Published in final edited form as:

Clin J Oncol Nurs. 2018 August 01; 22(4): 407–414. doi:10.1188/18.CJON.407-414.

Hypersensitivity Reactions: Priming practice change to reduce incidence in first-dose rituximab treatment

Carissa Laudati, BSN, RN, OCN, Caroline Clark, BSN, RN, OCN, Andrea Knezevic, MS, Zhigang Zhang, PhD, and Margaret Barton-Burke, PhD, RN, FAAN

Memorial Sloan Kettering Cancer Center

Abstract

Background: Rituximab is a widely used anti-cancer treatment with a high incidence of hypersensitivity reaction (HSR). Strategies to reduce the incidence of HSR include premedications and slow titration. There is a lack of literature reporting on the priming method used when preparing rituximab intravenous lines and the potential impact on incidence of HSR.

Objectives: The primary objective was to evaluate the incidence of HSR in titrated first-dose rituximab infusions when priming intravenous line with rituximab as compared to priming with diluent.

Methods: A retrospective, comparative descriptive study (n=200) with two arms (rituximab-prime versus diluent-prime) was conducted through chart review. Study variables included incidence of HSR in relation to priming method, age, sex, diagnosis, and premedications. For patients with HSR, severity, time to onset, and rate of infusion were examined.

Findings: Incidence of HSR was significantly higher in the diluent-primed arm (35%) versus the drug-primed arm (19%; $p=0.01$). Other significant findings included higher incidence of HSR in women (34.1% versus 21.1% in men; $p=0.04$), and a lower incidence of HSR in patients pre-medicated with dexamethasone (19.1% versus 36.7%; $p=0.005$).

Keywords

Rituximab; Cytokine release syndrome; Priming; Hypersensitivity Reaction or HSR; Intravenous lines

Background

Rituximab (Rituxan) is a widely used chimeric murine/human monoclonal antibody (MAB). It is the cornerstone of recommended treatment for B-cell lymphoid malignancies including Chronic Lymphocytic Leukemia (CLL), Non-Hodgkin's lymphoma (NHL), and Primary Central Nervous System Lymphoma (PCNSL) (NCCN, 2016a; NCCN, 2016b; NCCN 2016c; Plosker & Figgitt, 2003). Rituximab is administered weekly or intermittently in combination with chemotherapy regimens, or as part of a single agent maintenance schedule, depending on indication. Rituximab kills cancer cells through direct signaling against CD-20 antigens, complement dependent cellular cytotoxicity, and antibody dependent cellular cytotoxicity (Weiner, 2010). Similar to other MABs there is a high potential for

hypersensitivity reactions (HSRs) with rituximab; symptoms vary from mild to life-threatening (Chung, 2008).

The HSRs with MAB treatment are attributed to cytokine release syndrome due to their mechanism of targeting immune system antigens such as CD-20 (Chung, 2008; Gobel, 2007). As tumor antigen-expressing cells are destroyed, cytokines, such as tumor necrosis factor, interleukin, and interferon are released into the blood (Breslin, 2007; Chung, 2008; Gobel, 2007). Rising blood levels of cytokines can trigger symptoms similar to those observed with a natural inflammatory response and can include, fever, chills, rigors, rash, headache, hypotension, shortness of breath, bronchospasm, nausea, vomiting, and abdominal pain (Breslin, 2007; Chung, 2008; Gobel, 2007).

Genentech, the manufacturer of rituximab, reports a 77% incidence of HSR with the initial dose based on data from 2,783 patients treated with rituximab in their original studies (Genentech, 2016). The highest percentage of targeted cells are destroyed with this first dose resulting in a decreased tumor burden and less cytokine release with subsequent infusions, and therefore a reduced incidence of HSR (Breslin, 2007).

Colwell et al. (2007) studied the impact of infusion reactions on patients, their caregivers, and the healthcare providers treating the patients. In a survey of 202 oncology nurses it was reported that infusion reactions were most common in patients receiving rituximab, and were extremely or very disruptive to patients, caregivers, and nurses (Colwell et al., 2007). Other findings were that HSRs result in prolonged infusion time, require rescue medications, increase patient and caregiver anxiety, increase stress and anxiety for staff, and disrupt nursing workflow (Colwell et al., 2007). Additionally, severe HSRs can lead to discontinuation of a drug and replacement with an alternative agent that may be less effective or more toxic (Mezzano, Biavina-Bianchi, Picard, Caiado, & Castells, 2014). Every effort should be made to reduce the incidence of HSR to allow for adherence to the treatment regimen and reduce negative effects on the patient and their caregivers.

Strategies to reduce the incidence of HSR in patients being treated with rituximab include routine premedication with antihistamines and antipyretics and a titrated infusion. A slow titrated infusion allows for incremental exposure to drug and gradual release of cytokines into the blood (Breslin, 2007; Gobel, 2007). This practice has been found to reduce the incidence and severity of HSRs (Genentech, 2016; Gobel 2007; Swan et al., 2014; Vogel, 2010). Although some recent research indicates rapid intravenous infusion or subcutaneous administration of subsequent doses of rituximab are safe and well tolerated, the recommendation for first-dose rituximab continues to be slow intravenous titration over four to six hours to reduce the risk of HSR (FDA, 2017; Genentech, 2016; Lang, Hagger, & Pearson, 2011; Swan et al., 2014). In the original studies infusions were started at 50mg/hour and titrated to a maximum rate of 400mg/hour. However, there is no information from these studies indicating the manner in which the intravenous lines were primed (Coiffier et al., 1998; Coiffier et al., 2010; Davis et al., 1999; Davis et al., 2000; Habermann et al., 2006; Hallek et al., 2010; Hochster et al., 2009; Maloney et al., 1997; Marcus et al., 2005; McClaughlin et al., 1998; Pfreundschuh et al., 2006; Piro et al., 1999; Robak et al., 2010;

Salles et al., 2011). Therefore, it is unknown if variability in intravenous line priming impacts the incidence of rituximab-related HSR.

At Memorial Sloan Kettering Cancer Center where more than 5,000 doses of rituximab are dispensed annually, treatments were prepared by priming the intravenous line with a compatible diluent (normal saline or dextrose 5%). This practice results in patients receiving diluent rather than rituximab during early titration phases. The impact of priming titrated, highly reactive drugs, such as rituximab, with diluent is not reported in the literature.

A small pilot study (n=105) was conducted to determine if priming the intravenous line with drug would reduce the incidence of HSRs. This change in practice allowed for slow exposure to the drug as recommended in the literature. The pilot study demonstrated a decrease in the incidence of HSR for patients receiving the first-dose of rituximab from 31.8% (diluent) to 11.8% (rituximab), respectively (Laudati, Clark, Sumka, Timoney & Hamlin, 2017). Although these findings were not statistically significant, they were considered clinically significant, and an organization-wide practice change was implemented to prime all rituximab lines with drug. The purpose of this article is to present findings of a retrospective study that examined the HSR rates in a larger sample of patients receiving first-dose rituximab.

Study Objectives

The primary objective of this study was to evaluate the incidence of HSR in first-dose rituximab infusion when the intravenous line was primed with drug compared to when the intravenous line was primed with diluent. The secondary objectives of the study were to evaluate the relationship between demographic and histologic variables (age, sex, and diagnosis) and incidence of HSR with first-dose rituximab treatment; evaluate the time of onset of HSR recorded in minutes from beginning of infusion; report the rate of infusion at time of HSR and evaluate for relationship between rate of infusion and incidence of HSR; report severity of HSR as measured by grade of reaction; and evaluate the relationship between premedications given and incidence of HSR with first-dose rituximab treatment.

Prior to initiation of the study, a power analysis was calculated to determine the sample size necessary to meet study objectives. Pilot study results were used for this calculation (Laudati et al., 2017). It was determined that a minimum of 82 patients in each arm would provide 90% power for testing a 20% difference in incidence between study arms, using a one-sided two-sample test of proportion at alpha 0.05. Therefore, 100 patients were enrolled in each arm.

Methods

After Institutional Review Board approval, investigators conducted a descriptive study using a retrospective chart review method, with two study arms. Study Arm A included data from October 1, 2015-April 1, 2016, before the change in practice when rituximab intravenous lines were primed with diluent (normal saline). Study Arm B included data from October 1, 2016-April 1, 2017 after the change in practice when rituximab intravenous lines were primed with rituximab.

First-dose rituximab was administered starting at 50mg/hour and titrated by 50mg/hour increments every 30 minutes, to a maximum rate of 400mg/hour. Patients received standard premedications of acetaminophen 650mg and diphenhydramine 50mg intravenously. Patients receiving a chemotherapy-containing regimen received Dexamethasone 12mg in addition to acetaminophen and diphenhydramine as standard premedication. Investigators noted non-standard premedication administration when hydrocortisone was added to the regimen, or doses of acetaminophen and/or diphenhydramine were modified by provider.

Eligible subjects included patients 18 years of age and older, treated with first-dose of rituximab for NHL, CLL, or PCNSL. Charts were identified using a hospital computer patient data system which identified first-dose rituximab patients treated. Patients under 18 years of age, those who received rituximab in the past, those who received split dose rituximab, and those who received rituximab for an indication other than those above were excluded from recruitment for optimal control of the sample. The investigators confirmed that subjects met these criteria through chart review. 364 charts were reviewed; 164 were excluded due to previous rituximab exposure, split dose rituximab, different diagnosis and/or incomplete chart documentation. A total of 200 patients were included in the study; 100 patients in each arm.

Data points (Table 1) were collected from electronic medication administration records, infusion nurse documentation and the patient electronic health record. Patients were identified as having a HSR based on documentation of symptoms of HSR during rituximab infusion. HSR severity was graded according to Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 grading criteria for cytokine release and infusion related reaction (Table 2).

Statistical Methods

Demographic and clinical characteristics were summarized with descriptive statistics, overall and by study arms. Incidence of HSR was calculated in each study arm and compared between arms with an odds ratio. In addition, demographic and clinical characteristics were reported for patients who experienced HSR versus no HSR across study arms, and characteristics were compared between outcome groups with odds ratios. Group comparisons were performed with a chi-square test for categorical variables, except where small sample size necessitated the Fisher's exact test. Continuous variables with normal distributions were compared using the two-sample T-test and those with non-normal distributions were compared between groups using the Wilcoxon rank sum test. All tests were evaluated for statistical significance at alpha level 0.05. Statistical analysis was performed using SAS version 9.4 (Cary, NC).

Findings

The description of the study population is found in Table 3. Age, sex and diagnosis did not differ statistically between study arms. Overall, patients had a mean age of 63 years (range: 22, 93; Table 3). There were 109 men and 91 women included in the sample. The majority of patients (90.5%) had NHL, while 8% had CLL, and 1.5% had PCNSL. Almost every patient (99.5%) was premedicated with acetaminophen and antihistamine (Table 3).

Additionally, 55% of patients also received dexamethasone 12 mg, and 15% of patients received hydrocortisone. Frequency of these premedications did not differ statistically between study arms.

The overall incidence of HSR was 27% (Table 3). Incidence of HSR was significantly higher in the diluent-primed arm versus the drug-primed arm (35% versus 19% respectively; $p=0.01$; Table 3). All HSR events were reported to be CTCAE Grade 2. For patients who experienced HSR ($n=54$), the overall median time to HSR from beginning of infusion was 96 minutes (IQR: 75, 129). Patients in the drug-primed arm had a significantly shorter time to HSR (median: 86 minutes) versus patients in the diluent-primed arm (median: 105 minutes; $p=0.008$; Figure 1). For patients who experienced HSR, the overall median rate of infusion at time of HSR was 150 mg/hr (IQR: 100, 150). Patients in the drug-primed arm had a significantly lower rate of infusion (median: 100 mg/hr) than the diluent-primed arm (median: 150 mg/hr; $p=0.01$; Figure 2).

Comparison of demographic and clinical characteristics between patients who had a HSR with those who did not is presented in Table 4. There was no statistically significant difference in age or disease diagnosis between these groups ($p=0.92$, 0.49 , respectively; Table 4). Patients given the infusion primed with diluent were 2.3 times more likely to experience HSR than patients given infusion primed with drug (35% versus 19%; OR: 2.3; $p=0.01$). Women were nearly twice as likely to experience HSR as men (34.1% versus 21.1%; OR: 1.93; $p=0.04$). Patients given dexamethasone premedication were 59% less likely to experience HSR than patients not given dexamethasone (19.1% versus 36.7%; OR=0.41; $p=0.005$). Administration of standard premedications and hydrocortisone were not significantly associated with HSR, although the p -values were borderline statistically significant ($p=0.054$, 0.07 , respectively).

Discussion

The study findings indicate a lower incidence of HSR in patients receiving first-dose rituximab when the intravenous line is primed with drug. The overall incidence of HSR in this study was 27% which is lower than the 77% reported incidence of HSR for first-dose rituximab (Genentech, 2016). When the intravenous line was primed with drug, patients were 66% less likely to experience HSR than patients in the diluent-primed arm. These results indicate that priming the intravenous line with rituximab, as opposed to diluent, allows for a slow, incremental exposure to the drug; resulting in decreased incidence of HSR. These findings support the findings from the small pilot study evaluating this priming practice change and its impact on incidence of HSR (Laudati et al., 2017).

The study found no relationship between age or diagnosis and incidence of HSR. Surprisingly, the findings did show that women were nearly twice as likely to experience HSR as men. This was interesting to the researchers, as demographic variables in relation to HSR were not reported in the original studies (Coiffier et al., 1998; Coiffier et al., 2010; Davis et al., 1999; Davis et al., 2000; Habermann et al., 2006; Hallek et al., 2010; Hochster et al., 2009; Maloney et al., 1997; Marcus et al., 2005; McClaughlin et al., 1998; Pfreundschuh et al., 2006; Piro et al., 1999; Robak et al., 2010; Salles et al., 2011).

This study found that when the intravenous line was primed with rituximab, the time to HSR was significantly shorter and the rate of infusion at time of HSR was significantly lower than when primed with diluent. When the intravenous line is primed with rituximab, the patient is exposed to rituximab immediately upon initiation of the infusion. Upon this exposure, tumor cells are killed and cytokines are released into the blood which can result in HSR symptoms (Breslin, 2007; Chung, 2008; Gobel, 2007). However, when the intravenous line is primed with diluent, the patient receives only diluent for approximately 40 minutes before being exposed to the rituximab, resulting in delayed cell death and cytokine release. Therefore, it is not unexpected that the study found patients in the drug-primed arm experienced HSR symptoms earlier and at a lower rate of infusion than patients in the diluent-primed arm.

All HSR events, in both study arms, were reported as grade 2 according to CTCAE Version 4.03 guidelines. The priming method did not have an impact on the severity of HSR in those patients who experienced a reaction. This finding was consistent with reported grade of infusion reactions in the original studies (Coiffier et al., 1998; Coiffier et al., 2010; Davis et al., 1999; Davis et al., 2000; Habermann et al., 2006; Hallek et al., 2010; Hochster et al., 2009; Maloney et al., 1997; Marcus et al., 2005; McClaughlin et al., 1998; Pfreundschuh et al., 2006; Piro et al., 1999; Robak et al., 2010; Salles et al., 2011).

There was a significantly lower rate of HSR noted when dexamethasone was used as a premedication. Patients who received dexamethasone 12mg premedication, when receiving rituximab in combination with a chemotherapeutic regimen that required it, were 59% less likely to experience HSR as compared to patients not given dexamethasone. The addition of this steroid premedication appears to reduce the incidence of HSR in patients receiving first-dose rituximab. It would seem the addition of this premedication, when weighed against patient tolerability and side effects, may be a beneficial addition to the standard premedication regimen.

Limitations

One limitation of this study is the retrospective design. Data collected from charts relied on accurate and complete documentation in the patient's medical record, and some patients were excluded due to incomplete documentation. The setting of a single center site is a second limitation of the study. The population of patients treated with first-dose rituximab at this center may not be representative of the population at large. Additionally, this study did not exclude patients treated with rituximab in combination with chemotherapy. The chemotherapy agents could potentially reduce tumor burden and subsequent cytokine release upon exposure to rituximab. Furthermore, variation between premedication standards at other cancer centers could impact the incidence of HSR. Therefore, results may not be generalizable to the general hematologic oncology population.

Implications for Practice

Treatment with MABs, particularly first-dose rituximab, have a high risk for HSR. Reducing the incidence of HSR in this population can improve patient safety, reduce patient and caregiver anxiety, improve nursing workflow, and prevent treatment delays. Interventions to reduce incidence of HSR should be considered. Standard premedications and slow titration

of rituximab infusions are recommended to reduce HSR during rituximab infusion. Based on the study findings, researchers recommend incorporating priming rituximab intravenous lines with drug as best practice. To standardize practice, manufacturers could consider including recommendations for priming intravenous line with drug in the prescribing information. This can reduce the incidence of HSR and the negative associated effects. Adopting this practice change would require the nurse to anticipate HSR symptomatology earlier during the infusion than when primed with diluent due to earlier exposure to drug.

Additionally, many MABs other than rituximab have a high risk for HSR and therefore are also administered via a slow titrated infusion (i.e. daratumumab, obinutuzumab, ofatumumab, and elotuzumab). Priming these MABs with drug could be considered to reduce incidence of HSR, and is a potential area of future research. Variability in premedication standards is another area for future research to establish best practices to minimize risk for HSR.

For administrators, there are potential financial benefits to this change as well. Management of HSRs results in increased length of stay in the infusion unit, administration of additional medications, and complex nursing care. This impact on chair utilization and nursing productivity can be costly. Reducing the incidence of HSR is a potential area of cost savings for cancer centers.

With increased attention to personal exposure and the occupational risk with administration of antineoplastic agents, nurses may express concerns about handling of drug-primed intravenous lines versus diluent-primed intravenous lines. Although rituximab is not on the National Institute for Occupational Safety and Health (NIOSH) hazardous drug list, nurses should take precautions to minimize occupational exposure (Polovich, Olsen, & LeFebvre, 2014). Appropriate personal protective equipment (PPE) and a closed system transfer device can be used as a precaution when handling drug-primed intravenous lines.

The nurse is a key patient advocate and member of the multidisciplinary team who can coordinate efforts to minimize adverse events in patients undergoing treatment with high risk of HSR. This study lays the groundwork for setting priming practice standards for preparation of titrated MABs with high risk for HSR. Priming the intravenous line with drug is a simple intervention that can positively impact patient care.

Acknowledgements:

The authors gratefully acknowledge Erica Fischer-Carlidge DNP, CNS, CBCN, AOCNS and Jeanine Gordon MSN, RN, OCN for assistance with critical review and editing of the manuscript. The authors also gratefully acknowledge the support, encouragement, and resources provided by Michele Kranz, MA, RN, NE-BC, Paul Hamlin, MD, and James Sumka, Pharm D.

Funding: MSK Cancer Center Support Grant/Core Grant (P30 CA008748)

References

- Breslin S (2007). Cytokine-release syndrome: Overview and nursing implications. *Clinical Journal of Oncology Nursing*, 11(1), 37–42. doi: 10.1188/07.CJON.S1.37-42 [PubMed: 17471824]

- Chung C (2008). Managing premedications and the risk for reactions to infusional monoclonal antibody therapy. *The Oncologist*, 13, 725–732. doi: 10.1634/theoncologist.2008-0012 [PubMed: 18586928]
- Coiffier B, Haioun C, Ketterer N, Engert A, Tilly H, ... Reyes F (1998). Rituximab (anti-CD20 monoclonal antibody) for the treatment of patients with relapsing or refractory aggressive lymphoma: A multicenter phase II study. *Blood*, 92(6), 1927–1932. Retrieved from <http://www.bloodjournal.org/content/92/6/1927.long> [PubMed: 9731049]
- Coiffier B, Thieblemont C, Van Den Neste E, Lepeu G, Plantier I, ... Bordessoule D (2010). Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. *Blood*, 116(12), 2040–2045. doi: 10.1182/blood-2010-03-276246 [PubMed: 20548096]
- Colwell H, Mathias S, Ngo N, Gitlin M, Lu J, & Knoop T (2007). The impact of infusion reactions on oncology patients and clinicians in the inpatient and outpatient practice settings: Oncology nurses' perspectives. *Journal of Infusion Nursing*, 30(3), 153–160. doi: 10.1097/01.NAN.0000270674.13439.5b [PubMed: 17505216]
- Davis T, White C, Grillo-Lopez A, Velasquez W, Link B, Maloney D, ... Levy R (1999). Single-agent monoclonal antibody efficacy in bulky non-Hodgkin's lymphoma: Results of a phase II trial of rituximab. *Journal of Clinical Oncology*, 17, 1851–1857. doi: 10.1200/JCO.1999.17.6.1851 [PubMed: 10561225]
- Davis T, Grillo-Lopez A, White C, McLaughlin P, Czuczman M, Link B, ... Levy R (2000). Rituximab Anti-CD20 monoclonal antibody therapy in non-Hodgkin's lymphoma: Safety and efficacy of re-treatment. *Journal of Clinical Oncology*, 18 (17), 3135–3143. doi: 10.1200/JCO.2000.18.17.3135 [PubMed: 10963642]
- Genentech. (2016). Rituximab: Full prescribing information. San Francisco, CA: Genentech Retrieved from https://www.gene.com/download/pdf/rituxan_prescribing.pdf
- Gobel B (2007). Hypersensitivity reactions to biological drugs. *Seminars in Oncology Nursing*, 23(3), 191–200. doi: 10.1016/j.soncn.2007.05.009 [PubMed: 17693346]
- Habermann T, Weller E, Morrison V, Gascoyne R, Cassileth P, ... Horning S (2006). Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. *Journal of Clinical Oncology*, 24(19), 3121–3127. doi: 10.1200/JCO.2005.05.1003 [PubMed: 16754935]
- Hallek M, Fischer K, Fingerle-Rowson G, Fink A, Busch R, ... Stilgenbauer S (2010). Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. *The Lancet*, 376 (9747), 1164–1174. doi: 10.1016/S0140-6736(10)61381-5/S0140-6736(10)61381-5
- Hochster H, Weller E, Gascoyne R, Habermann T, Gordon L, ... Horning S (2009). Maintenance rituximab after cyclophosphamide, vincristine, and prednisone prolongs progression-free survival in advanced indolent lymphoma: results of the randomized phase III ECOG 1496 study. *Journal of Clinical Oncology*, 27(10), 1607–1614. doi: 10.1200/JCO.2008.17.1561 [PubMed: 19255334]
- Lang D, Hagger C, & Pearson A (2011). Safety of rapid rituximab infusion in adult cancer patients: A systematic review. *International Journal of Nursing Practice*, 17(4), 357–369. doi: 10.1111/j.1440-172X.2011.01950.x [PubMed: 21781215]
- Laudati C, Clark C, Sumka J, Timoney J, & Hamlin P (2017, 5). Implication of rituximab priming practices. Poster session presented at the Oncology Nursing Society 42nd Annual Congress, Denver, CO.
- Maloney D, Grillo-Lopez A, White C, Bodkin D, Schilder R, ... Levy R (1997). IDEC-C2B8 (rituximab) anti-CD20 monoclonal antibody therapy in patients with relapsed low-grade non-Hodgkin's lymphoma. *Blood*, 90(6), 2188–2195. Retrieved from <http://www.bloodjournal.org/content/90/6/2188.long?sso-checked=true> [PubMed: 9310469]
- Marcus R, Imrie K, Belch A, Cunningham D, Flores E, Catalano J, ... Smith P (2005). CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. *Blood*, 105, 1417–1423. doi: 10.1182/blood-2004-08-3175 [PubMed: 15494430]
- McLaughlin P, Grillo-Lopez A, Link B, Levy R, Czuczman M, Williams M, ... Dallaire B (1998). Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma:

Half of patients respond to a four-dose treatment program. *Journal of Clinical Oncology*, 16, 2825–2833. doi: 10.1200/JCO.1998.16.8.2825 [PubMed: 9704735]

Mezzano V, Giavina-Bianchi P, Picard M, Caiado J, & Castells M (2014). Drug desensitization in the management of hypersensitivity reactions to monoclonal antibodies and chemotherapy. *BioDrugs*, 28, 133–144. doi: 10.1007/s40259-013-0066-x [PubMed: 23990250]

National Comprehensive Cancer Network, Inc. (NCCN). (2016a). NCCN Clinical Practice Guidelines in Oncology Version 1.2016: Central Nervous System Cancers. Retrieved from <https://www.nccn.org/about/nhl.pdf>

National Comprehensive Cancer Network, Inc. (NCCN). (2016b). NCCN Clinical Practice Guidelines in Oncology Version 1.2017: Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/ell.pdf

National Comprehensive Cancer Network, Inc. (NCCN). (2016c). NCCN Clinical Practice Guidelines in Oncology Version 4.2014 Updates: Non-Hodgkin's lymphomas. Retrieved from <https://www.nccn.org/about/nhl.pdf>

National Institutes of Health (NIH). (2010). Common Terminology Criteria for Adverse Events Version 4.03 (CTCAE). Retrieved from https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Pfreundschuh M, Trumper L, Osterborg A, Pettengell R, Tineny M, ... Loeffler M (2006). CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: A randomized controlled trial by the MabThera International Trial Group. *The Lancet*, 7, 379–391. doi: 10.1016/S1470-2045(06)70664-7 [PubMed: 16648042]

Piro L, White C, Grillo-Lopez A, Janakiraman N, Saven A, Beck T, ...Janin V (1999). Extended Rituximab therapy for relapsed or refractory low-grade or follicular non-Hodgkin's lymphoma. *Annals of Oncology*, 10, 655–661. doi: 10.1023/A:1008389119525 [PubMed: 10442187]

Plosker G, & Figgitt D (2003). Rituximab: a review of its use in non-Hodgkin's lymphoma and chronic lymphocytic leukaemia. *Drugs*, 63(8), 803–843. doi: 10.2165/00003495-200363080-00005 [PubMed: 12662126]

Polovich M, Olsen M & LeFebvre KB (2014). Nursing considerations in cancer treatment In Polovich M, Olsen M, & LeFebvre KB (Eds.), *Chemotherapy and Biotherapy Guidelines and Recommendations for Practice* (5th ed., pp 97–119). Pittsburgh, PA: Oncology Nursing Society. doi: 10.1200/JCO.2009.26.4556

Robak T, Dmoszynska A, Solal-Celigny P, Warzocha K, Loscertales J, Catalano J, ...Moiseev S (2010). Rituximab plus fludarabine and cyclophosphamide prolongs progression-free survival compared with fludarabine and cyclophosphamide alone in previously treated chronic lymphocytic leukemia. *Journal of Clinical Oncology*, 28(10), 1756–1765. doi: 10.1200/JCO.2009.26.4556 [PubMed: 20194844]

Salles G, Seymour J, Offner F, Lopez-Guillermo A, Belada D, ...Tilly H (2011). Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomized controlled trial. *The Lancet*, 377, 42–51. doi: 10.1016/S0140-6736(10)62175-7

Swan J, Zaghloul H, Cox J, & Murillo J (2014). Use of a pharmacy protocol to convert standard rituximab infusions to rapid infusion shortens outpatient infusion clinic visits. *Pharmacotherapy*, 34(7), 686–694. doi: 10.1002/phar.1420 [PubMed: 24706572]

Vogel W (2010). Infusion reactions: Diagnosis, assessment, and management. *Clinical Journal of Oncology Nursing*, 14(2), E10–21. doi: 10.1188/10.CJON.E10-E-21 [PubMed: 20350882]

U.S. Food and Drug Administration (FDA). (2017). FDA approves rituximab plus hyaluronidase combination for Treatment of FL, DLBCL and CLL. Retrieved from <https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm564235.htm>

Weiner G (2010). Rituximab: mechanism of action. *Seminars in Hematology*, 47(2), 115–123. doi: 10.1053/j.seminhematol.2010.01.011 [PubMed: 20350658]

Implications for Practice:

1. Hypersensitivity reactions to first-dose rituximab treatment can be reduced by priming intravenous lines with drug.
2. Standardized premedications, including acetaminophen, diphenhydramine and dexamethasone should be considered for all patients receiving first-dose rituximab infusions to reduce hypersensitivity.
3. A closed system transfer device and personal protective equipment should be used to minimize exposure with drug-primed intravenous lines.

Figure 1.
Time to HSR by type of intravenous line prime (N=54)

Figure 2.
Infusion Rate at time of HSR by type of intravenous line prime (N=54)

Table 1

Study Data Points

Demographic	Clinical Characteristics
Age	Diagnosis
Sex	Premedications given
	Intravenous line priming method
	Hypersensitivity reaction (HSR) symptomatology
	Grade of HSR per CTCAE Version 4.03 criteria
	Patients with HSR <ul style="list-style-type: none">•Time to onset from beginning of infusion•Rate of infusion at onset

Table 2:*CTCAE Version 4.03 – Infusion related reaction, and cytokine release syndrome (NIH, 2010)*

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Infusion related reaction Definition: A disorder characterized by adverse reaction to the infusion of pharmacological or biological substances	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for <=24 hours	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated	Death
Cytokine release syndrome Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and shortness of breath: it is caused by the release of cytokines from the cells	Mild reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for <=24 hours	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening consequences; pressor or ventilatory support indicated	Death

Table 3

Demographic and Clinical Characteristics, Overall and by Study Arm

	Overall (N=200)	Arm A Diluent prime (N=100)	Arm B Rituximab prime (N=100)	P*
Age – mean (range)	63 (22, 93)	63 (32, 93)	64 (22, 89)	0.80
Sex				
Female	91 (45.5)	48	43	0.47
Male	109 (54.5)	52	57	
Diagnosis				
Non-Hodgkin's lymphoma	181 (90.5)	89	92	0.06
Chronic lymphocytic leukemia	16 (8.0)	11	5	
Primary CNS lymphoma	3 (1.5)	0	3	
Premedications [†]				
Standard premedications	169 (84.5)	89	80	0.08
Hydrocortisone, 100mg	30 (15.0)	11	19	0.11
Dexamethasone, 12mg	110 (55.0)	53	57	0.57
Hypersensitivity reaction				
HSR [‡]	54 (27.0)	35	19	0.01
Time to HSR (minutes) [§] – median (IQR)	96 (75, 129)	105 (85, 141)	86 (60, 95)	0.008
Rate of infusion at time of HSR (mg/hr) [§] – median (IQR)	150 (100, 150)	150 (100, 200)	100 (50, 150)	0.01

Note. HSR = hypersensitivity reaction, IQR = interquartile range.

Values reported as frequency (percent) unless otherwise noted. Frequency, only, reported where denominator is 100.

* Chi-square test result for all categorical variables except diagnosis where Fisher's exact test is reported. Two-sample T-test for age (mean comparison) and Wilcoxon test for time to HSR and rate of infusion (median comparison).

[†] All patients received antihistamine 50mg and all patients except for one in study arm B received acetaminophen 650mg; no group comparisons shown.

[‡] All HSR events were reported to be Grade 2 by the Common Terminology for Adverse Events, Version 4.03.

[§] Reported in 54 patients with HSR.

Table 4

Demographic and Clinical Characteristics, by HSR

	HSR (N=54)	No HSR (N=146)	Odds Ratio (95% CI)	P*
Age – mean (range)	63 (22, 93)	63 (26, 93)		0.92
Sex				
Female	31 (34.1)	60 (65.9)	1.93	0.04
Male	23 (21.1)	86 (78.9)	[1.03, 3.64]	
Diagnosis				
Non-Hodgkin's lymphoma	47 (26.0)	134 (74.0)		0.49
Chronic lymphocytic leukemia	6 (37.5)	10 (62.5)		
Primary CNS lymphoma	1 (33.3)	2 (66.7)		
Primer				
Diluent	35 (35%)	65 (65%)	2.30	0.01
Rituximab	19 (19%)	81 (81%)	[1.20, 4.38]	
Premedications				
Standard premedications				
Given	50 (29.6)	119 (70.4)	2.83	0.054
Not given	4 (12.9)	27 (87.1)	[0.94, 8.5]	
Hydrocortisone, 100mg				
Given	4 (13.3)	26 (86.7)	0.37	0.07
Not given	50 (29.4)	120 (70.6)	[0.12, 1.11]	
Dexamethasone, 12mg				
Given	21 (19.1)	89 (80.9)	0.41	0.005
Not given	33 (36.7)	57 (63.3)	[0.21, 0.77]	

Note. HSR = hypersensitivity reaction; CI = confidence interval.

Values reported as frequency (row percent) unless otherwise noted.

* Chi-square test result for sex and medication; Fisher's exact test for diagnosis and two-sample T-test for age.