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Chemotherapy Administration-Related Adverse Events and Impact on Management: The Case of Rituximab

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Abstract:
Introduction: Rituximab is a monoclonal antibody that targets CD20 and is indicated for the treatment of certain autoimmune diseases and certain types of blood cancer such as non-Hodgkin's lymphoma and chronic lymphocytic leukaemia. Rituximab may also cause side effects. Some of the possible side effects include allergic reactions, infections, infusion-related reactions and skin reactions. The aim of this study is to evaluate the efficacy and safety of rituximab administration.
Materials & Methods: This is a retrospective descriptive study conducted at the pharmacovigilance unit of the pharmacy of Ibn Sina Rabat hospital from January 2017 to December 2022 on the cases of adverse reactions notified to the hospital, whose aim is to identify the causality of the adverse reaction that occurred following the administration of Rituximab using the French imputability method
Results & Discussion: The number of reported cases of adverse events related to the administration of Rituximab in the context of chemotherapy reported by the haematology oncology department is 17. Mild adverse events constituted 29.4% and 70.6% of the cases required prolongation of hospitalisation with increased medical follow-up. Following the numerous reports of rituximab infusion, the risk minimisation action opted for by the pharmacist was to adjust the infusion rate, starting with an infusion rate of 50mg/hr for 30 minutes, then increasing by 50mg/hr every 30 minutes up to a maximum of 400mg/hr.
Conclusion: This study illustrates the importance of the role of the pharmacist in detecting pharmacovigilance alerts, as well as raising the awareness of nurses and physicians to the risks of administering drugs that can cause angioedema, in particular rituximab. In order to prevent and reduce the risk of incidence and improve vital prognosis.
Keyswords: Rituximab, Adverse effect, Perfusion, Angioedema, Chemotherapy

Chemotherapy Administration-Related Adverse Events and Impact on Management: The Case of Rituximab

Introduction

Rituximab is a monoclonal antibody used to treat certain autoimmune diseases such as; Non-Hodgkin's Lymphoma, Chronic Lymphocytic Leukaemia (CLL), Rheumatoid Arthritis (RA), Granulomatosis with Polyangiitis (GPA), Microscopic Polyangiitis (MPA), and Pemphigus vulgaris. Rituximab primarily targets the CD20 protein, which is found on the surface of immune cells (B cells). By binding to CD20, rituximab helps to reduce the number of B cells in the body and modulate the immune response [1].

There are some pharmacovigilance warning signs associated with Rituximab. This medicine can cause severe allergic reactions, including anaphylactic reactions, in some people who have a sensitivity to certain molecules. Symptoms of a severe allergic reaction may include breathing difficulties, rash, itching, swelling of the face, lips, tongue or throat. It is important to monitor patients during the administration of Rituximab for any potential allergic reaction [2]. Other adverse events associated with Rituximab may include injection site reactions, cardiac disorders, haematological reactions, pulmonary disorders and skin reactions. It is therefore important to report any suspected side effects or adverse reactions, which can then be followed up appropriately [3].

The severity and frequency of side effects associated with rituximab may affect the effectiveness of treatment and the quality of life of patients. Patients may require additional medical interventions to manage side effects, such as drugs to treat infusion reactions or antibiotics to prevent infections. The cost of treatment may also increase due to additional medical care and monitoring. Patients may experience anxiety and stress related to the potential side effects of Rituximab, which may influence their general well-being.

The objective of this study is to evaluate the effectiveness and safety of rituximab administration by determining the suspected cause/effect relationship in patients undergoing chemotherapy. Additionally, it aims to monitor patients for any signs of side effects in order to improve the management of patients receiving rituximab.

Materials & Methods:

A retrospective descriptive study was conducted at the pharmacovigilance unit of the pharmacy of Ibn Sina Rabat Hospital from January 2017 to December 2022. The study included all cases of adverse reactions related to rituximab and notified to the hospital at this period. The aim of this study was to identify the causality of the adverse event following the administration of Rituximab was conducted using the French imputability. This method is based on chronological and semiological criteria with a score ranging from I0 to I6 and completed by the bibliographical study with a score of B1 to B4. The seven criteria of intrinsic causality are divided into two categories: chronological criteria and semiological criteria. It results from the combination of an evaluation of the chronological criteria and an evaluation of the semiological criteria of the adverse event/medication pair under consideration. The objective is to obtain a numerical score using solely clinical and paraclinical data.

The chronological criteria include the time interval between medication administration and the onset of the effect, the evolution of the effect after the medication is stopped or continued, and the outcome of potential re-administration of the medication. The chronological score is determined by combining these three criteria, with a score ranging from C0 to C3.

The semiological criteria encompass signs and symptoms suggestive of the medications role in the occurrence of the effect, predisposing factors (patient characteristics or situations), reliable results from specific complementary examinations, and the search for an alternative non-drug-related cause, with a score ranging from S0 to S3.

Extrinsic causality, or bibliographic scoring, is a systematic rating of data from scientific literature. This scoring is organized into several levels (B1 to B4), based on the systematic analysis of reference documents or databases [4].

The safety of the infusion was evaluated in order to ensure good patient management [4].

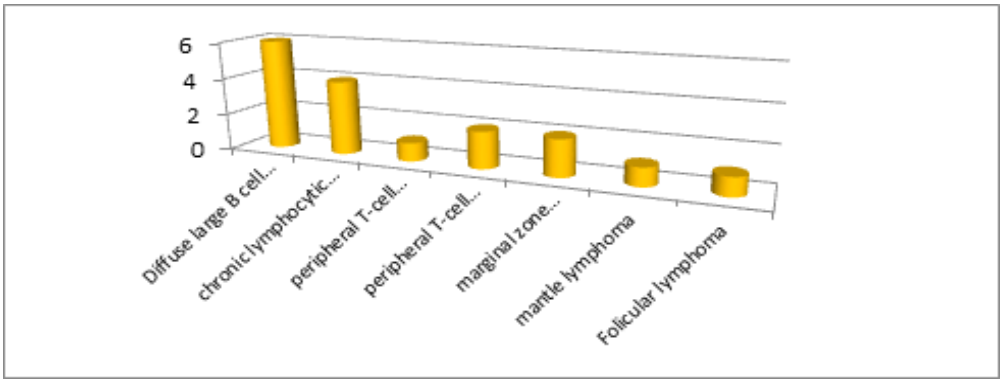
The statistical analysis of the results was performed using Jamovi software version 2.3.17.

Results:

The number of reported cases of adverse reactions related to the administration of Rituximab in the context of chemotherapy reported by the haematology oncology department was 17, the total number of adverse effect notifications following Rituximab administration in the period of study was 53. the prevalence of adverse effect following Rituximab administration in the context of chemotherapy is 32%.

The distribution of reported cases in our study shows a predominance of females with a sex ratio M/F of 1.12.

This frequency graph presents various indications related to the concept of French imputability. The highest frequency is observed in "Diffuse large B-cell lymphoma," accounting for 35.3% of the total with a quantity of 6. "Chronic lymphocytic leukemia" follows with 23.5%. Other indications such as "Peripheral T-cell lymphoma," "Marginal zone lymphoma," "Mantle lymphoma," and "Follicular lymphoma" have lower frequencies ranging from 5.9% with a quantity of 1 to 11.8% with a quantity of 2.



Graph 1: the frequencies for the indication of rituximab.

These frequencies provide information about the distribution of adverse effects in the study, highlighting the most commonly observed effects.

The cumulative percentages show the incremental contribution of each adverse effect to the total number of cases (table 1).

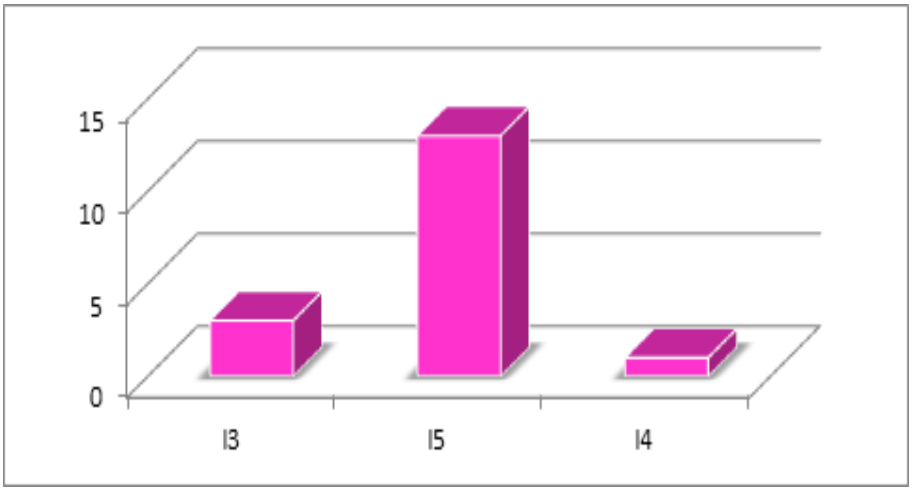
Table 1 : Frequencies of Adverse reaction post administration (MedDRA)

"Adverse effect (MedDRA)"	Quantités	% du Total	% cumulés
Maculopapular rash	2	11.8 %	11.8 %
Angioedema	3	17.6 %	29.4 %
Facial oedema	2	11.8 %	41.2 %
Thrombocytopenia	1	5.9 %	47.1 %
Tachycardia	2	11.8 %	58.8 %
Chills, fever	1	5.9 %	64.7 %
Headaches	2	11.8 %	76.5 %
Pruritus	1	5.9 %	82.4 %
Rash	2	11.8 %	94.1 %
Hypotension, rash	1	5.9 %	100.0 %

The category "Favourable" has the highest frequency, accounting for 16 cases, which represents 94 % of the total cases and the category "Death" has a frequency of 1 case, accounting for 6 % of the total cases.

The French imputability results showed that Rituximab was incriminated with an intrinsic imputability score of I5 for 77% of the cases and an extrinsic score of B4 for the totality of the notified cases (Graph 2)

From the investigation conducted in the haematology oncology department, we found that the adverse events that occurred were caused by the very high administration rate of 200mg/h from the start of the infusion.



Graph 2: French imputability results

Discussion:

Rituximab is a very potent drug that works by targeting the abnormal B cells that cause tumour growth. Although effective, this drug can cause side effects of varying severity. Mild side effects make up 29.4% and 70.6% of the cases required prolonged hospitalisation with increased medical monitoring.

The side effects of Rituximab administration are numerous and varied. They vary depending on the dose given, the type of cancer treated and the duration of treatment. According to the literature, the most frequently observed adverse events in patients receiving intravenous Rituximab were infusion-related reactions, which occurred with the first infusion in most patients. The incidence of infusion-related symptoms decreased significantly with subsequent infusions to less than 1% after the eighth course of Rituximab [5,6].

The most common types of adverse events in our report were angioedema, facial oedema, rash, tachycardia and headache.

The Rituximab Product Monograph point out that signs and symptoms suggestive of an infusion-related reaction were reported in more than 50% of patients in clinical studies, and were mainly observed during the first infusion, usually within the first two hours. These symptoms mainly included fever, chills and tremors. Other symptoms included tachycardia, angioedema, vomiting, nausea, urticaria/rash, fatigue, headache, laryngeal irritation, rhinitis, pruritus, pain, tachycardia, hypertension, hypotension, dyspnoea, dyspepsia, asthenia and symptoms suggestive of tumour lysis syndrome [7].

Severe infusion-related reactions such as angioedema, bronchospasm, hypotension have occurred in up to 12% of cases. It is therefore important to monitor patients closely during treatment for these symptoms [8].

Other reactions reported include myocardial infarction, atrial fibrillation, pulmonary oedema and acute reversible thrombocytopenia. Exacerbations of pre-existing cardiac disorders such as angina pectoris, congestive heart failure or severe cardiac events (heart failure, myocardial infarction, atrial fibrillation), pulmonary oedema,

multi-visceral failure, tumour lysis syndrome, cytokine release syndrome, renal failure, and respiratory failure have been reported at lower or unknown frequencies. The incidence of infusion-related symptoms decreased significantly with subsequent infusions to less than 1% by the eighth course of Rituximab [9,10].

The adverse events in our study are classified as "infusion-related reactions" which occur very frequently. The evolution of our cases was favourable for 16 cases (94%). only one patient died.

To limit the occurrence of this type of adverse event it is recommended that:

- Rituximab should be administered under the close supervision of an experienced healthcare professional and in an environment where full resuscitation facilities are immediately available
- Administer premedication (antipyretic, antihistamine, antiemetic and corticosteroid) 30 minutes prior to Rituximab infusion
- Adhere to protocol dosages:
  - Single agent 375mg/m2/week on d1, d8, d15 and d22 or 1000mg on d1 and d15
  - Multidrug therapy: 375mg/m2/cycle of 21 days
  - Maintenance dose: 500mg/m2/cycle of 21 days
  - Do not give Rituximab by rapid intravenous injection at a rate of 200mg/h
- For the first infusion, it is recommended to start the infusion at a rate of 50 mg/hr; after the first 30 minutes, the infusion rate may be increased in steps of 50 mg/hr every 30 minutes up to a maximum of 400 mg/hr.
- For subsequent infusions of Rituximab, the initial rate may be 100 mg/hr and then increased by 100 mg/hr every 30 minutes to a maximum of 400 mg/hr [11].

This study illustrates the essential role of the pharmacist in monitoring the efficacy and safety of drug administration in order to make health professionals aware of the risks of administering drugs that can cause serious and life-threatening adverse effects, in particular rituximab. In order to ensure better medical surveillance to improve management.

Despite the legal obligation to report, there is a real problem of under-reporting of cases, which makes the frequency of occurrence of adverse events following rituximab infusion unknown.

Conclusion:

The reporting of adverse events related to Rituximab allowed us to detect a pharmacovigilance signal. From the qualitative analysis of the 17 cases notified by the haemato-oncology department, we can deduce that these were adverse reactions linked to the infusion, for which the Rituximab administration procedure was not well respected, and for which we noticed that the occurrence of adverse effects is periodic, which may be linked to the arrival of new groups of paramedical staff, thus insisting on good practices for the administration of cytotoxic drugs in order to train the new nurses assigned to the department well.

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