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ARTICLE

Safety and tolerability of a 90-minute rapid infusion of Sandoz biosimilar rituximab in B-cell lymphoproliferative disorders in a real-world setting

Ana Muntañola[1] | José María Arguiñano-Pérez[2] | Julio Dávila[3] | Sonia González de Villambrosia[4] | Cecilia Carpio[5,6] | Ana Jiménez-Ubieto[7] | Antonio Salar[8,9,10] | the GELTAMO (Grupo español de linfomas y trasplante de médula ósea)

[1]Department of Hematology, Hospital Universitari Mutua Terrassa, Terrassa, Spain

[2]Department of Hematology, Hospital Universitario de Navarra, Pamplona, Spain

[3]Department of Hematology, Complejo Asistencial de Ávila, Ávila, Spain

[4]Department of Hematology, Hospital Universitario Marqués de Valdecilla/IDIVAL, Santander, Spain

[5]Department of Hematology, Experimental Hematology, Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital, Barcelona, Spain

[6]Department of Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain

[7]Department of Hematology, Hospital 12 de Octubre, Madrid, Spain

[8]Department of Hematology, Hospital del Mar, Barcelona, Spain

[9]Group of Applied Clinical Research in Hematology, Cancer Research Program-IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain

[10]Pompeu Fabra University, Barcelona, Spain

Correspondence
Antonio Salar Silvestre, Passeig Marítim 25-29, 08003 Barcelona, Spain.
Email: asalar@psmar.cat

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Sandoz

Abstract

Although rituximab is generally well-tolerated, infusion-related reactions (IRRs) are common with the initial dose when administered intravenously according to standard recommendations. To prevent IRRs, premedication and low-speed infusion rates have been recommended. Consequently, intravenous (i.v.) infusion of rituximab can become a labor-intensive process. Rapid i.v. rituximab infusion over 90 min has demonstrated a favorable safety profile for the second and subsequent infusions during the course of therapy. The aim of this study was to investigate the safety and tolerability of 90-min rapid infusion of Sandoz rituximab biosimilar (SDZ-RTX) for patients with CD20+ lymphoma or chronic lymphocytic leukemia (CLL). We retrospectively reviewed all patients with CD20+ lymphoma or CLL who received SDZ-RTX infusions in 90 min from July 2019 to July 2021 at seven Spanish hospitals. The primary end point was the incidence of IRRs. We identified 124 patients and 576 rapid administrations of SDZ-RTX, with an average of five rapid infusions per patient. Most rapid infusions of SDZ-RTX were in combination with CHOP/CHOP-like therapy (48.4%), followed by

SDZ-RTX alone (15.1%), in combination with bendamustine (14.5%), or with other regimens (22%). The 90-min SDZ-RTX infusion schedule was well-tolerated with no grade 3/4 IRRs. The incidence of any grade IRR during the first rapid infusion was 1% (5 grade 1 IRRs and 1 grade 2 IRR). In conclusion, rapid 90-min i.v. administration of SDZ-RTX for the second and subsequent infusions during the course of therapy is well-tolerated in patients with CD20+ lymphoma or CLL.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Rituximab, an anti-CD20 monoclonal antibody, is associated with infusion-related reactions (IRRs). To reduce the risk of IRRs, premedication with acetaminophen and an antihistamine, together with slow infusion of rituximab, are recommended.

WHAT QUESTION DID THIS STUDY ADDRESS?

This study aimed to investigate the safety and tolerability of 90-min rapid i.v. infusion of SDZ-RTX for patients with CD20+ lymphoma or chronic lymphocytic leukemia (CLL).

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Intravenous administration of SDZ-RTX in a rapid infusion is well-tolerated and feasible for patients with CD20+ lymphoma or CLL.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Our study provides meaningful information for clinical practice, as rapid i.v. infusions of SDZ-RTX could lead to improved patient convenience and reduced burden on healthcare systems, including resources and costs.

INTRODUCTION

Rituximab is a chimeric monoclonal antibody against the CD20 antigen. It is currently an integral component of therapy for B-cell non-Hodgkin's lymphomas (NHL), chronic lymphocytic leukemia (CLL), and other non-malignant conditions.[1] Compared with classical chemotherapy, rituximab has a more favorable safety profile. However, intravenous (i.v.) administration of the drug is associated with infusion-related reactions (IRRs), including hypersensitivity reactions that can result in fever, rash, cardiovascular and/or respiratory compromise, and, rarely, cytokine release syndrome. It is well known that the incidence and severity of these IRRs decrease with the second and subsequent administrations of rituximab.[2] In addition, several risk factors for developing IRRs have been identified, such as bulky tumors, pulmonary infiltrates, elderly patients, and type of tumor.[3] Indeed, IRRs are more frequent in CLL or mantle cell lymphoma, likely due to high lymphocyte counts in peripheral blood.[3]

To reduce the risk of IRRs, premedicating patients with acetaminophen and an antihistamine, as well as administering rituximab over a prolonged period of time, generally 5–6 h for the first infusion and 3–4 h for subsequent infusions, are recommended.[4] The mean time for rituximab i.v. infusion varies across countries as shown in clinical and real-world studies.[5–7] This labor-intensive process is not only inconvenient and impacts quality of life for patients, but also consumes healthcare resources and reduces treatment capacity in day-care units. Several studies have confirmed the favorable safety profile of rapid i.v. infusion of rituximab over 90 min (or even 60 min) if the previous i.v. administration was well-tolerated.[8–14] Consequently, rapid i.v. infusion of rituximab has been granted approval by several medical agencies and has been widely adopted as the standard form of administration in many centers worldwide.

Biosimilars are biologics that match their reference biologic in terms of safety, efficacy, and quality.[15–18] Sandoz biosimilar rituximab (SDZ-RTX) is a biosimilar of rituximab (MabThera; Roche). SDZ-RTX (Rixathon) received a marketing authorization valid throughout the European Union on June 15, 2017 (further information on Rixathon is publicly available at the European Medicines Agency's webpage: ema.europa.eu/medicines/human/EPAR/Rixathon). Therefore, it is expected

that rapid i.v. administration of SDZ-RTX will match that of reference rituximab. For this reason, we retrospectively analyzed the safety of rapid i.v. infusion of SDZ-RTX in a cohort of patients with B-cell lymphoid malignancies.

METHODS

Study design

This was an open-label, multicenter, retrospective, observational, post-authorization study designed to investigate the safety of 90-min rapid i.v. infusion of SDZ-RTX in adult patients with B-cell lymphoid malignancies who received treatment with rituximab in Spain. All participating centers had extensive experience with 90-min i.v. infusions of reference rituximab. Physicians included all patients treated with 90-min i.v. infusions of SDZ-RTX in the study. The study was performed in seven Spanish centers and was approved by the Scientific Committee of GELTAMO, and the Ethics Committee of Hospital Mutua Terrassa, and was performed in accordance with the Declaration of Helsinki.

The primary objective of this study was to evaluate the incidence of grade greater than or equal to 3 IRRs following rapid i.v. infusion of SDZ-RTX in patients who had previously received rituximab at the standard infusion rate without experiencing a grade 3 or 4 IRR according to the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0). Secondary objectives were the incidence of IRRs per rapid infusion cycle regardless of grade, and the incidence and severity of all adverse events (AEs) occurring in the first 24 h following rapid SDZ-RTX administration.

Rapid rituximab infusion protocol

Inclusion criteria were: age greater than or equal to 18 years; histological diagnosis of any type of CD20+ NHL or CLL amenable to treatment with rituximab as monotherapy, in combination with chemotherapy or in maintenance; previous standard i.v. infusion of SDZ-RTX with CTCAE v5.0. toxicity grade less than or equal to 2; and administration of rapid SDZ-RTX infusion before July 12, 2021. Exclusion criteria were: lymphocytosis greater than 5×10^9/L prior to administration of SDZ-RTX in rapid infusion; experience of toxicity grade greater than or equal to 2 during the previous SDZ-RTX infusion; and dose less than 375 mg/m^2 in the previous or planned treatment schedule and hypersensitivity to rituximab or other anti-CD20 monoclonal antibodies.[11]

Patients were treated with i.v. SDZ-RTX administered over 90 min with a total volume of 250 ml. During the 90-min infusion, 20% of the total volume (50 ml) was given in the first 30 min and the remaining 80% (200 ml) over 60 min.[11] Premedication was administered 30 min prior to i.v. infusion and consisted of acetaminophen and diphenhydramine according to label information. Steroid premedication was also allowed in patients who were receiving steroid-containing chemotherapy or at the discretion of the treating physician. Patients were monitored and vital signs were measured according to standard practice in the treating centers. In the absence of IRRs, patients continued to receive rapid SDZ-RTX infusion for their remaining cycles. Most of the infusions were administered on an outpatient basis.

Data analysis

Patient information was reviewed from databases and medical records. IRRs were categorized according to CTCAE v5.0. All data were de-identified and secured to ensure patient privacy. A descriptive analysis of patient characteristics, as well as incidence and type of IRR, was performed.

RESULTS

Of 130 patients treated with SDZ-RTX in the seven Spanish sites, six patients received their first dose of rapid i.v. SDZ-RTX after July 12, 2021 and were excluded from this analysis. The remaining 124 patients were included in the analysis (Table S1-S2).

Overall, 115 patients (92.7%) had B-cell lymphoma and nine (7.3%) had CLL. CD20 positivity was confirmed in all cases. Patient characteristics are listed in Table 1. Patients received a cumulative total of 576 rapid i.v. SDZ-RTX infusions. Each patient received a median of five rapid infusions (range, 1–11). Overall, 86 patients (69.4%) received rapid SDZ-RTX infusion as part of first-line treatment. All patients received initial standard SDZ-RTX infusion, followed by rapid SDZ-RTX infusion. The cycle immediately prior to the first rapid SDZ-RTX infusion was: the first cycle in 101 patients (81.5%), the second in 12 (9.7%), the third in five (4.0%), and the fourth in six (4.8%). Fourteen out of 124 patients (11.3%) had an AE in the SDZ-RTX standard infusion cycle immediately before the first rapid SDZ-RTX infusion (all but one were grade 1). The median time from the previous standard i.v. infusion of SDZ-RTX to the first rapid i.v. infusion of SDZ-RTX was 21 days (range, 6–64).

Schedules for the first rapid SDZ-RTX infusion were: R-CHOP/R-CHOP-like 48.4%, R-bendamustine 14.5%,

TABLE 1 Baseline patient characteristics

	N, %
Age, years, median (range)	71 (32–99)
≤60	26 (21)
>60	98 (79)
Gender	
Male	66 (53.2)
Female	58 (46.8)
Diagnosis	
Diffuse large B-cell lymphoma	49 (39.5)
High grade lymphoma (DH/TH)	4 (3.2)
Follicular lymphoma	27 (21.8)
Marginal zone lymphoma	10 (8.1)
Mantle-cell lymphoma	9 (7.3)
Post-transplant lymphoproliferative disease	5 (4.0)
Transformed large B cell lymphoma	7 (5.6)
Other lymphomas	4 (3.2)
Chronic lymphocytic leukemia	9 (7.3)
Line of therapy of first rapid infusion	
First	86 (69.4)
Second	29 (23.4)
Third or later	9 (7.3)

Note: Other lymphomas: lymphoplasmacytic lymphoma (1), nodular lymphocyte predominant lymphoma (1), B-cell lymphoma not otherwise specified.

Abbreviation: DH/TH, double/triple hit.

R-gemcitabine/R-GEMOX 8.9%, rituximab 15.1% (monotherapy in 11.3% or maintenance in 3.8%), and others 13.1%. The dose of SDZ-RTX was 375 mg/m^2 in 115 patients (92.7%) and 500 mg/m^2 in nine patients (7.3%). Schedules used for all 576 rapid SDZ-RTX infusions are described in Table S2. All patients received standard premedication: 31.4% with acetaminophen and diphenhydramine, and 68.6% with acetaminophen, diphenhydramine, and steroids.

Overall, a total of 12 (2.1%) AEs were recorded after rapid i.v. SDZ-RTX infusion. Of these, six (50%) occurred after the first rapid infusion, five (42%) between infusions two and six, and one (8%) beyond infusion seven. There were no severe or fatal AEs, or AEs leading to SDZ-RTX interruption or dose modification. A detailed summary of each AE is provided in Table 2. No grade greater than or equal to 3 IRRs were reported (primary end point). The incidence of IRRs grade 1–2 during the first rapid SDZ-RTX infusion was 1.2% ($n = 7$), but only six of these were related to SDZ-RTX. Only one patient with splenic marginal zone lymphoma treated with SDZ-RTX monotherapy suffered a grade 2 IRR (hypotension). All patients with IRRs grade less than or equal to 2 continued to receive rapid SDZ-RTX infusions and tolerated therapy without any further complications.

DISCUSSION

Our study showed that rapid i.v. infusion of SDZ-RTX in a 90-min infusion schedule was well-tolerated in a cohort of patients with B-cell malignancies in the real-world setting, with no safety concerns identified. In our cohort of 124 patients, including nine patients with CLL, a total of 576 rapid i.v. infusions of SDZ-RTX were administered. Only 12 (2.1%) AEs were reported during i.v. infusions, six of which were considered to be related to SDZ-RTX administration, thereby indicating a favorable safety profile of the rapid infusion. All but one of the AEs related to SDZ-RTX were grade 1. The patient who experienced a grade 2 AE after the first rapid infusion had been diagnosed with marginal zone lymphoma and was receiving SDZ-RTX as monotherapy induction therapy[19]; the four subsequent infusions of SDZ-RTX were administered over 90 min and were well-tolerated by the patient with no further clinically significant toxicity. In terms of IRRs, the safety profile of SDZ-RTX was comparable to that reported with reference rituximab, suggesting that SDZ-RTX could replace reference rituximab in a rapid infusion setting.[3]

It is well known that most IRRs occur during the first infusion of rituximab, with a decreased incidence during the second and subsequent infusions. For instance, in a phase III study in 425 patients with lymphoma who received the first infusion at the standard rate, 85.4% were able to receive the 90-min infusion for the second cycle. Interestingly, only 1.1% of patients experienced a grade 3 IRR with the rapid infusion during the second cycle, and only 2.8% experienced a grade 3/4 IRR during cycles 2–8.[8] In the present study, the frequency of IRRs occurring after the first rapid i.v. SDZ-RTX infusion was low, but in our cohort, patients could receive their first rapid i.v. SDZ-RTX infusion for the second cycle or beyond, and those patients who presented with a grade greater than or equal to 2 AE in the previous cycle were excluded from the analysis. Curiously, all our patients experiencing IRRs received standard premedication plus corticosteroids. At present, there is still some controversy around the role of corticosteroids for preventing or reducing the occurrence of IRRs during rituximab i.v. administrations at standard or rapid infusion rates. Mechanisms for IRRs include IgE mediated hypersensitivity, immunogenicity of rituximab, complement activation, and cytokine-release syndrome.[20,21] Unfortunately, clinicians may not be able to clinically discriminate between IgE-mediated and non-IgE-mediated reactions.[22]

TABLE 2 Adverse events

Case	Rapid infusion cycle	Type of AE	AE grade	Time of appearance in relation to infusion	Relationship with SDZ-RTX	Outcome of AE	Diagnosis	Treatment	Dose (mg/m^2)	Premedication
1	1	Hypotension	2	During	Yes	Resolved	MZL	R monotherapy	375	A-PP-S
2	1	Paresthesia	1	>24 h	No	Resolved	DLBCL	R-CHOP	375	A-PP-S
3	1	Rash	1	>24 h	No	Resolved	FL	R-B	375	A-PP-S
4	1	Anemia	3	>24 h	No	Improved to Grade 1	HGL	R-CHOP	375	A-PP-S
5	1	IRR	1	During	Yes	Resolved	DLBCL	R-EPOCH	375	A-PP-S
6	1	Febrile neutropenia	3	>24 h	No	Resolved	DLBCL	R-CHOP	375	A-PP-S
7	2	Dyspepsia	1	During	Yes	Resolved	FL	R-CHOP	375	A-PP-S
8	3	Pruritus	1	During	Yes	Resolved	FL	R-B	375	A-PP-S
9	3	Paresthesia	1	>24 h	No	Resolved	DLBCL	R-CHOP	375	A-PP-S
10	3	IRR	1	During	Yes	Resolved	LPL	R-B	375	A-PP-S
11	5	Rash	1	During	Yes	Resolved	DLBCL	R-GEMOX	375	A-PP-S
12	10	Vomiting	1	During	No	Resolved	DLBCL	R-B + polatuzumab	375	A-PP-S

Abbreviations: AE, adverse event; A-PP-S, antipyretic plus antihistaminic plus steroid; B, bendamustine; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CVP, cyclophosphamide, vincristine, prednisone; DLBCL, diffuse large B-cell lymphoma; EPOCH, etoposide, vincristine, doxorubicin, cyclophosphamide, methylprednisolone; ESHAP, etoposide, methylprednisolone, cisplatin, cytarabine; FL, follicular lymphoma; GEMOX, gemcitabine, oxaliplatin; HGL, high grade lymphoma; LPL, lymphoplasmacytic lymphoma; MZL, marginal zone lymphoma; R, rituximab.

Corticosteroids may prevent or dampen non-IgE mediated infusion or inflammatory reactions, but have little impact in preventing IgE-mediated hypersensitivity.[22,23] To date, there is no definitive consensus on the role of premedication or even its components, because a specific schedule has never been validated in controlled studies.[24] Meanwhile, our current results and previous data from our group and others show that rapid i.v. rituximab infusion is well-tolerated in patients whether they receive premedication with or without corticosteroids.[8–14] Further studies are needed to provide high-quality evidence regarding the role of premedication in this setting.

Rituximab has become a standard component of treatment regimens for CD20+ NHL. In our study, rapid i.v. SDZ-RTX was administered alongside various standard chemotherapies, such as CHOP, CVP, and GEMOX, but also with chemo-free schedules, such as lenalidomide or venetoclax. Rituximab-lenalidomide (R2) has become frequently used for treatment of relapsed FL,[25] and combination of R2 with other agents is being studied.[26,27] Rituximab-venetoclax is licensed in the European Union for relapsed CLL,[28] and the combination of this regimen with other agents is also been explored in MCL and other malignancies.[29,30] The favorable safety profile of chemo-free schedules shown in this study is therefore relevant, because many of these are becoming part of standard clinical practice.

Rapid i.v. infusions of rituximab have previously been administered at a dose of 375 mg/m^2. Recently, rapid infusion of rituximab at doses ranging from 500–750 mg/m^2 were administered in a cohort of 11 patients with primary central nervous system lymphoma and no IRRs of any grade were observed during the 44 rapid rituximab infusions.[31] In our cohort, patients with CLL were treated with SDZ-RTX-chlorambucil or SDZ-RTX-venetoclax, both with rituximab at a dose of 500 mg/m^2.[32,33] Our data show that patients with CLL fulfilling our inclusion and exclusion criteria (in particular, lymphocytosis $<5 \times 10^9$/L and prior tolerance of a standard rituximab i.v. infusion) can receive a 90-min i.v. infusion of SDZ-RTX at 500 mg/m^2 without additional safety concerns.

In addition, as previously reported,[11] most of the rapid infusions were administered in the outpatient setting, which is very convenient for patients, as well as for reducing healthcare costs. Rapid infusion of rituximab over 90 min has been shown to improve patient satisfaction.[3] The mean infusion time saved in a single rapid i.v. infusion is ~2.9 h.[34] Moreover, rapid i.v. rituximab infusions save an average of 10.2 h per patient over the course of rituximab treatment, thereby offering an economic advantage by reducing chair time, resource utilization, and nursing monitoring.[35] Subcutaneous rituximab is administered at a fixed-dose of 1400 mg and has also shown improvement in these factors, although this formulation is associated with higher costs and is not available in all centers.[5,7,36,37]

Limitations of this analysis include the relatively small sample size of patients and SDZ-RTX infusions, as well as the retrospective nature of data collection on IRRs and their outcome. Despite these limitations, our study provides relevant clinical findings that could guide physicians considering introducing a 90-min SDZ-RTX infusion as a treatment option for hematologic malignancies.

In conclusion, 90-min rapid i.v. infusion of SDZ-RTX is feasible and well-tolerated in select patients with B-cell lymphoma and CLL who did not experience severe IRRs with the standard administration rate during the previous cycle. Our results support previous evidence with reference rituximab, and indicate an opportunity to improve patient convenience and reduce the burden on healthcare resources.

AUTHOR CONTRIBUTIONS

A.M. and A.S. wrote the manuscript. A.M. and A.S. designed the research. A.M., J.M.A.-P., J.D., S.GdV., C.C., A.J.-U., and A.S. performed the research. A.S. analyzed the data.

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CONFLICT OF INTEREST

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ORCID

Antonio Salar https://orcid.org/0000-0002-4652-4825

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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