

Implementation and Evaluation of a 90-Minute Rituximab Infusion Protocol at the Richard L. Roudebush VA Medical Center

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Background: The use of IV rituximab for the treatment of a variety of malignant and nonmalignant indications has been associated with significant challenges related to time and labor. To help alleviate some of these logistic challenges, institutions have implemented protocols to shorten the time in which rituximab is infused. The purpose of this study was to support the safe implementation of a 90-minute rapid infusion protocol for rituximab at the Richard L. Roudebush VA Medical Center (RLRVAMC).

Methods: A 90-minute rituximab protocol was developed, and proactive measures were taken to educate physicians, pharmacists, and nurses on ordering, processing, compounding, and administering rituximab. A weekly report of patients who received rituximab at RLRVAMC was generated November 1, 2018 through April 1, 2019. Patients then were screened for rapid infusion of the drug based on eligibility criteria, and health care providers (HCPs) were notified. After each patient received a rapid infusion, a retrospective chart review was performed to

evaluate patient tolerability and assess for any safety concerns that would require protocol modification. The primary endpoint for this study was the incidence of grade 3 and 4 infusion-related reactions (IRRs) associated with rapid infusions of rituximab based on the Common Terminology Criteria for Adverse Events Version 5.0.

Results: Eleven patients received 24 rapid infusions of rituximab. Of these infusions, 1 (4.2%) resulted in a grade 3 IRR; no infusions resulted in a reaction of grade ≥ 4 . The use of rapid infusion of rituximab when compared with nonrapid infusion saved 39.3 minutes on average per patient.

Conclusions: The proactive measures that were used to implement the rapid infusion rituximab protocol improved HCP prescribing rates, nursing satisfaction, and the management of IRRs. This study confirmed appropriateness of rapid administration of rituximab in this veteran population and has increased interest in implementing other rapid infusion protocols.

Rituximab is a genetically engineered chimeric immunoglobulin G1 monoclonal antibody. It functions by binding to the CD20 antigen on the surface of B-cell lymphocytes, leading to complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity.¹ The US Food and Drug Administration approved this therapy to treat patients with B-cell non-Hodgkin lymphoma and chronic lymphocytic leukemia, along with other non-malignant indications, including pemphigus vulgaris and rheumatoid arthritis (RA). Historically, a significant amount of time and labor on behalf of medical personnel has been required to administer rituximab according to the original manufacturer's labeling due to the boxed warning associated with infusion-related reactions (IRRs).²

Originally, the elongated infusion times that were recommended for rituximab were largely due to the perceived risk of serious infusion-related adverse drug reactions. Slower infusion times should reduce the risk of a reaction and are considered to be a good option for those patients who are at a high risk of having a severe IRRs to rituximab. Examples of high-risk patients from previ-

ous studies include those with significant cardiovascular disease, a circulating lymphocyte count $\leq 5,000/\mu\text{L}$ at the start of infusion, and those who have previously had a reaction to rituximab.³⁻⁵ In appropriate patients, research has shown a decreasing incidence of all-grade IRRs for patients who are prescribed rituximab as they receive more doses of the drug.^{2,6} The ability to identify suitable patients for 90-minute infusions of rituximab and the prospect of better health system resource utilization has led investigators to study the effects of shortened infusion times.

The RATE trial addressed this subject with a phase 3 safety study on the effects of a 90-minute rituximab infusion for patients with previously untreated diffuse large B-cell and follicular lymphoma.³ The patients in this study received their first dose of rituximab using the traditional infusion approach. If it was well-tolerated, they received subsequent rituximab infusions using a 90-minute protocol. Only 1.1% of patients who had previously received a rituximab infusion developed a grade 3 or 4 IRR when receiving a faster infusion of the drug for the first time.³ This result led to the addition of

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TABLE 1 Baseline Characteristics (N = 24)

Characteristics	Results
Demographics	
Age, mean, y	67.2
Male, %	95.8
Diagnosis, %	
Antineoplastic	91.7
Nonantineoplastic	8.3
Laboratory results	
Absolute lymphocyte count, mean, k/uL	0.9
White blood cell count, mean, k/uL	6.2
Lactate dehydrogenase, mean, U/L	246.5
Premedication	
Steroid given prior to treatment, %	66.7

instructions for a 90-minute infusion to the package insert.²

In contrast to the RATE trial, the RATE-RA trial evaluated the incidence of IRRs in patients who received rituximab for non-malignant indications. This study assessed patients with RA receiving rituximab for > 120 minutes. The authors reported 0.6% of the patients in the study developed a grade 3 or 4 IRR associated with the first 120-minute infusion of the medication.⁵ The researchers concluded that rituximab can be administered at a faster rate during second and subsequent infusions in patients who have been shown to tolerate traditional infusions without increasing the risk or severity of IRRs.⁵

The US Department of Veterans Affairs (VA) Richard L. Roudebush VA Medical Center (RLRVAMC) in Indianapolis, Indiana, uses traditional directions for the infusion of rituximab due to perceived tolerability and safety concerns specifically in a veteran population—even while other VA medical centers have implemented shortened infusion protocols. This also is despite the fact that available research shows rapid infusions of the drug are well tolerated in a variety of community settings.^{7,8} Anticipated benefits of implementing a protocol include savings in chair time at the institution's infusion clinic along with increased nursing and patient satisfaction. This project was conducted to prepare, implement, and assess the safety of a 90-minute rituximab protocol at the RLRVAMC.

METHODS

Proactive measures were required before and during the implementation of the 90-minute

protocol to ensure patient safety and staff satisfaction. Updates to the RLRVAMC policy for the management of medical emergencies within the infusion center were reviewed and approved by the acute care committee and nursing leadership. A protocol was developed to identify eligible patients, outline the hypersensitivity protocol, instruct pharmacy personnel on admixture preparation, and provide a titration schedule based on dose. Order sets also were created to assist health care providers (HCPs) with the prescribing of rituximab for nonantineoplastic indications. Educational materials were crafted to assist with order verification, product preparation, labeling, and programming of infusion pumps. Live education was provided for physicians, pharmacists, and nurses to ensure smooth implementation of the protocol and appropriate management of medical emergencies based on the updated policy.

Study Design

Nursing staff in the infusion clinic were surveyed once before a live education session and again after the conclusion of the study. The purpose of the survey was to assess the prior experience and current comfort level of the nursing staff with administering rituximab over 90 minutes. Nurses were asked the following questions: (1) Do you have prior experience administering rituximab via 90-minute infusion; and (2) do you feel comfortable administering rituximab via 90-minute infusion?

A weekly report of patients who received rituximab between November 1, 2018 through April 1, 2019 at the RLRVAMC was generated. HCPs were alerted to eligible patients based on protocol requirements. The HCPs then made the final determination and entered orders accordingly.

This study was a retrospective chart review of all who patients received a rapid infusion of rituximab. Patients who were included if they were aged ≥ 18 years, received rituximab infusions in the RLRVAMC infusion clinic, had an absolute lymphocyte count $\leq 5,000/\text{mm}^3$ at the time of their rapid infusions, had no significant baseline cardiovascular disease or respiratory compromise, and had no prior grade 3 or 4 rituximab IRRs as defined by Common Terminology Criteria for Adverse Events (CTCAE)

Version 5.0.⁹ This study was a quality improvement initiative and considered exempt by the institutional review board. All data were deidentified and secured to ensure patient privacy.

The primary endpoint for this study was the incidence of grade 3 or 4 IRRs associated with the rapid infusion of rituximab. Secondary endpoints included the proportion of patients who experienced a grade 3 or 4 infusion reaction, who received proper treatment according to the institution's hypersensitivity protocol, savings in infusion clinic chair time, and nursing satisfaction with education and implementation of the rapid infusion rituximab protocol.

The following data were collected for all included patients: demographics, lactic acid dehydrogenase level, white blood cell count, and absolute lymphocyte count prior to rituximab infusion, indication for treatment, dose of rituximab for 90-minute infusion, date of infusion, starting time, ending time, number of previous rituximab infusions within the past 3 months, symptoms of infusion reactions during rituximab infusion, and grade of any infusion reactions that occurred.

Estimated savings in infusion clinic chair time was calculated by taking the difference in time between each completed rapid infusion and the estimated amount of time it would have taken for each patient to receive a traditional infusion. The estimated amount of time for traditional infusion was determined by following the institution's protocol for administering rituximab to patients who previously tolerated their first dose of the drug (eg, 100 mg/h starting rate and increasing by 100 mg/h every 30 minutes to a maximum infusion rate of 400 mg/h). All endpoints were analyzed using descriptive statistics.

RESULTS

Between November 1, 2018 and April 1, 2019, 11 patients received a total of 24 rapid infusions of rituximab. The majority of patients included in the study were older males, and the most common indication for rapid infusion was follicular lymphoma (Table 1).

Primary Endpoint

All patients who received a rapid infusion of rituximab were reviewed in the analysis of the

TABLE 2 Primary and Secondary Results (N = 24)

Endpoints	Descriptions	Results
Primary	Incidence of infusion related reactions in patients receiving rapid infusions of rituximab, %	4.2
Secondary	Patients who experienced infusion related reaction managed appropriately, %	100
Secondary	Nurses reporting comfort with rapid rituximab infusion poststudy, %	100
Secondary	Average savings in infusion clinic chair time for patients completing rapid infusions, min	39.3

primary and secondary endpoints. Among the 24 rapid infusions of rituximab, 1 infusion was stopped due to the patient experiencing a grade 3 IRR according to criteria from CTCAE Version 5.0. The patient was found to have dysphagia at baseline and experienced severe symptoms in the days following the first infusion that put the patient at high risk for subsequent infusion related concerns. Eligibility criteria for the 90-minute protocol were updated based on these findings. No patient experienced a grade 4 or 5 IRR. The remaining 23 infusions were well tolerated by the patients with no clinically significant events.

Secondary Endpoints

The patient who experienced a grade 3 IRR to rituximab received proper treatment by infusion clinic nurses according to the RLRVAMC hypersensitivity protocol. Patients who received rapid infusions of rituximab had a mean length of infusion of 95.0 minutes. This was in contrast to the mean time of each patient's previous nonrapid infusion of 134.3 minutes. The difference between the 2 values equated to a savings in infusion clinic chair mean time of 39.3 minutes per patient.

Nurses were asked whether they had prior experience administering rituximab via 90-minute infusion and whether they felt comfortable administering a 90-minute rituximab infusion. Before the live education session, none of the nurses surveyed had prior experience or felt comfortable administering rituximab over 90 minutes. When the nurses were surveyed poststudy, all reported that they were experienced administering rituximab and felt comfortable with the process (Table 2).

DISCUSSION

The infusion of rituximab has been associated with significant challenges related to the time and labor required. Although a vast number of institutions across the country now infuse the medication over an abbreviated time, HCP concerns for patient safety and appropriate use of hypersensitivity protocol in a veteran population delayed implementation at RLRVAMC. The results from this quality improvement initiative highlight the positive impact of the proactive measures that were used to implement the rapid infusion protocol for rituximab on improving HCP prescribing rates, nursing satisfaction, and appropriate management of IRRs.

Rapid infusion saved on average 39.3 minutes per patient in infusion clinic chair time. Each successful rapid infusion of rituximab potentially opened additional time in clinic for ≥ 1 patients to receive an infusion therapy. The RLRVAMC usually operated at maximum capacity, so the ability to accommodate more patients helped decrease hospital admittances for time-sensitive infusions.

The initial criteria used to screen patients to determine whether a rapid infusion of rituximab would be appropriate was based on inclusion and exclusion criteria for past studies on the same subject.³⁻⁵ The incidence of hypersensitivity reactions associated with study participants who received rapid rituximab infusions also resembles past research done on the subject, which is important to note due to prior misconceptions of staff at the institution of a higher risk of reaction in this specific veteran population. One patient with RA experienced a grade 3 IRR in this study. Although this patient met the original inclusion criteria, the patient had baseline dysphagia, and following the first infusion, reported to the emergency department (ED) with symptoms of delayed anaphylaxis. In this case, the order for rapid infusion was placed in advance and the prescriber was unaware of the ED visit. Based on this event, eligibility criteria for 90-minute rituximab infusions were updated to include additional information specifying that candidates for a rapid infusion also may have no baseline airway compromise. This hypersensitivity reaction also highlighted the need for decision

support technology to assist HCPs in patient selection as well as empowering nursing and pharmacy staff to identify concerns once they place orders.

Over the course of the study, investigators assisted the HCPs with preparation of orders for the rapid infusion of rituximab for antineoplastic indications. Due to feasibility issues with this practice moving forward, order sets containing rituximab were updated to include a 90-minute option. This created a more standardized process that allowed HCPs to screen potential patients on their own. The expectation is that HCPs will be more likely to order 90-minute infusions for eligible patients in the future with this efficient and safer process.

Limitations

The small sample size in this study was a limitation. Retrospective data related to the management of infusion reactions and length of infusions were collected from nursing notes. The prospective use of a standardized evaluation tool for adverse drug reactions as well as bar code medication administration technology would improve the data available for this study. Additional studies also would be useful to validate the results.

CONCLUSIONS

The proactive measures that were used to implement the rapid infusion rituximab protocol improved HCP prescribing rates, nursing satisfaction, and the management of IRRs. Potential time savings with each infusion was significant. This study confirmed appropriateness of rapid administration of rituximab in this veteran population and has increased interest in implementing other rapid infusion protocols. Protocols, education, and order sets are being developed for daratumumab and infliximab.

Author disclosures

The authors report no actual or potential conflicts of interest with regard to this article.

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