Hypersensitivity Reactions

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

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BACKGROUND: Strategies to reduce hypersensitivity reaction (HSR) incidence with rituximab include premedications and slow titration. Literature is lacking on the priming method used when preparing rituximab IV lines and the potential impact on HSR incidence.

OBJECTIVES: The primary objective is to evaluate HSR incidence in titrated first-dose rituximab infusions when priming IV lines with rituximab, as compared to priming with diluent.

METHODS: A retrospective, comparative, descriptive study with two arms (rituximab- versus diluent-primed) was conducted. Variables were HSR incidence in relation to priming method, age, sex, diagnosis, and premedications. For patients with HSR, severity, time to onset, and infusion rate were examined.

FINDINGS: HSR incidence was significantly higher in the diluent- versus the drug-primed arm. Other significant findings included higher HSR incidence in women and lower HSR incidence in patients premedicated with dexamethasone.

KEYWORDS
rituximab; cytokine release syndrome; priming; hypersensitivity reaction; IV lines

DIGITAL OBJECT IDENTIFIER
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RITUXIMAB (RITUXAN®) IS A WIDELY USED chimeric murine/human monoclonal antibody (MAB) and is the cornerstone of recommended treatment for B-cell lymphoid malignancies, including chronic lymphocytic leukemia (CLL), non-Hodgkin lymphoma (NHL), and primary central nervous system lymphoma (PCNSL) (National Comprehensive Cancer Network [NCCN], 2014, 2018a, 2018b; 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 CD20 antigens, complement-dependent cellular cytotoxicity, and antibody-dependent cellular cytotoxicity (Weiner, 2010). Similar to other MABs, rituximab has a high potential for hypersensitivity reactions (HSRs); symptoms vary from mild to life threatening (Chung, 2008).

HSRs with MAB treatment are attributed to cytokine release syndrome because of their mechanism of targeting immune system antigens such as CD20 (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 (2016), the manufacturer of rituximab, reported a 77% incidence of HSR with the initial dose based on data from 2,783 patients treated with rituximab in its original studies. 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, Colwell et al. (2007) reported that infusion reactions were most common in patients receiving rituximab and were extremely or very disruptive to patients, caregivers, and nurses. Other findings were that HSRs

resulted in prolonged infusion time, required rescue medications, increased patient and caregiver anxiety, more stress and anxiety for staff, and disrupted nursing workflow (Colwell et al., 2007). In addition, severe HSRs can lead to discontinuation of a drug and replacement with an alternative agent that may be less effective or more toxic (Mezzano, Giavina-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 to reduce negative effects on patients 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 the 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, Zaghloul, Cox, & Murillo, 2014; Vogel, 2010). Although some research indicates that rapid IV infusion or subcutaneous administration of subsequent doses of rituximab are safe and well tolerated, the recommendation for first-dose rituximab continues to be slow IV titration during four to six hours to reduce the risk of HSR (Genentech, 2016; Lang, Hagger, & Pearson, 2011; Swan et al., 2014; U.S. Food and Drug Administration, 2017). In the original studies, infusions were started at 50 mg per hour and titrated to a maximum rate of 400 mg per hour; however, no information from these studies indicates the manner in which the IV lines were primed (Coiffier et al., 1998, 2010; Davis et al., 1999, 2000; Habermann et al., 2006; Hallek et al., 2010; Hochster et al., 2009; Maloney et al., 1997; Marcus et al., 2005; McLaughlin et al., 1998; Pfreundschuh et al., 2006; Piro et al., 1999; Robak et al., 2010; Salles et al., 2011). Therefore, whether variability in IV line priming affects the incidence of rituximab-related HSR is unknown.

Objectives

At Memorial Sloan Kettering Cancer Center in New York, New York, where more than 5,000 doses of rituximab are given annually, treatments were prepared by priming the IV 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 whether priming the IV line with the 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) (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 the 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.

"Priming the IV line with rituximab allows for a slow, incremental exposure, resulting in decreased hypersensitivity reaction incidence."

The primary objective of this study was to evaluate the incidence of HSR in first-dose rituximab infusion when the IV line was primed with the drug compared to when the IV line was primed with diluent. The secondary objectives of the study were to evaluate the relationship among 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, to April 1, 2016, before the change in practice when rituximab IV lines were primed with diluent (normal saline). Study arm B included data from October 1, 2016, to April 1, 2017, after the change in practice when rituximab IV lines were primed with rituximab.

First-dose rituximab was administered starting at 50 mg per hour and titrated by 50 mg per hour increments every 30 minutes,

to a maximum rate of 400 mg per hour. Patients received standard premedications of acetaminophen 650 mg and diphenhydramine 50 mg IV. Patients receiving a chemotherapy-containing regimen received dexamethasone 12 mg in addition to acetaminophen and diphenhydramine as standard premedication. Investigators noted nonstandard premedication administration when hydrocortisone was added to the regimen, or doses of acetaminophen and/or diphenhydramine were modified by the provider.

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

Data points were collected from electronic medication administration records, infusion nurse documentation, and the patient electronic health record. Patients were identified as having an 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 (see Table 1).

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.

Findings

The description of the study population is found in Table 2. Age, sex, and diagnosis did not differ statistically among study arms.

TABLE 1.
CYTOKINE RELEASE SYNDROME AND INFUSION-RELATED REACTION

ADVERSE EVENT AND DEFINITION	GRADE 1	GRADE 2	GRADE 3	GRADE 4	GRADE 5
Cytokine release syndrome: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and shortness of breath; 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 or less	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
Infusion-related reaction: A disorder characterized by adverse reaction to the infusion of pharmacologic or biologic 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 or less	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

NSAID—nonsteroidal anti-inflammatory drug
Note. From *Common Terminology Criteria for Adverse Events* [v.4.03], by National Cancer Institute Cancer Therapy Evaluation Program, 2010. Retrieved from https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Overall, patients had a mean age of 63 years (range = 22–93). There were 109 men and 91 women included in the sample. The majority of patients (n = 181, 91%) had NHL, 16 (8%) had CLL, and 3 (2%) had PCNSL. Almost every patient (n = 199, 99.5%) was premedicated with acetaminophen and antihistamine. In addition, 110 patients (55%) also received dexamethasone 12 mg and 30 patients (15%) received hydrocortisone. Frequency of these premedications did not differ statistically between study arms.

The overall incidence of HSR was 27%. Incidence of HSR was significantly higher in the diluent-primed arm versus the drug-primed arm (35% versus 19%, respectively; p = 0.01). 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 (interquartile range [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). For patients who experienced HSR, the overall median rate of infusion at time of HSR was 150 mg per hour (IQR = 100–150). Patients in the drug-primed arm had a significantly lower rate of

TABLE 2.
DEMOGRAPHIC AND CLINICAL CHARACTERISTICS BY STUDY ARM

	DILUENT-PRIMED (N = 100)		RITUXIMAB-PRIMED (N = 100)		
CHARACTERISTIC	**$\bar{X}$**	**RANGE**	**$\bar{X}$**	**RANGE**	**p[a]**
Age (years)	63	32–93	64	22–89	0.8
CHARACTERISTIC	**MEDIAN**	**IQR**	**MEDIAN**	**IQR**	**p[a]**
Time to HSR (minutes)[b]	105	85–141	86	60–95	0.008
Rate of infusion at time of HSR (mg/hour)[b]	150	100–200	100	50–100	0.01
CHARACTERISTIC		**n**		**n**	**p[a]**
Sex					0.47
Male		52		57	
Female		48		43	
Diagnosis					0.06
Non-Hodgkin lymphoma		89		92	
Chronic lymphocytic leukemia		11		5	
Primary central nervous system lymphoma		–		3	
Premedications[c]					
Standard		89		80	0.08
Dexamethasone 12 mg		53		57	0.57
Hydrocortisone 100 mg		11		19	0.11
HSR[d]					0.01
No		65		81	
Yes		35		19	

[a] Chi-square test result for all categorical values 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)
[b] Reported in 54 patients with HSR
[c] All patients received antihistamine 50 mg, and all patients except one in the rituximab-primed arm received acetaminophen 650 mg; no group comparisons are shown.
[d] All HSR events were reported to be grade 2 by the Common Terminology Criteria for Adverse Events, version 4.03.
HSR—hypersensitivity reaction; IQR—interquartile range

infusion (median = 100 mg per hour) than the diluent-primed arm (median = 150 mg per hour; p = 0.01).

Comparison of demographic and clinical characteristics between patients who had an HSR with those who did not is presented in Table 3. No statistically significant difference was found in age or disease diagnosis between these groups (p = 0.92 and 0.49, respectively). Patients given the infusion primed with diluent were 2.3 times more likely to experience HSR than patients given the infusion primed with the drug (35% versus 19%, respectively; odds ratio [OR] = 2.3; p = 0.01). Women were nearly twice as likely to experience HSR as men (34% versus 21%; OR = 1.93; p = 0.04). Patients given dexamethasone premedication were 59% less likely to experience HSR than patients not given dexamethasone (19% versus 37%, respectively; 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 and 0.07, respectively).

Discussion

The study findings indicate a lower incidence of HSR in patients receiving first-dose rituximab when the IV line is primed with the 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 IV line was primed with the drug, patients were 66% less likely to experience HSR than patients in the diluent-primed arm. These results indicate that priming the IV 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 those 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. However, the findings did show that women were nearly twice as likely to experience HSR as men. This was interesting to the researchers, because demographic variables in relation to HSR were not reported in the original studies (Coiffier et al., 1998, 2010; Davis et al., 1999, 2000; Habermann et al., 2006; Hallek et al., 2010; Hochster et al., 2009; Maloney et al., 1997; Marcus et al., 2005; McLaughlin 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 IV 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 IV line is primed with rituximab, the patient is exposed to rituximab immediately on initiation of the infusion. On 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 IV line is primed with diluent, patients receive only diluent for about 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 that 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 (National Cancer Institute Cancer Therapy Evaluation Program, 2010). The priming method did not have an impact on the severity of HSR in patients who experienced a reaction. This finding was consistent with reported grade of infusion reactions in the original studies (Coiffier et al., 1998, 2010; Davis et al., 1999, 2000; Habermann et al., 2006; Hallek et al., 2010; Hochster et al., 2009; Maloney et al., 1997; Marcus et al., 2005; McLaughlin et al., 1998; Pfreundschuh et al., 2006; Piro et al., 1999; Robak et al., 2010; Salles et al., 2011).

A significantly lower rate of HSR was noted when dexamethasone was used as a premedication. Patients who received dexamethasone 12 mg premedication, when receiving rituximab in combination with a chemotherapeutic regimen that required it, were 59% less likely to experience HSR 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. When weighed against patient tolerability and side effects, the use of this premedication seems to 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 patients' medical records, and some patients were excluded because of 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. In addition, this study did not exclude patients treated with rituximab in combination with chemotherapy. The chemotherapy agents potentially could reduce tumor burden and subsequent cytokine release on exposure to rituximab. In addition, variation between premedication standards at other cancer centers could affect 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 of HSR. Reducing the incidence of HSR in this population can improve patient safety, reduce patient and caregiver

IMPLICATIONS FOR PRACTICE

- Reduce hypersensitivity reactions to first-dose rituximab treatment by priming IV lines with the drug.
- Consider standardized premedications, including acetaminophen, diphenhydramine, and dexamethasone, for all patients receiving first-dose rituximab infusions to reduce hypersensitivity.
- Use a closed system transfer device and personal protective equipment to minimize exposure with drug-primed IV lines.

TABLE 3.
DEMOGRAPHIC AND CLINICAL CHARACTERISTICS BY HSR

	HSR (N = 54)		NO HSR (N = 146)				
CHARACTERISTIC	**X̄**	**RANGE**	**X̄**	**RANGE**	**ODDS RATIO**	**95% CI**	**p[a]**
Age (years)	63	22–93	63	26–93	–	–	0.92
CHARACTERISTIC	**n**	**%**	**n**	**%**	**ODDS RATIO**	**95% CI**	**p[a]**
Sex					1.93	[1.03, 3.64]	0.04
Female	31	57	60	41			
Male	23	43	86	59			
Diagnosis					–	–	0.49
Non-Hodgkin lymphoma	47	87	134	92			
CLL	6	11	10	7			
Primary CNS lymphoma	1	2	2	1			
Primer					2.3	[1.2, 4.38]	0.01
Diluent	35	65	65	45			
Rituximab	19	35	81	55			
Standard premedication					2.83	[0.94, 8.5]	0.054
Given	50	93	119	82			
Not given	4	7	27	18			
Hydrocortisone 100 mg					0.37	[0.12, 1.11]	0.07
Given	4	7	26	18			
Not given	50	93	120	82			
Dexamethasone 12 mg					0.41	[0.21, 0.77]	0.005
Given	21	39	89	61			
Not given	33	61	57	39			

[a]Chi-square test result for sex and medication, Fisher's exact test for diagnosis, and two-sample t test for age
CI—confidence interval; CLL—chronic lymphocytic leukemia; CNS—central nervous system; HSR—hypersensitivity reaction

anxiety, refine 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, the researchers recommend incorporating the priming of rituximab IV lines with the drug as best practice. To standardize practice, manufacturers could consider including recommendations for priming the IV line with the drug in the prescribing information. This can reduce the incidence of HSR and the negative associated effects. Adopting this practice change would require nurses to anticipate HSR symptomatology earlier during the infusion than when primed with diluent because of earlier exposure to the drug.

In addition, many MABs other than rituximab have a high risk of HSR and, therefore, also are administered via a slow titrated infusion (i.e., daratumumab, obinutuzumab, ofatumumab, and elotuzumab). Priming these MABs with the 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, this change has potential financial benefits 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 use 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 IV lines versus diluent-primed IV lines. Although rituximab is not on the National Institute for Occupational Safety and Health hazardous drug list, nurses should take precautions to minimize occupational exposure (Polovich, Olsen, & LeFebvre, 2014). Appropriate personal protective equipment and a closed system transfer device can be used as a precaution when handling drug-primed IV lines.

Conclusion

Nurses are 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 IV line with the drug is a simple intervention that can positively affect patient care.

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