Good practices in Rituximab Administration: Integrative Literature Review

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Boas Práticas na Administração do Rituximab: Revisão Integrativa da Literatura

Buenas Prácticas en la Administración de Rituximab: Revisión Integradora de la Literatura

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ABSTRACT

Introduction: Rituximab is a murine/human chimeric monoclonal antibody, widely used in the therapeutic setting of various diagnoses, due to its different administration, management and adverse effects protocols; its use requires attention by the healthcare team. **Objective:** Describe the infusion protocols for rituximab in the first, subsequent and desensitization infusions, and characterize their safety. **Method:** Integrative literature review. The search was performed in databases and electronic libraries: LILACS, PubMed, MEDLINE, SciELO and BDEnf. **Results:** In all, 413 articles were eligible after crossing the descriptors. Of these, 113 were read in full and eventually, 16 articles matched the study design. The articles were published from 2016 to 2020, predominantly in English (87.5%). Concerning the main routes of administration in the studies included, nine addressed the intravenous infusion (in different modalities of time) and seven, subcutaneously. **Conclusion:** According to the scientific literature, all intravenous and subcutaneous infusion modalities are shown to be safe and effective if the protocols are correctly selected and applied.

Key words: rituximab/administration & dosage; antineoplastic combined chemotherapy protocols; antineoplastic protocols.

RESUMO

Introdução: O rituximab é um anticorpo monoclonal quimérico camundongo/humano, amplamente utilizado no cenário terapêutico de vários diagnósticos. Por apresentar diferentes protocolos de administração, manejo e efeitos adversos, seu uso requer atenção da equipe de saúde. **Objetivo:** Descrever os protocolos infusionais do rituximab na primeira infusão, nas subsequentes e na dessensibilização, e caracterizar a sua segurança. **Método:** Revisão integrativa da literatura. A busca pelos periódicos foi realizada nas bases de dados e bibliotecas eletrônicas: LILACS, PubMed, MEDLINE, SciELO e BDEnf. **Resultados:** O cruzamento dos descritores proporcionou a identificação de 413 artigos. Destes, 113 foram lidos na íntegra e, ao final, 16 artigos foram aplicáveis ao desenho do estudo. Os artigos foram publicados entre os anos de 2016 e 2020, com predomínio da língua inglesa (87,5%). Quanto às principais formas de administração do medicamento, nove estudos abordaram a infusão por via intravenosa (em variadas modalidades de tempo) e sete por via subcutânea. **Conclusão:** De acordo com a literatura científica, todas as modalidades de infusão intravenosa e subcutânea demostram ser seguras e eficazes se os protocolos forem adequadamente indicados e corretamente aplicados.

Palavras-chave: rituximab/administração & dosagem; protocolos de quimioterapia combinada antineoplásica; protocolos antineoplásicos.

RESUMEN

Introducción: Rituximab es un anticuerpo monoclonal quimérico de ratón/humano, ampliamente utilizado em el ámbito terapéutico de diversos diagnósticos. Debido a sus diferentes protocolos de administración, manejo y efectos adversos, su uso requiere la atención del equipo de salud. **Objetivo:** Describirlos protocolos de infusión de rituximab em la primera, subsiguiente y desensibilización, y caracterizar su seguridad. **Método:** Es una revisión integradora de la literatura. La búsqueda de revistas se realizó en bases de datos y bibliotecas electrónicas: LILACS, PubMed, MEDLINE, SciELO y BDEnf. **Resultados:** Cruzar los descriptores proporciono la elegibilidad de 413 artículos. De estos, 113 fueron leí dos íntegramente y al final, 16 artículos fueron aplicables al diseño del estudio. Los artículos fueron publicados entre 2016 y 2020, con predominio del inglés (87,5%). En cuanto a las principales formas de administración del fármaco, entre los estudios incluidos, nueve abordaron la infusión intravenosa (en diferentes modalidades de tiempo) y siete la vía subcutánea. **Conclusión:** Según la literatura científica, todas las modalidades de infusión intravenosa y subcutánea se muestran seguras y efectivas si los protocolos están debidamente indicados y correctamente aplicados.

Palabras clave: rituximab/administración & dosificación; protocolos de quimioterapia combinada antineoplásica; protocolos antineoplásicos.

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INTRODUCTION

Rituximab is a murine human chimeric monoclonal antibody which specifically binds to CD20 found in pre-B lymphocytes and mature B lymphocytes. CD20 is a transmembrane protein present in more than 95% of all cells B of non-Hodgkin's lymphomas and leukemias. The US Food and Drug Administration (FDA) approved the drug in 1997 and its package insert indicates for treatment of Non-Hodgkin's lymphomas (NHL), chronic lymphoid leukemia (CLL), rheumatoid arthritis, Wegener granulomatosis and microscopic polyangiitis. It is being investigated and applied for systemic erythematous lupus, multiple sclerosis, pemphigus and glomerulopathy in adults; is part of the standard treatment for NHLs and can be used in association with chemotherapy or monotherapy[1,2].

Because it is a monoclonal antibody, the health team must be aware of adverse events and safety. Clinical studies showed that 77% of the patients had infusion reactions at first exposure to intravenous infusion such as fever, chills, rash, headache, hypotension, shortness of breath, bronchospasm, nausea, vomit and abdominal pain. Severe reactions as anaphylaxis can occur too[1,3].

Some measures are recommended to avoid and minimize rituximab-related adverse events. It is important that health teams are aware of specific knowledge about the administration and know how to classify infusion reactions according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE)[4].

Due to the widely use of rituximab in the therapeutic scenario of several diagnosis and actual adverse events, it is necessary to review and compile the scientific literature related to its administration to help professionals to adopt good practices for patients' safety. The aim of the present study was to describe rituximab infusion protocols at the first infusion, the subsequent and desensitization and characterize the safety.

METHOD

Integrative review of the literature based in the identification of the theme and research question, sampling, categorization of the studies, analysis of the data extracted, discussion and interpretation of the results, presentation of the integrative review and synthesis[5].

The research question was elaborated in the first phase: What are the protocol-based guidelines for the first and next rituximab infusions and desensitization? Is patient safety addressed by the protocols?

The research questions were converted to the acronym SPIDER: the Sample consisted in adult patients receiving rituximab. The Phenomenon of Interest is related to the evidences about the infusion of the medication in question. The Design is related to experimental, observational and integrative and systematic reviews of the literature classified in evidence levels defined by the Joanna Briggs Institute (JBI). For the Evaluation, protocols were selected to promote the safe administration of rituximab for patients and health professionals. The Research Type addressed by the inclusion criteria were quantitative, qualitative and mixed studies[6].

The second stage encompassed the selection of the key-words infusion reaction, infusion control, fast infusion, slow infusion and of the Descriptors of Sciences of Health (DeCS): patients, rituximab, monoclonal antibody, oncology, intravenous administration, subcutaneous administration, nursing, antineoplastic protocols, cytokine release syndrome and hypersensitiveness. The search was performed at the databases and/or electronic libraries LILACS, PubMed, MEDLINE, SciELO and BDEnf in English and Spanish too for the publication period from 2016 to 2020.

The inclusion criteria were full articles in Portuguese, English and Spanish about rituximab in adult patients published in the referenced period addressing the forms of administration and infusion reaction to the drug. Thesis, dissertations, opinion articles and editorials were excluded (Figure 1).

The instrument to collect and analyze the data included the following items; title of the article, authors, name of the journal, language, year of publication, type of article, objective, results conclusion, limitation and form of administration of rituximab. The scientific evidences were classified according to JBI[7] which recommends the pyramid where the base is level 5 (experts' opinion), and the other levels are 4 (observational and descriptive studies), 3 (observational analytical design), 2 (quasi-experimental designs) and 1 (experimental). Each level is subdivided in letters from a to e.

While selecting the articles, the abstracts were read by the authors and after the identification, those selected were read in full. The data were chosen to meet the study goals according to a data collection instrument, all the investigators participated of the description of the synthesis.

RESULTS

The crossing of the descriptors resulted in the identification of 413 articles. Of these, 16 matched the research question. The period of publication was 2016-2020, predominantly in English (87.5%) and in Portuguese (12.5%). The publication countries were:

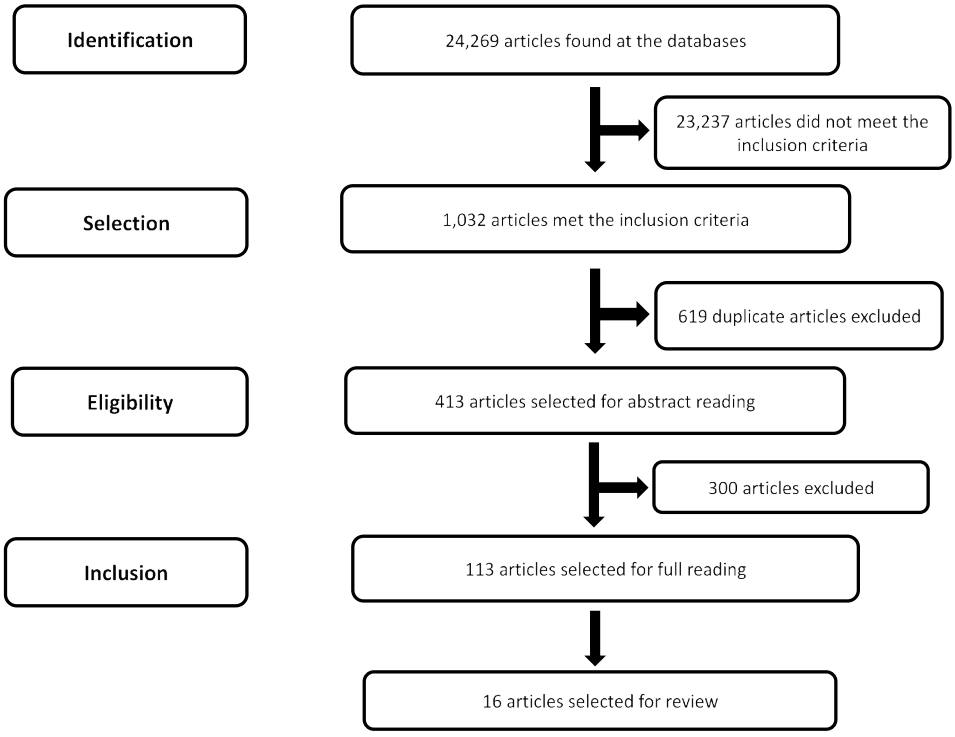

Figure 1. Flowchart of selection of the study articles

USA (43.75%), Brazil (12.5%), Canada (12.5%), Spain (12.5%), United Kingdom (6.5%), Czech Republic (6.25%) and South Kora (6.25%).

Chart 1[8-23] shows the summary of the search results per title, authors, year and country, method and evidence level according to JBI, objectives of the studies, results and recommendations. The analysis of each study type of administration of rituximab is presented in the last column.

According to JBI, the levels of evidence of the articles selected were: 56.25% (n=9) phase 3 studies; 31.25% (n=5) phase IV studies, considered as actual life-based recommendations through observational method and 12.5% (n=2) phase 1 studies[7].

Nine studies addressed intravenous infusion (various time modalities) and seven, subcutaneous infusion.

The articles highlighted important topics of infusion-related risk stratification management, hypersensitivity, drugs storage and clinical decision about choice of infusion route (Chart 2)[12-16,20,24].

Infusion-related all grades recognition and management are required from medical team who should grade reactions per NCI CTCAE and record the full procedure at the patient's chart; correct record is essential to define timing in subsequent infusions[12,13].

DISCUSSION

The studies reviewed highlight more than one mechanism involved in infusion reactions: cytokines release syndrome, mastocytes-mediated reactions (acute cases) and mechanisms involved in tumor lysis and serum disease (late reactions)[1,2].

NCI CTCAE is an important tool to help health professionals to grade the infusion reactions. Chart 3[25] shows the infusion-related reactions.

Six modalities of intravenous infusion described in the literature were identified, classified as slow (n=2) and fast (n=4). The first infusion will always be slow, this recommendation is valid to this day with the objective of exposing the patient gradually to the drug and slow release of cytokines into the blood, lessening the risk of severe acute reaction. The infusion should be initiated at a rate of 50 mg/h and if reaction does not occur, increase 50 mg/h at every 30 minutes to maximum 400 mg/h. Total infusion time can range from 3.5 to 6 hours in a non-reaction scenario depending on the volume of the solution where the drug is diluted[8,10,23].

The second option of slow infusion is utilized in patients who are hypersensitive to the drug; this modality is already addressed in 8-16 steps desensitization protocols with two to four bags in different concentrations for each protocol and time of infusion from 4.7 to 16 hours. Desensitization refers to giving a patient a safe form of using the drug when they had severe reactions in past exposure even with precaution measures[14-16].

Whether the patient had severe past reaction (grades 3 or 4), an allergist should evaluate and perform an intradermal test with rituximab 0.1%. If the evaluation

Chart 1. Analysis of the studies reviewed

Title/authors/ country	Method and level of evidence (JBI)	Objectives	Results and safety recommendations	Infusion Protocols
Reactions to rituximab in an outpatient infusion center: a 5-year Review Levin et al.[8], 2016/USA	Cross-sectional NE 4.b	To better understand clinical decision making surrounding rituximab reactions and subsequent rechallenge	Patients with grade 1 reactions can be safely rechallenged the same day Grade 3 and 4 reactions need risk evaluation prior to rechallenging More studies needed to better understand ideal management of grade 2 reactions	FIRST IV INFUSION - First infusion initiated at a rate of 50 mg/h - Increase 50 mg/h at every 30 min to a maximum of 400 mg/h if no reaction occurs SUBSEQUENT INFUSIONS - Started at 100 mg/h at every 30 minutes to a maximum of 400 mg/h without any infusion reaction
Tolerance and safety of rapid 2-hour infusion of rituximab in patients with kidney-affecting autoimmune diseases and glomerulonephritides: a single-centre experience Hartinger et al.[9], 2019/ Czech Republic	Control group cohort study NE 3.c	Evaluate the tolerance and safety of rapid 2-hour infusion in patients with autoimmune diseases and glomerulonephritides	Fast infusion in 2 hours appears to be safe for several autoimmune diseases with renal involvement. Pre-medication methylprednisolone can be replaced by hydrocortisone safely. Slow infusions are time-consuming and uncomfortable for patients and medical staff, fast infusion can save time and cut costs	SUBSEQUENT INFUSIONS Recommendations for 2-hour IV infusion - 2-hour infusion may be preferred for non-initial infusion reaction - Rituximab infusion to be initiated at a rate of 250 mg/h in the first 30 minutes and increased to 600 mg/h
Implementation and evaluation of a 90-minute rituximab infusion protocol at the Richard L. Roudebush VA Medical Center Fenton et al.[10], 2020/USA	Retrospective cross-sectional study NE 4.b	Assist the safe implementation of 90-minute fast rituximab infusion protocol at the Richard L. Roudebush VA	Pro-active measures taken to implement 90-minute fast infusion protocol improved ordering by health professionals, nurses satisfaction and management of infusion reactions with significant time-saving	SUBSEQUENT INFUSIONS Recommendations for 90-minute IV infusion - 90-minute infusion to be chosen for patients with non-initial (grades 3 and 4) infusion reaction - Rituximab infusion can be initiated at 20% of the prescribed dosage for the first 30 minutes and the remaining 80% in 60 minutes
Sixty-minute infusion rituximab protocol allows for safe and efficient workflow Dotson et al.[11], 2016/ USA	Control group cohort study NE 3.c	Assess the safety and feasibility of a 60-minute fast infusion rituximab protocol at an outpatient treatment area of a comprehensive cancer center	Subsequent rituximab infusions can be safely administered over 60 min and without steroid premedication in an experienced outpatient infusion center when patients are appropriately screened. This time-saving protocol does not compromise the patient safety and increased nurse satisfaction	SUBSEQUENT INFUSIONS Recommendations for 60-minute IV infusion - 60-minute infusion to be chosen for patients with non-initial (grades 3 and 4) infusion reaction - Rituximab can be initiated at 100 mg/h for 15 min and the remaining during 45 minutes
Clinical significance of rituximab infusion-related reaction in diffuse large B-cell lymphoma patients receiving R-CHOP Cho et al.[12], 2019/ South Korea	Retrospective cross-sectional study NE 4.b	Evaluate the clinical significance of infusion-related reaction (IRR) of rituximab in diffuse large-B-cell lymphoma patients who received R-CHOP	IRR was not associated with overall survival or progression-free survival of diffuse large-B-cell lymphoma patients as compared to those who did not have IRR. The study suggests a need for more careful observation for IRR in patients with B symptoms or bone marrow involvement	FIRST IV INFUSION - First infusion at a rate of 50 mg/h. Increase 50 mg/h at every 30 min up to a maximum of 400 mg/h in non-initial infusion reaction SUBSEQUENT INFUSIONS - Start at a rate of 100 mg/h at every 30 minutes up to a maximum of 400 mg/h in non-initial IRR patients

to be continued

Chart 1. continuation

Title/authors/ country	Method and level of evidence (JBI)	Objectives	Results and safety recommendations	Infusion Protocols
Anticorpos monoclonais no tratamento oncológico: revisão de literatura para o atendimento ao paciente e manejo das reações infusionais Bruneto et al.[13], 2019/ Brasil	Systematic literature review NE 3.b	Identify how to manage infusion reactions related to monoclonal antibodies; describe the protocol of conduct to manage infusion reaction; identify major infusion reactions related to monoclonal antibodies	The protocol of infusion reaction management includes: explain the patient the procedure, educate the patient to self-monitor the treatment regimen and ensure that the staff know who the patients in initial infusion are and associated risks; infusion to be applied in a room with cardiovascular resuscitation and standard evaluation of patients, monitoring signs and symptoms of infusion reactions and other aggravating factors	FIRST IV INFUSION - First infusion at a rate of 50 mg/h. Increase 50 mg/h at every 30 min up to a maximum of 400 mg/h in non-initial infusion reaction SUBSEQUENT INFUSIONS - non-initial infusion reactions (grades 3 and 4) patients: • 90-minute IV infusion • 60-minute IV infusion
Rituximab hypersensitivity and desensitization: a personalized approach to treat cancer and connective tissue diseases Yang e Castells[14], 2019/ USA	Case-series NE 4.c	Offer 3 clinical scenarios with an approach to evaluation of the initial reaction, risk stratification and proposed recommendations for desensitization	Fast desensitization able to overcome hypersensitivity and return to treatment. Conduct: if reaction occurs, the patient is classified as risky to determine the feasibility of desensitization. One of the protocols is selected and adapted to overcome specific symptoms experienced by the patient during initial reaction with correct pre-medication	IV INFUSION IN DESENSITIZATION PROTOCOL - 16-step protocol for a 765 mg dose in 4 bags with gradual dilutions one after the other: • Bag 1 with 0.383 mg/250 ml – initial infusion at a rate of 2.5 ml/h for 15 min doubled at every 15 min up to step 4 • Bag 2 with 7.650 mg/250 ml – initial infusion at a rate of 2.5 ml/h for 15 min doubled at every 15 min up to step 8 • Bag 3 initial infusion with 76.500 mg/250 ml at a rate of 5 ml/h for 15 min doubled at every 15 min until step 12 • Bag 4 initial infusion with 758. 961 mg/250 ml at a rate of 10 ml/h for 15 min doubled at every 15 min up to step 16 reaching 80 ml/h until the bag is empty. 7-hour total infusion time - 12-steps protocol for an 858.75 mg dose in 3 bags of gradual dilution one after the other: • Bag 1 with 8.588 mg/250 ml initial infusion at a rate of 2 ml/h for 15 min, increasing to 5 ml/h doubled at every 15 minutes up to step 4 • Bag 2 with 85.875 mg/250 ml initial infusion at a rate of 5ml/h for 15 min doubled at every 15 minutes up to step 8 • Bag 3 with 851.992 mg/250 ml initial infusion at a rate of 10 ml/h for 15 min doubled at every 15 min up to step 12, reaching 80 ml/h until the bag is empty. 6-hours approximate total infusion time

to be continued

Chart 1. continuation

Title/authors/ country	Method and level of evidence (JBI)	Objectives	Results and safety recommendations	Infusion Protocols
Rituximab hypersensitivity: evaluation, desensitization, and potential mechanisms Wong e Long[15], 2017/ USA	Retrospective cross-sectional study NE 4.b	Analyze RITS (rituximab hypersensitivity) patient characteristics, pattern, and desensitization outcomes to optimize management.	25 patients were submitted to continuous 170 desensitization based in 3 protocols: 168 successful desensitization IgE mediated mechanism and degranulation of mastocytes, further to the cytokine release syndrome and tumor lysis syndrome can contribute to a significant portion of patients' hypersensitivity reactions	IV INFUSION IN MODALITY OF DESENSITIZATION PROTOCOL Protocol 1: fast 8-steps 500 ml dose in 2 250 ml bags with gradual dilutions one after the other: • Bag 1 with 0.2 mg/ml initial infusion at a rate of 5 ml/h for 15 min doubled at every 15 min up to step 4 • Bag 2 with com 2 mg/ml initial infusion at a rate of 10 ml/h for 15 min doubled every 15 min up to step 8, reaching the flow of 80 ml/h to the end of the bag Protocol 2: intermediate 13-steps 500 mg infusion divided in 3 250 ml bags with gradual dilutions one after the other: • Bag 1 with 0.02 initial infusion at a rate of 2.5 ml/h for 15 min doubled every 15 min up to step 4 • Bag 2 with 0.2 mg/ml initial infusion at a rate of 5 ml/h for 15 min doubled every 15 min up to step 8 • Bag 3 with 2 mg/ml initial infusion at a rate of 10 ml/h for 15 min doubled every 15 min up to step 13, reaching 80 ml/h to the end of the bag Protocol 3: high risk 13-steps 500 mg in four 1,000 ml bags with gradual dilutions one after the other: • Bag 1 with 0.0005 mg/ml initial infusion at a rate of 20 ml/h for 15 min doubled at every 15 min up to step 3 • Bag 2 with 0.005 mg/ml initial infusion at a rate of 20 ml/h for 15 min doubled at every 15 min until step 6 • Bag 3 with 0.05 mg/ml initial infusion at a rate of 20 ml/h for 15 min doubled at every 15 min up to step 9 • Bag 4 with 0.5 mg/ml initial infusion at a rate of 20 ml/h for 15 min doubled at every 15 min up to step 13 reaching 80 ml/h until the bag is empty
Assessment of confirmed clinical hypersensitivity to rituximab in patients affected with B-Cell neoplasia Novelli et al.[16], 2020/ Spain	Control group cohort study NE 3.c	To describe the use of the 12-step protocol for desensitization to intravenous rituximab in clinical practice and the complementary study of a possible IgE-mediated HSR in the context of B-cell lymphoma treatment.	Desensitization protocol helped 70% of the patients to complete the scheduled immunochemotherapy The 12-step desensitization protocol is very effective and assumable within healthcare practice. There is a need to determine the mechanism underlying the infusion reaction in a large proportion of cases due to the risk of future drug exposure.	IV INFUSION IN DESENSITIZATION PROTOCOL - 12-step protocol, 675 mg in 3 bags with gradual dilutions one after the other: • Bag 1, 1.5 mg/50 ml initial infusion at a rate of 2 ml/h for 15 min doubled at every 15 min up to step 4 • Bag 2, 15 mg/50 ml initial infusion at a rate of 5 ml/h for 15 min doubled at every 15 min up to step 8 • Bag 3, 669 mg/250 ml initial infusion at a rate of 10 ml/h for 15 min doubled at every 15 min up to step 12, reaching 80 ml/h until the bag is empty. 6-hour approximate total infusion time

to be continued

Chart 1. continuation

Title/authors/ country	Method and level of evidence (JBI)	Objectives	Results and safety recommendations	Infusion Protocols
Update on the subcutaneous administration of rituximab in Canadian Cancer Centres Stewart et al.[17], 2020/ Canada	Retrospective observational study NE 3e	Report data from the SCuBA study and provide perspectives about the practical experience with the SC formulation of rituximab among oncologists, nurses, pharmacists and patient advocacy groups	Average drug preparation cost reduction of 33.5% with the SC formulation compared with IV formulation Average chair time and administration was greater with the IV formulation Participants also reported an average reduction in drug wastage of 62.0% with the SC formulation	SUBCUTANEOUS INFUSION - Only after the second cycle of rituximab NON-HODGKIN LYMPHOMA - Syringe to inject 1,400 mg of rituximab in 11.7 ml of solution with hyaluronidase exclusively at the hypodermis of the abdomen during 5-6 minutes. Monitor patient for at least 15 min CHRONIC LYMPHOID LEUKEMIA - Syringe to inject 1,600 mg/13.4 ml of solution containing hyaluronidase exclusively at the hypodermis if the abdomen for 7 minutes. Monitor patient for at least 15 min
Modelo de impacto orçamentário do rituximabe subcutâneo comparado ao intravenoso no tratamento do linfoma não Hodgkin difuso de grandes células B, CD-20 positivo, no sistema de saúde suplementar brasileiro Kashiura et. al.[18], 2018/ Brazil	Control group cohort study NE 3.c	Estimate the budget impact of incorporating rituximab SC compared with IV formulation in the perspective of the Brazilian private health system	3,846 patients with diffuse NHL during five years were found in the private health system The progressive incorporation of rituximab SC into the system can cut costs of approximately R$ 15,835,969.11 Treat diffuse large-B cells NHL by the Brazilian private health system can cost less R$ 15.8 million	SUBCUTANEOUS INFUSION - Only after the second cycle of rituximab NON-HODGKIN LYMPHOMA - Syringe to inject 1,400 mg of rituximab in 11.7 ml of solution with hyaluronidase exclusively at the hypodermis of the abdomen during 5 minutes. Monitor patient for at least 15 min
Efficacy and safety of subcutaneous and intravenous rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone in first-line diffuse large B-cell lymphoma: the randomized MabEase study Lugtenburg et al.[19], 2017/USA	Clinical trial NE 1	Investigate the efficacy and safety of rituximab SC vs. IV formulation as part of a R-CHOP regimen	Of 576 randomized patients, 572 (378 subcutaneous; 194 intravenous) received treatment. End of induction complete response/unconfirmed complete response rates were 50.6% (subcutaneous) and 42.4% (intravenous). After a median 35 months, median overall, event-free and progression-free survivals were not reached. Grade $\geq$3 adverse events (subcutaneous 58.3%; intravenous 54.3%) and administration-related adverse events (both groups 21%) were similar between arms. Combined with former evidences, the results of this study support the use of rituximab SC in this scenario	SUBCUTANEOUS INFUSION - Only after the second cycle of rituximab NON-HODGKIN LYMPHOMA - Syringe to inject 1,400 mg of rituximab in 11.7 ml of solution with hyaluronidase exclusively at the hypodermis of the abdomen during 5 minutes. Monitor patient for at least 15 min

to be continued

Chart 1. continuation

Title/authors/ country	Method and level of evidence (JBI)	Objectives	Results and safety recommendations	Infusion Protocols
Subcutaneous rituximab for the treatment of b-cell hematologic malignancies: a review of the scientific rationale and clinical development Davies et al.[20], 2017/ United Kingdom	Review of the Literature NE 3.b	Summarize the justification and main clinical studies of SC rituximab	SC formulation has undergone a detailed, sequential clinical development program demonstrating that at fixed doses rituximab SC achieves non-inferior serum trough concentrations in patients with Non-Hodgkin lymphoma and chronic lymphocytic leukemia with comparable efficacy and safety relative to the IV formulation. The added benefit of rituximab SC is to allow simplified and shortened drug preparation and administration times resulting in improved resources utilization, time and potentially cost-saving	SUBCUTANEOUS INFUSION - Only after the second cycle of rituximab NON-HODGKIN LYMPHOMA - Syringe to inject 1,400 mg of rituximab in 11.7 ml of solution with hyaluronidase exclusively at the hypodermis of the abdomen during 5-6 minutes. Monitor patient for at least 15 min
A Canadian perspective on the subcutaneous administration of rituximab in non-Hodgkin lymphoma MacDonald et al.[21], 2017/Canada	Review of the Literature NE 3.b	Discuss the use of rituximab SC as a potential alternative to IV in Canada	Results indicate that the pharmacokinetics are noninferior and response rates are comparable to those obtained with the IV formulation. Moreover, the SC formulation is preferred by patients and health care providers and reduces administration and chair time. Additional advantages include a lesser potential for dosing errors, shorter preparation time, reduced drug wastage, and fewer infusion-related reactions.	SUBCUTANEOUS INFUSION - Only after the second cycle of rituximab NON-HODGKIN LYMPHOMA - Syringe to inject 1,400 mg of rituximab in 11.7 ml of solution with hyaluronidase exclusively at the hypodermis of the abdomen during 5 minutes. Monitor patient at least for 15 min
Preference for subcutaneous or Intravenous Administration of rituximab among patients with untreated CD20+ diffuse large B-cell lymphoma or follicular lymphoma: results from a prospective, randomized, open-label, crossover study (PrefMab) Rummel et al.[22], 2017/ USA	Clinical trial NE 1	Evaluate patient preference and satisfaction for the subcutaneous (SC) versus intravenous (IV) formulation of rituximab given with chemotherapy in previously untreated patients with CD20+diffuse large B-cell lymphoma (DLBCL) or follicular lymphoma (FL).	At cycle 8, 81% of patients completing the Patient Preference Questionnaire preferred rituximab SC. Preference was not impacted by treatment sequence or disease type. Patient satisfaction as measured by Rituximab Administration Satisfaction Questionnaire was higher for SC versus IV. Cancer Therapy Satisfaction Questionnaire scores were similar between arms. Adverse events were generally balanced between administration routes and no new safety signals were detected.	SUBCUTANEOUS INFUSION - Only after the second cycle of rituximab NON-HODGKIN LYMPHOMA - Syringe to inject 1,400 mg of rituximab in 11.7 ml of solution with hyaluronidase exclusively at the hypodermis of the abdomen during 5 minutes. Monitor patient at least for 15 min CHRONIC LYMPHOID LEUKEMIA - Syringe ready to inject 1,600 mg/13.4 ml of solution containing hyaluronidases - Injection to be applied exclusively at abdominal hypodermis for 7 minutes. Monitor patient for at least 15 minutes

to be continued

Chart 1. continuation

Title/authors/ country	Method and level of evidence (JBI)	Objectives	Results and safety recommendations	Infusion Protocols
Time savings with rituximab subcutaneous injection versus rituximab intravenous infusion: a time and motion study in eight countries De Cock et al.[23], 2016/ Spain	Control group cohort study NE 3.c	Quantify active healthcare professional (HCP) time and patient chair time for rituximab SC and IV, including potential time savings.	Mean active HCP time was 35.0 and 23.7 minutes for IV and SC process, respectively (-32%, p <0.0001). By country, relative reduction in time was 27–58%. Absolute reduction in extrapolated active HCP time (first year of treatment) was 1.1–5.2 hours. Mean chair time was 262.1 minutes for IV, including 180.9 minutes infusion duration, vs. 67.3 minutes for SC, including 8.3 minutes SC injection administration. In comparison with rituximab IV, rituximab SC was associated with reduction of chair time and active HCP	SUBCUTANEOUS INFUSION SC only after the second cycle of rituximab

Captions: IRR = infusion related reaction ; R-CHOP = rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; IV = intravenous; SC = subcutaneous; LE = level of evidence; IgE = immunoglobulin E; JBI = Joanna Briggs Institute; CD20 = B-lymphocyte antigen CD20; NHL = non-Hodgkin lymphoma.

determined the application of desensitization protocol, the infusion should take place in clinics with available intensive care resources in case of necessity. A 2019 USA study demonstrated three cases of patients with moderate and severe reaction who were given a 12 and 16 steps protocol and were able to receive the complete dosage of rituximab[14-16].

Fast infusions are eligible after the second cycle if grade 3 or 4 reactions did not occur. The oldest option is described in the first package insert of the drug: administration initiates at a rate of 100 mg/h and if no infusion reaction occurs, increase 100 mg/h at every 30 minutes to reach 400 mg/h maximum. Total infusion time can range from 2.5 to 3.5 hours in a non-reaction scenario depending on the volume of the solution[8,10].

Other modalities of fast infusions appeared in a scenario whose goal was to reduce the time the patient spent in infusion centers, increasing chair time and beds rotation, optimizing the active time of the health professionals and improving patient's comfort. One of them is 2-hour infusion to be initiated at 250 mg/h for the first 30 minutes, increasing to 600 mg/h up to the end of the bag[9].

The option to administer 90-minute anti-CD20 is indicated in the package insert of one of rituximab manufacturers and was validated after a multicenter phase III study. Should be initiated with 20% of the prescribed dosage to be infused in the first 30 minutes and the remaining 80%, in 60 minutes[10].

The fast infusion described in the literature is 60-minutes, initiated at a rate of 100 mg/h for 15 minutes, and the remaining dosage in 45 minutes. The patients eligible according to the study by Dotson et al.[11], were those who, in addition of non-grade 3 or 4 initial infusion, had no heart comorbidities, had no high initial lymphocytes (over 10 × 103 cells/μL), without diagnostic of aggressive lymphoma (Burkitt's or lymphoblasts) and no history of murine-based drugs allergy. In this same study, 50 patients received 60-minute rituximab protocol and none presented 3 or 4 grade reaction[11].

For all the modalities of intravenous infusion, the drug dilution is pivotal for dosage programming preferentially at 1:4 mg for each ml of dilutant (saline 0.9% or glucose serum 5%) as the recommendation is in mg/h and not in ml/h. Each infusion modality has the initial and maximum milligrams, the health professional in charge of the infusion must verify the volume matched to the milligrams and determine the correct flow of the infusion[24].

If 1 mg/ml is the proportion of dilution of rituximab bags, the infusion pump is determined to be 1/1 proportionally (for example, 50 ml/h is equal to 50 mg/h, or 100 ml/h is equal to 100 mg/h). However, if the proportion was bigger than 1 mg/ml, calculation will always be necessary using the rule of three to determine the volume of concentration of the milligrams matched to each modality. The package insert and the studies investigated fail to present the rule of three, the reader has to do this. Firstly, in the 90-minute infusion, the rule

Chart 2. Good practices for rituximab administration

Infusion-related risk factors[12,13]	• High tumor load, lung infiltrations, advanced age, patients with chronic lymphocytic leukemia or mantle cell lymphoma and patients with pre-existing cardiac and/or lung diseases • The first infusion of the patient
Reaction prevention[12,13]	• Thirty-sixty minutes before rituximab, patients were given analgesics, antihistamines and glucocorticoid • Drug administered only by infusion pump, follow grading rate per protocol • Guide the patient about infusion-related warning signs
Infusion-related management[12,13]	• Interrupt infusion immediately, report to the medical team, check vital signs, pulse oximeter and physical exam • Specific conducts depend on reaction grade • Crash-car in case of severe reaction
Hypersensitiveness management[14-16]	• Intradermal test • Evaluate whether the patient is eligible to rituximab based in desensitization protocols
Choice of infusion route[20]	According to: • number of the cycle (1st always IV) • diagnostic indication (SC only for NHL and CLL) • material available at the hospital
Drug storage[24]	• Rituximab stored at 2°C to 8°C, removed 30 minutes prior to administration to room temperature • Nurse checks expiry date, typically 24 h frozen and 12 h at room temperature

Captions: IV = intravenous; SC = subcutaneous; NHL = non-Hodgkin's Lymphoma; CLL= chronic lymphocytic leukemia.

Chart 3. NCI CTCAE Adverse Events Criteria

Classification (CTCAE)[25]	Characteristics and actions indicated
Grade 1	Mild transient reaction; infusion interruption not indicated; intervention not indicated
Grade 2	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (i.e., antihistamines, NSAIDs, narcotics, intravenous fluids); prophylactic medication indicated for less than or equal to 24 hours, fluids IV)
Grade 3	Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae
Grade 4	Life-threatening consequences, urgent intervention indicated
Grade 5	Death

Captions: CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; NSAIDS = Non-Steroidal Anti-Inflammatory Drugs.

of three is to be used to define the 20% and 80% of the dose to determine the infusion flow; if the proportion of dilution is not 1/1, the rule must be applied once more to define the flow in ml[24,26].

A study[3] conducted at the Memorial Sloan Kettering Cancer Center in 2018 draws attention for a practice until then unchartered: the filling of the infusion set with the dilutant instead of the drug solution. The incidence of hypersensitivity was 35% in the arm initiated with the dilutant *versus* 19% in the arm initiated with the drug, showing that when the set is prepared with the drug, the exposure of the patient to rituximab is immediate soon after the infusion. However, when the set is prepared with the dilutant the patient receives it for approximately 40 minutes prior to being exposed to rituximab, resulting in delayed cell death and cytokine release. The new practice of preparing the set with the drug was adopted and recommended by the institution[3].

Rituximab can also be administered subcutaneously, approved since 2014 and recommended in package inserts only for NHL and CLL. Its efficacy and equivalence compared to intravenous were widely proven by clinical trials. Like fast infusions, this modality can only be eligible since the second cycle when no grades 3 and 4 reactions occur in the first infusion[1,19,22].

Two subcutaneous infusion presentations are applied: for NHL (1,400 mg/11.7 ml syringe administered in 5 minutes) and for CLL (1,600 mg/13.4 ml syringe

administered in 7 minutes), both containing recombinant human hyaluronidases, an enzyme favoring the perfusion of subcutaneous tissue substances kept at 2ºC to 8ºC refrigeration, stable for 48 hours at this temperature. At room temperature, the stability drops to 8 hours. The abdominal region is the preferred for application. Adverse events hold a similar profile to IV's in addition to injection-related local bruises as pain and erythema where the injection was applied. It is important that nurses and patient are instructed about the 5-6 minutes slow administration for better understanding of the procedure[17,20,21].

A clinical trial (PrefMab)[22] evaluated the patients' preference and satisfaction for rituximab subcutaneous *versus* intravenous and 81% of them sided with subcutaneous[22]. The benefits for them are less chair time, time-saving, less parking fees, receive treatment without extended length of stay and oral premedication[17,20].

The benefits for health professionals are cost-effectiveness, less time to provide care to the patient, improved reassignment of time gained with subcutaneous administration improving the number of outpatient consultations, more availability of professionals for clinic visits, less treatment waiting lists, cost-saving of intravenous administration materials, low dosage errors and less waste because of fixed doses further to less time of pharmacy manipulation[17,23].

The conversion rate in Canada for intravenous to subcutaneous is 55%, except Quebec and Saskatchewan. After three years of implementation of subcutaneous rituximab it was estimated that 5,762 Canadians have received the injection, a total of 128,715 hours were spared and 40 million dollars were saved[17]. A Brazilian study concluded that the implementation of subcutaneous by the private health system would have saved around 15 million Reais in 5-years[18].

The main study limitation is that most of the studies address international realities and experiences, requiring efforts to migrate to the national structures and infusion practices. An additional limitation is the scope of the integrative review which covers the state-of-the art of the object but is unable to indicate the most effective.

CONCLUSION

There are different evidences-based options of administration of rituximab to be considered according to the patient's status, diagnosis, posology and institutional resources and clinical experience of health professionals directly involved. The scientific literature determines that all the modalities of either intravenous or subcutaneous infusion have shown to be effective and safe if protocols are followed correctly.

In short, the first infusion must be slow and intravenous. For the second, subcutaneous infusion was the best option for eligible patients even compared to fast infusion due to less time and resources than intravenous, usually preferred by the patients. For moderate and severe reactions when drug benefits offset reaction risks, desensitization protocols can be a safe and plausible option.

Rituximab draws increasing attention as treatment option for other than onco-hematological diseases. Some studies strengthen the importance of comprehensive clinical evaluation and a health professional team (doctors, nurses and pharmacists) in place to ensure the safety of the process for the patient. Institutional protocols should support the scientific-evidence based safe practice for each use and route of administration.

CONTRIBUTIONS

All the authors contributed substantially to the study design, acquisition, analysis and interpretation of the data, wording and critical review. They approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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