; most R-chemo)</td>
<td>In each subsequent infusion, initial rate increased by 100 mg/h to a maximal rate of 700 mg/h</td>
<td>Concluded that rituximab could be administered safely as a one-hour infusion without steroid pre-medication in patients with normal cardiac function who had already received at least one rituximab dose in the previous three months</td>
</tr>
<tr>
<td><strong>Pre-medication:</strong> Standard antihistamines and acetaminophen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wenger M, et al.</td>
<td>375 mg/m² administered every 8 weeks for a maximum of 2 years</td>
<td>Data from 545 patients and 5,579 combined standard and rapid infusions</td>
</tr>
<tr>
<td>EHA 2008: Abstract 0272</td>
<td>82.5% of patients used standard infusion rate for the first maintenance infusion</td>
<td>One SAE with standard infusion, but otherwise no SAEs within 24 hours of the maintenance infusion, including those receiving rapid infusion</td>
</tr>
<tr>
<td>Witzens-Harig M, et al.</td>
<td>At one year, 54% patients were receiving rapid infusion</td>
<td>141 SAEs recorded in 104 patients who received at least 1 infusion (all but 19 considered unrelated)</td>
</tr>
<tr>
<td>ASH 2008: Abstract 1998</td>
<td><strong>Pre-medication:</strong> Standard antihistamines and acetaminophen</td>
<td>Rapid infusion protocol was well tolerated as maintenance therapy</td>
</tr>
<tr>
<td>Foa R, et al.</td>
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<tr>
<td>ASH 2010: Abstract 3945</td>
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<tr>
<td>(MAXIMA)</td>
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<td></td>
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<tr>
<td>(FL; R-maintenance)</td>
<td></td>
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<tr>
<td>Al Zahrani A, et al.</td>
<td>375 mg/m² using standard infusion rate for first course</td>
<td>Data from 21 patients and 126 infusions</td>
</tr>
<tr>
<td>J Oncol Pharm Pract 2009</td>
<td>Subsequent courses over 90 minutes (20% of the dose in the first 30 minutes and the remaining 80% over 60 minutes)</td>
<td>Rapid infusion was well tolerated with no grade 3/4 IRRs</td>
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<tr>
<td><strong>Oncology setting</strong></td>
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</tbody>
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| Peinert S, et al.        | • Standard infusion rate for first infusion  
| EHA 2009: Abstract 0424 | • Subsequent infusions over 90 minutes (20% of the dose in the first 30 minutes and the remaining 80% over 60 minutes)  
| (DLBCL, FL, CLL, indolent NHL; most R-chemo) | Pre-medications: Standard including corticosteroids | • Data from 2 cohorts totalling 108 patients and 284 rapid infusions  
|                          | • No grade 3/4 AEs  
|                          | • Only 2/284 (0.7%) administrations associated with IRRs, which were resolved with interruption for 30 minutes and additional antihistamine and corticosteroids  
|                          | • Liberated resources as a result of reduced infusion times were used for 15 additional treatments |
| Provencio M, et al.      | • See Provencio M, et al. 2006 | • Data from 42 patients  
| Leuk Lymphoma 2009       |                          | • Data suggest that rapid infusion does not cause relevant cardiac toxicity; however, there was a high percentage of reductions in LVEF >10% |
| (NHL; R-chemo)           | • 375 mg/m² using standard infusion rate for first infusion  
|                          | • Subsequent infusions given over 60 minutes  
|                          | Pre-medications: hydrocortisone (100 mg IV), oral acetaminophen (1000 mg) and chlorphenamine (10 mg IV) | • Data from 54 patients and 105 rapid infusions  
|                          | • No significant IRRs were noted  
|                          | • Survey of 20 major cancer centres in the UK showed that 70% of centres were using rapid 90-minute infusion protocol |
| Tuthill M, et al.        | • First infusion of first course using standard infusion rate  
| Eur J Haematol 2009      | • All subsequent infusions in all courses over 2 hours, with an increase in dose every 30 minutes, for a total of 1000 mg per infusion  
| (NHL, Maltoma, ITP)      | Pre-medications: acetaminophen (1000 mg orally), diphenhydramine (50 mg orally), methylprednisolone (100 mg IV) | • Data from 10 patients and 40 infusions (30 rapid infusions)  
|                          | • One patient reported minor IRR, which was resolved during the infusion  
|                          | • Rapid infusion protocol was safe and well tolerated in this community setting |
| Bukh G, et al.           | • Initial infusion rate for the first cycle was 50 mL/h, increased by 50 mL/h every 30 minutes up to 200 mL/h (3.25 hours in total)  
| ACR 2008: Abstract 1885 | • Next cycle was given initially at 200 mL/h, increased by 200 mL/h after 30 minutes up to 400 mL/h (1.5 hours in total)  
|                          | Pre-medications: acetaminophen (1 g orally), methylprednisolone (100 mg IV), clemastine (1 mg IV) | • Data from 13 patients and 14 treatment courses  
|                          | • One patient experienced a grade 1 AE and one patient had to stop treatment after one hour due to IRRs  
|                          | • No unexpected or serious AEs were recorded |
| Schoeffel DA, et al.     | • First infusion of each course using standard infusion rate  
| EULAR 2008: Abstract FRI0161 | • Second infusion of each course over 67 minutes (range: 37–150 minutes) | • Data from 42 patients and 74 treatment courses  
|                          | • Rapid infusion was found to be well tolerated in all patients |

**ACR** = American College of Rheumatology; **AE** = adverse event; **SAR** = serious adverse event; **ASH** = American Society of Hematology; **CLL** = chronic lymphocytic leukemia; **DLBCL** = diffuse large B-cell lymphoma; **EHA** = European Hematology Association; **EULAR** = European League Against Rheumatism; **FL** = follicular lymphoma; **IRR** = infusion-related reaction; **ITP** = idiopathic thromocytopenic purpura; **IV** = intravenous; **LVEF** = left ventricular ejection fraction; **NHL** = non-Hodgkin’s lymphoma; **R** = rituximab; **R-chemo** = rituximab plus chemotherapy; **R-maintenance** = rituximab maintenance; **R-monotherapy** = rituximab as single agent; **SLL** = small lymphocytic leukemia
Appendix B. Rituximab infusion protocol at Princess Margaret Hospital

Rituximab (Rituxan®) Infusion Rate Guidelines and Hypersensitivity Reaction Algorithm

First infusion: Rituximab in normal saline (1 mg/mL) – Infuse 50 mL/hr for first hour, then increase by 50 mg/hour every 30 minutes to a maximum of 400 mg/hr

Patient reacts

Assess patient for hypersensitivity reaction
See below for toxicity grading

Patient tolerates

Continue with infusion schedule

Grade 1 or 2 reactions
May continue with rituximab infusion
Administer PRN medications appropriate to reactions
- Diphenhydramine (Benadryl®) 50 mg iv x 1 for flushing, rash, urticaria
- Acetaminophen (Tylenol®) 650 mg po x 1 for fever
- Meperidine (Demerol®) 25–50 mg iv x 1 for rigors/chills
- Dimenhydrinate (Gravol®) 50 mg iv x 1 for nausea and/or vomiting
- Normal saline bolus 500–1000 mL iv for hypotension
- Famotidine (Pepcid®) 20 mg iv x 1 for additional histamine blocker
- O2 2–4 L nasal prongs
- Ventolin inhaler 2 puffs x 1 for wheezing

Grade 3 or 4 reactions – STOP infusion
Give PRN medications appropriate for reactions. If no resolution of symptoms, add hydrocortisone sodium succinate (SoluCortef®) 100 mg iv x 1 over 5 minutes. If still no improvement, page physician STAT

If symptoms improve, restart rituximab infusion at 50% of the iv rate at which the reaction occurred and continue with the escalation schedule

If patient reacts a 2nd time, restart after the clearance of symptoms at one infusion rate lower and continue at the rate without further escalation

For subsequent rituximab infusion, if patient experienced:
No reactions: Proceed with the accelerated rituximab infusion (90 minutes)*
Grade 1 or 2 reaction: Proceed with the accelerated rituximab infusion (90 minutes)*
Grade 3 or 4 reaction: Consult with physician to determine rate for subsequent infusion

*Accelerated rituximab infusion rate (90 minutes)
Rituximab in 250 mL of normal saline – Infuse 50 mL of the dose over 30 minutes (100 mL/hr), then infuse the remaining 200 mL over 60 minutes (200 mL/hr)

Toxicity grading

Grade 1 and 2
- Fever of 38° C up to and including 40° C
- Mild to moderate rigors/chills
- Intense and wide spread itching or pruritis
- Rash, flushing, and urticaria (duration is less than 24 hours)
- Hypoxia – decrease O2 saturation with activity and requires intermittent oxygen treatment
- Symptomatic cough (may require narcotic medication, such as codeine)
- Dizziness that is not interfering with activity
- Wheezing and/or bronchospasm that is not interfering with activity
- Hypertension with or without symptoms (greater than 20 mmHg from baseline) – drug intervention may be required
- Hypotension with or without symptoms (less than 20 mmHg from baseline), that responds to intravenous fluid

Based on assessment finding, RN may treat patient’s symptoms accordingly with PRN medications

Grade 3 and 4
- Fever greater than 40° C
- Severe rigors/chills that are not responding to narcotics
- Urticaria and rash that lasts longer than 24 hours
- Symptomatic cough that is interfering with sleep or activity of daily living (ADL)
- Dizziness that is not interfering with ADL
- Wheezing, bronchospasm that are interfering with activity
- Hypoxia – O2 saturation is less than 88% at rest and requires continuous oxygen treatment
- Uncontrolled hypertension that requires more than one drug intervention
- Sustained hypotension that is equal to or lasting longer than 24 hours

Notify physician and respiratory therapist STAT if patient experiencing acute respiratory distress
References: