Rapid-Infusion Rituximab in a Pediatric Population

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OBJECTIVES The use of rapid rituximab infusion in certain pediatric populations has generally been regarded as safe. The safety of our institution's rapid rituximab protocol was evaluated.

METHODS The primary end point was the number of and severity of adverse drug reactions. Secondary end points included a description of the patient population defined by the indication, dose, and number of rituximab infusions administered. Additionally, the difference in infusion times in hours of those receiving rapid rituximab infusions versus the theoretical infusion time of subsequent administration rate schedules was defined.

RESULTS A total of 88 infusions for 22 patients were reviewed. No dose-limiting adverse reactions were observed. Three patients experienced grade 1 isolated infusion-related adverse events during a single infusion encounter. Two of the three patients received additional doses of rapid rituximab infusions without incident, whereas the other patient no longer required rituximab therapy.

CONCLUSIONS The use of a 90-minute rituximab infusion protocol in pediatric patients with non-rheumatic diseases was well tolerated.

KEYWORDS hospital protocol; infusion time; pediatrics; rapid infusion; rapid rituximab infusion; rituximab; safety

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Introduction

Rituximab is a monoclonal antibody that mediates cell lysis through the targeting and binding of the CD20 antigen expressed on the surface of B lymphocytes. Originally approved for the treatment of B-cell non-Hodgkin lymphoma, its labeled and off-label use has expanded to a wide variety of disease states. The administration of rituximab has been associated with infusion reactions, attributed in part to the rapid release of various cytokines, such as tumor necrosis factor- α and interleukin-6.¹ These reactions are observed in more than 75% of patients and range from mild severity, such as flushing, urticaria, and pain at injection site, to severe and even fatal reactions due to hypotension, bronchospasm, angioedema, and cardiogenic shock.^{2,3} Because of the high incidence of reaction, it has become common practice to premedicate patients with at least acetaminophen and histamine₁ receptor antagonists. Corticosteroids could be added as a premedication per physician discretion. Despite these pretreatment medications, nearly 25% of patients still experience infusion-related reactions.³ The highest risk of reaction is observed at time of first administration, with 77% of patients experiencing infusion-related symptoms, with approximately 7% of patients at risk for a reaction classified as grade 3 or 4. Because of the depletion of B cells after each dose, the risk of reaction decreases with subsequent administration in those who

had previously tolerated the medication.⁴ For example, 30% of patients are at risk for an infusion-related reaction (2% grade 3 or 4) by the fourth dose and only 14% are shown to be at risk by the eighth dose (0% grade 3 or 4), with the condition that all previous doses were tolerated.^{3,5,6}

As a result of the risk of infusion reactions, the first dose of rituximab in pediatrics is traditionally given slowly, administered at an initial rate of 0.5 mg/kg/hr for the first hour, and is gradually increased by 0.5 mg/kg/hr every 30 minutes based on the patient's response (maximum rate of 50 mg/hr). Subsequent doses may be infused at an initial rate of 1 mg/kg/hr.⁷ This titration method results in rituximab administration during the course of 4 to 6 hours for the first dose and 2 to 4 hours for subsequent infusions. Long infusion times result in a significant burden on both the patient and the health care institution, requiring increased nursing resources and extended chair time. In an attempt to overcome this limitation of time and resources, hospital and infusion centers have trialed the rapid administration of rituximab during the course of 60 to 120 minutes in adult and pediatric patients. Rapid infusion has largely been shown as safe in adults who have tolerated the initial first dose infused during the traditional 4 to 6 hours.^{5,6,8–19} The use of rapid-infusion rituximab in pediatrics was first reported by Wallace and colleagues²⁰ in patients with non-malignant conditions. Soon after,

Legeay et al²¹ reported their findings regarding the safety of rapid-infusion rituximab in a heterogeneous pediatric patient population. Most recently, the first prospective study of rapid rituximab infusion in pediatric patients with hematologic, oncologic, and rheumatologic disorders was published.⁷ Rapid infusion of rituximab in the pediatric patients in these studies was well tolerated in 90% to 97% of patients.

Based on the data from Legeay et al,⁴ a 90-minute rapid infusion rituximab protocol was implemented at Cleveland Clinic Children's Hospital for pediatric patients in 2016. The purpose of this report is to add to the safety data of rapid rituximab infusion in a diverse pediatric patient population.

Materials and Methods

This retrospective, single-center observational study was developed to evaluate and describe the safety of rituximab infusions in a pediatric patient population. The study was performed at a large, not-for-profit, academic medical center with extensive pediatric specialty services, such as dermatology, hematology and oncology, rheumatology, and solid organ transplantation.

All patients who received at least 1 dose of rapid rituximab infusion per the Cleveland Clinic Children's Hospital protocol were included. Our institution's protocol was implemented on March 1, 2016. Data were collected from this time until December 31, 2017. During this time period, patients with rheumatologic conditions were not eligible to receive rapid-infusion rituximab.

The Cleveland Clinic Children's Hospital protocol required all patients to be clinically stable and have received a traditionally administered initial infusion rate of rituximab infusion with no history of grade 3 or 4 reactions. Additionally, for leukemia and lymphoma patients, the absolute lymphocyte count was required to be $<5000/\text{mm}^3$ because an elevated lymphocyte count has been identified as an independent predictor of infusion-related reactions from rapid rituximab infusion.²² All doses were to be administered during the course of 90 minutes, with 20% of the dose administered during the first 30 minutes, followed by the remaining 80% during 60 minutes. Rituximab doses less than 375 mg were compounded in normal saline to a total volume of 100 mL, and doses greater than or equal to 375 mg were compounded in normal saline to a total volume of 250 mL. Per the protocol, all patients were premedicated 30 minutes prior to rituximab infusion with both oral acetaminophen 15 mg/kg once and either oral or intravenous diphenhydramine 0.5 to 1 mg/kg. Additional premedications were administered per physician discretion.

A comprehensive review of the medical record was performed for all patients. Demographic information, including patient age, sex, and body surface area, were recorded. Information regarding the rituximab infusion, including indication, rituximab dose, and total number

of rapid rituximab infusions, was collected. Other data collected include the following: premedication use, most recent absolute lymphocyte count prior to infusion, and actual time of administration. If actual time of administration was not documented in the medical record, time of administration was documented as the protocol-specified 90 minutes.

The primary end point was the number of and severity of adverse drug reactions. The severity of adverse drug reactions was determined using the *Common Terminology Criteria for Adverse Events (CTCAE)* version 4.0.²³ Patient vital signs, including temperature, blood pressure, respiratory rate, and heart rate, were recorded prior to and every 30 minutes after the initiation of the infusion and until 30 minutes after the infusion was complete. The values considered within range for patient vital signs were those specified in Pediatric Advanced Life Support Medical Training provided by the American Heart Association. All data were collected by a single reviewer. The severity of adverse events was determined by this same reviewer and independently reviewed and confirmed by a second reviewer.

Secondary end points included a description of the patient population administered rapid rituximab infusion, defined by the indication, dose, and number of rituximab infusions administered. Additionally, the difference in infusion times in hours of those receiving rapid rituximab infusions versus the theoretical infusion time of subsequent administration rate schedules was defined. The theoretical infusion time of subsequent administration schedules was determined using an institution-specific rituximab pediatric infusion rate chart. For subsequent infusions rituximab would be initiated at a rate of 1 mg/kg/hr for the first 60 minutes; if there is no infusion reaction, the rate would be increased by 1 mg/kg/hr increments every 30 minutes, to a maximum rate of 400 mg/hr. For both the primary and secondary end points, descriptive statistics were used.

Results

A total of 88 rapid rituximab infusions for 22 patients were reviewed. Patient baseline characteristics as well as infusion information may be found in the Table. A total of 13 patients (59%) were female, and the median age at time of first rapid rituximab infusion was 14 years (range, 0.7–25 years). No dose-limiting adverse reactions were observed. A total of 3 patients (14%) experienced isolated infusion-related adverse events during a single infusion encounter. The first patient experienced a grade 1 injection site reaction that was described as slightly swollen, non-tender, soft, and painless. The patient's caregiver was instructed to elevate the child's extremity when possible to help with the swelling; no other acute intervention was required. This was determined to not be an infiltration of the drug. This patient did not receive any additional rapid rituximab infusions for reasons unrelated to the swelling reaction.

Table. Rapid Rituximab Infusion Patient Characteristics

Patient	Sex	Age, yr	Indication	Rapid, No.	Reaction	Infusion Reacted, No.
1	M	5	AHA–SOT	3	Yes	3
2	F	6	AHA–SOT	3	Yes	1
3	M	16	B-cell lymphoma	2	No	n/a
4	F	17	B-cell lymphoma	3	No	n/a
5	F	18	B-cell lymphoma	4	No	n/a
6	M	0.67	Burkitt lymphoma	5	No	n/a
7	M	15	Burkitt lymphoma	10	Yes	6
8	M	14	EBV viremia–allogeneic BMT	3	No	n/a
9	F	21	EBV viremia–allogeneic BMT	3	No	n/a
10	F	7	GVHD–allogeneic BMT	10	No	n/a
11	F	15	GVHD–allogeneic BMT	3	No	n/a
12	F	14	GVHD–allogeneic BMT	3	No	n/a
13	F	2	GVHD–SOT	1	No	n/a
14	F	14	Hodgkin lymphoma	2	No	n/a
15	F	14	ITP	3	No	n/a
16	F	3	ITP	3	No	n/a
17	M	15	ITP	3	No	n/a
18	M	16	ITP	2	No	n/a
19	M	8	SOT rejection	2	No	n/a
20	M	25	PTLD–SOT	12	No	n/a
21	F	2	Pre-B ALL	1	No	n/a
22	F	18	TTP	7	No	n/a

AHA, autoimmune hemolytic anemia; ALL, acute lymphoblastic leukemia; BMT, bone marrow transplant; EBV, Epstein-Barr virus; GVHD, graft-versus-host disease; ITP, idiopathic thrombocytopenic purpura; PTLD, posttransplantation lymphoproliferative disease; SOT, solid-organ transplant; TTP, thrombotic thrombocytopenic purpura

The second patient experienced grade 1 hypotension during the infusion. The primary team was notified, but no acute intervention was deemed necessary. This patient received 4 additional doses of rapid rituximab without issue. The third patient experienced high blood pressures during the infusion; however, the patient was actively prescribed home medications for high blood pressure. The provider was notified and the patient received a second dose of diphenhydramine. This patient received 2 additional doses of rapid rituximab without incident. An overall reaction event rate of 3.4% was seen for all rapid rituximab infusions.

The most common indications for rituximab included B-cell lymphoma (27%), idiopathic thrombocytopenic purpura (18%), and graft-versus-host disease (18%). The median number of doses of rapid rituximab infusion received per patient was 4 (range, 1–12). All patients received a rituximab dose of 375 mg/m². Total doses ranged from 160 to 820 mg. All patients were premedicated with acetaminophen and an antihistamine. The antihistamine of choice was diphenhydramine (97%); however, hydroxyzine was ordered for 1 patient who

received 3 rituximab infusions. A total of 69 of the infusions (78%) were administered to patients who had received oral corticosteroids. For 28 of these infusions (41%), the corticosteroid was administered for the purpose of infusion premedication; the remaining 41 patient infusion encounters (59%) had corticosteroids on the active medication list for other indications. Of the premedication corticosteroid administrations, 23 (82%) received hydrocortisone, and 1 patient (4%) received prednisone. Rapid infusion of rituximab per our protocol potentially saved an average of 57 minutes of infusion time per encounter based on our method of comparison.

Discussion

The safety profile of rapid rituximab found within our institution is similar to that of other reports. Our institution's protocol calls for the administration of rituximab during the course of 90 minutes in a titrated manner similar to that described by Legeay et al²¹ and Bernhardt et al.⁷ Bernhardt et al⁷ were also the first to report the

use of rapid-infusion rituximab in pediatric rheumatologic patients, which was given as a 120-minute infusion as opposed to 90 minutes. In the report by Wallace et al,²⁰ rituximab was administered during the course of 60 minutes in patients with non-malignant conditions. They examined 80 rituximab infusions in 22 patients and found a total adverse event rate of 2.5%. Legeay et al²¹ reported a 2.7% incidence in 17 patients who received a total of 37 infusions. Bernhardt et al⁷ noted a higher incidence of adverse events (10%); however, these events were categorized as low grade, and there were no dose-limiting, infusion-related adverse events.

Our patient cohort included both malignant and non-malignant indications. The most common indication for rapid rituximab was B-cell lymphoma. Of note, 5 patients received rituximab for solid organ transplant complications, including autoimmune hemolytic anemia (n = 2), rejection (n = 1), graft-versus-host disease (n = 1), and posttransplantation lymphoproliferative disorder (n = 1). Many B-cell lymphoma regimens include corticosteroids as a key treatment component. Therefore, many of our patients were actively receiving corticosteroid therapy at time of rituximab infusion and likely did not require additional corticosteroid premedication. All patients in this cohort received both acetaminophen and an antihistamine prior to rituximab infusion, a practice that is similar to that of other centers.

The estimated infusion time saved of 57 minutes was lower than expected and lower than the approximate 2 hours per infusion that has been reported by other pediatric institutions.^{20,21} However, infusion time saved was defined differently among institutions. The low amount of time saved per this report may be attributed to the method in which we estimated saved infusion time. The institution-specific rituximab pediatric infusion rate chart was used to determine the *minimum* amount of time subsequent rituximab infusions would take, assuming patients tolerated each infusion and the titration schedule was followed exactly. Therefore, the reported estimated infusion savings time was the minimum time saved.

With the addition of our data to the currently available literature, rapid infusion of rituximab may be considered safe for pediatric patient populations in hematology, oncology, rheumatology, and solid organ transplantation. Of note, rapid infusion of rituximab for pediatric patients with rheumatologic conditions, such as systemic lupus erythematosus, should be administered during the course of 120 minutes as reported by Bernhardt et al⁷ because there are no other data evaluating rapid rituximab in pediatric patients with rheumatologic conditions at a different rate as of the writing of this report.

The use of a 90-minute rapid rituximab infusion protocol in a diverse, non-rheumatologic pediatric patient population is well tolerated and can be generally regarded as safe in patients who have tolerated an initial

rituximab infusion and are administered premedications. A total of 3 of the 22 patients (14%) experienced a grade 1 or 2 adverse event; no infusions resulted in a grade 3 or 4 adverse event.

ARTICLE INFORMATION

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Ethical Approval and Informed Consent The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and have been approved by the appropriate committees by the Cleveland Clinic Institutional Review Board. Given the nature of the study, the committee did not require HIPAA Waiver of Authorization, Waiver of Assent, and Waiver of Parental Permission.

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