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Efectividad de Rituximab en pacientes con leucemia linfoblástica y su relación con el número de infecciones obtenidas durante su primer año de tratamiento

Effectiveness of Rituximab in patients with lymphoblastic leukemia and its relationship with the number of infections obtained during their first year of treatment

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Palabras claves:
Rituximab; anticuerpos monoclonales; protocolos antineoplásicos.

Resumen

Introducción: El cáncer como una enfermedad que se caracteriza por la proliferación descontrolada de células, pudiendo así invadir otros tejidos y la multiplicación de manera autónoma; así, existen hace algunos años una amplia gama de alternativas en materia de anticuerpos monoclonales para el tratamiento del cáncer, entre estos rituximab que se dirige contra el antígeno CD20 de los linfocitos B, siendo su mecanismo de acción la disminución de la célula B, apareciendo como una opción dentro del tratamiento en niños con enfermedades autoinmunitarias graves y resistentes dando buenos resultados **Objeto:** determinar la eficacia del Rituximab en pacientes con leucemia linfoblástica durante su primer año de tratamiento . **Metodología:** se realizó una búsqueda no sistemática de artículos originales, reportes de caso y revisiones bibliográficas publicadas en SciElo, ScienceDirect, UpToDate; descriptores: Rituximab; anticuerpos monoclonales; protocolos antineoplásicos. Se incluyó trabajos con antigüedad menor a 5 años, idioma inglés y/o español. **Resultados:** Se construyó un documento científico de fácil lectura y que aborda los principales tópicos para el conocimiento del personal de todos los niveles de atención. **Conclusión:** Para mejorar los resultados se deberían de administrar vacunas antes de la terapia con rituximab debido a que puede producir una hipogammaglobulinemia lo que representaría un aumento en el riesgo de infecciones. En casos donde existen pacientes con infecciones recurrentes después de la terapia con rituximab se sugiere una profilaxis antibiótica o incluso un reemplazo de inmunoglobulina. **Área de estudio general:** medicina**. Área de estudio específica:** oncología. **Tipo de estudio:** revisión narrativa.

Keywords:
Rituximab; antibodies, monoclonal; antineoplastic protocols.

Abstract

Background: Cancer as a disease that is characterized by the uncontrolled proliferation of cells, thus being able to invade other tissues and multiply autonomously; Thus, for some years now there has been a wide range of alternatives in terms of monoclonal antibodies for the treatment of cancer, including rituximab, which is directed against the CD20 antigen of B lymphocytes, its mechanism of action being the reduction of

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the B cell , appearing as an option within the treatment in children with severe and resistant autoimmune diseases giving good results. Objective: to determine the effectiveness of Rituximab in patients with lymphoblastic leukemia during their first year of treatment. Methodology: a non-systematic search of original articles, case reports and bibliographic reviews published in SciElo, ScienceDirect, UpToDate was carried out; descriptors: Rituximab; monoclonal antibodies; antineoplastic protocols. Included are jobs with less than 5 years of seniority, English and/or Spanish language. Results: An easy-to-read scientific document was constructed that addresses the main topics for the knowledge of staff at all levels of care. Conclusion: To improve results, vaccines should be administered before therapy with rituximab because it can produce hypogammaglobulinemia, which would represent an increased risk of infections. In cases where there are patients with recurrent infections after therapy with rituximab, antibiotic prophylaxis or even immunoglobulin replacement is suggested. General area of study: medicine. Specific study area: oncology. Type of study: narrative review.

Introduction

Nowadays, the word cancer is defined as a disease characterized by the uncontrolled proliferation of cells, which can invade other tissues and multiply autonomously.(1)It refers to the fact that carcinogenesis is initiated by epigenetic and genetic changes that change the structure of the genome, and at the same time allow an abrupt alteration in the cell by adding mechanisms such as apoptosis, proliferation and instability in the extracellular matrix.

When there is a disorder in the hematopoietic system causing a malignant transformation of progenitor cells starting in the bone marrow and traveling through the body through the blood to lodge in other parts of the body, we can be sure that we are facing a neoplasia called leukemia, which is divided into two types: acute type and chronic type. In the subtype of acute leukemias are lymphoid, such as acute lymphoblastic leukemia (ALL). This produces excess lymphocytes generating the neoplasia.(2).

The most common neoplasia in pediatric age with 80% of cases is acute lymphoblastic leukemia, this includes clinical manifestations such as asthenia, thermal rise, night sweats, arthralgia and joint infections in addition to hematomas and hemorrhages that are generated very easily.(3).

Approximately 30 to 40% of B-cell acute lymphoblastic leukemias present the CD20 antigen. The monoclonal antibody rituximab is directed against the CD20 antigen of B lymphocytes, and its mechanism of action is the reduction of B cells, appearing as an option within the treatment of children with severe and resistant autoimmune diseases, giving good results.(1–3).

Methodology

The research work was carried out in accordance with the objective of determining the effectiveness of Rituximab in patients with lymphoblastic leukemia during their first year of treatment; it is classified in explanatory form of documents found on the web, for example: thesis, scientific articles from the portal, among others. These supporting documents were collected in recently published scientific health journals within the last 5 years. According to the updated information, the subject can be studied more easily, in this way the research will be manifested towards the public area where the effectiveness of the use of Rituximab in patients with lymphoblastic leukemia can be observed and what the infections obtained during the first year of treatment consist of.

The information obtained from the different scientific articles and with the topic to be discussed "Effectiveness of Rituximab in patients with lymphoblastic leukemia and its relationship with the number of infections obtained during their first year of treatment" could be evidenced which are the concepts that predominate the most and are generalized with the topic according to the objectives raised, scientific journals such as "Elsevier" "ScienceDirect" and UpToDate were used, which is a medical resource software system at the point of care, the UpToDate system is an evidence-based clinical resource. Nowadays, technology helps us treat different types of diseases and carry out an adequate treatment to achieve good results in patients.

Results and discussion

Acute lymphoblastic leukemia is the most common oncological disorder in childhood. It is leukemia, which is characterized by a bone marrow condition that produces excessive immature cells, which are called blasts. These leukemias have a wide variety of characteristics that allow them to be classified in different ways. Depending on their cell type, they can be lymphoblastic or myeloblastic. In this case, lymphoblastic leukemias are those that appear from lymphoid cells, such as B and T lymphocytes respectively.(4).

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There are factors that make the presence of acute lymphoblastic anemia favorable or unfavorable, the effectiveness of the treatment and the mortality of the patients depend on them. See table 1. Broadly speaking, the treatments consist of 3 phases, induction, consolidation and maintenance. However, in recent years certain changes have been made in the treatment of ALL, mainly rooted in immunotherapy and which has shown good results in patients with relapse, these being currently investigated as useful in the first line of attack such as(5,6):

- Monoclonal antibodies (Rituximab, Ozogamicin, Blinatumomab).
- Modifications of T lymphocytes that attack leukemic cells.

Rituximab is a monoclonal antibody directed to the CD20 antigen, the dose and route of administration of which varies depending on the treatment for each patient. More than 50% of the first infusions with rituximab are accompanied by a reaction to its infusion, some of the side effects being headache, fever, chills, rash, dyspnea, mild hypotension, nausea, angioedema and asthenia. These symptoms are usually more common within 30 to 120 minutes after exposure and usually resolve once the infusion is stopped.(5).

Mark Ballow Mentions that biological products can have undesirable effects on the immune system that compromise its defenses and cause infections, development of autoimmune diseases or malignancies. To manage these immunodeficiencies induced by drugs such as rituximab, prophylactic antibiotics, antivirals or immunoglobulin in cases of hypogammaglobulinemia are included. With any biological agent there is a significant probability of infection, the degree of infection depends mainly on the actions of the drug to be used, its dose and the duration of treatment.(7).

Board1 Prognostic factors of acute lymphoblastic leukemia

Feature	Favorable	Unfavorable
Age (years)	Child 1-9 Adult 15-30	Children <1 or >9 Adult >30
Leukocytes (x100,000)	<50 >30 (adult LAL type B)	>50 (childhood ALL type B) >100 (T-type LAL)
Phenotype		Pro T and Pro B
Cytogenetics	Hyperdiploidy >50 chrom t (12.21) (TEL-AML1)	Hyperdiploidy >44 chrom t (4:11) (MLL.AF4) t (9.22) (BCR. SBL)
CNS infiltration	No	Yeah
Response to treatment	Rapid (blast <5-10%)	Slow (blast>10%)

Table 1 Prognostic factors for acute lymphoblastic leukemia (continued)

Feature	Favorable	Unfavorable
Residual disease	Rapid and sustained decline.	Slow decrease or persistence. Positive after induction or later.

Negative after induction or consolidated.

The selection of the initial therapy for lymphocytic leukemia on a series of monoclonal antibodies, among which are those anti-CD20 antibodies such as Rituximab, Rituximab, Rituximab. Mentioned author indicates that these drugs may be related to adverse reactions such as reactivation of the hepatitis B virus, who recommends that all patients should be tested for hepatitis B before starting treatment with any of these drugs. All this under the evidence of reactivation during therapy and for several months after completing therapy. Anti-CD20 monoclonal antibodies target B cells and can cause secondary immunodeficiency, in addition there is a small risk of presenting progressive multifocal leukoencephalopathy with the use of these drugs, presenting subacute neurological deficits, including altered mental status, visual symptoms, ataxia and paralysis(8.9).

Rituximab is said to transfer B cells from the pre-B stage to the pre-plasma stage through antibody-dependent cell-mediated lysis. This drug is primarily used in B-cell malignancies and selected autoimmune disorders, including rheumatoid arthritis, autoimmune cytopenias, autoimmune skin diseases, and some forms of vasculitis. It often disrupts B-cell and T-cell interactions, resulting in impaired cellular immunity and leading to an increased risk of viral reactivation.(8.9).

Rituximab depletes the B cells found in peripheral blood, and it takes six to nine months or even longer for this number of B cells to return to normal. In one study of patients, recovery of B cells occurred in a range of 8 to 44 months. As B cells become depleted, the patient's ability to respond to vaccines is affected, and some degree of transient hypogammaglobulinemia is very common.(7).

The impact of rituximab use in vaccination has evolved over the course of clinical trials, with some studies suggesting that the use of the drug may impair vaccine response to a certain degree, especially in polysaccharide vaccines. Therefore, it is suggested that polysaccharide vaccines and non-live primary vaccines should be administered at least four weeks before starting rituximab therapy in order to maximize responses and improve patient protection during the period of B-cell immunosuppression. In the case of live vaccines such as measles or varicella zoster, there is currently no safety data available, so it is advised not to apply them before or during treatment, but up to six months after the treatment has finished.(10).

The impact of vaccines with rituximab therapy was evaluated in a study of 75 patients receiving treatment for one month and then evaluating the results after twelve months, concluding the following from this study:(10):

- Pre-existing immunity to standard vaccines was not affected by treatment, emphasizing that no vaccines were administered during the study.

- Most patients responded to vaccines administered twelve months after rituximab therapy, giving the patient an additional protective titer thanks to vaccines such as tetanus and hepatitis A.

Rituximab does not decrease substantial levels of preexisting antibodies in most patients because plasma cells that do not express CD20 on their surface produce antigen-specific IgG. However, some patients develop hypogammaglobulinemia, which may be persistent and clinically significant, leading to infection. Serious antibiotic prophylaxis or immunoglobulin replacement therapy is required to prevent infection. The incidence of new hypogammaglobulinemia after rituximab treatment is unknown, in part because in many specialties in which rituximab is widely used, pretreatment serum immunoglobulins have not yet become standard.(10).

In a study of 179 patients with B-cell lymphoma with normal baseline serum IgG levels, 39% of patients developed hypogammaglobulinemia. Recurrent pulmonary infections occurred in 6.6%. About 7% of patients required immunoglobulin replacement therapy to control infections.(11).

In a retrospective investigation of 114 patients who had received rituximab for any disease over a one-year period in four London hospitals, 24% developed hypogammaglobulinemia. Nineteen patients were subsequently evaluated for persistent, symptomatic hypogammaglobulinemia in the absence of neutropenia. In nearly two-thirds of this subgroup, IgG, IgA, and IgM decreased. Specific antibodies against Haemiphilus influenza type b, tetanus toxoid, and pneumococcus decreased, and patients did not develop an antibody response after vaccination. The majority experienced recurrent bronchitis, rhinosinusitis, and pneumonia, but three patients had enterovirus meningoencephalitis with fatalities. Although most were initially treated with prophylactic antibiotics, approximately 18 percent required immunoglobulin replacement therapy.(11).

Additional issues related to cases of rituximab-induced hypogammaglobulinemia were investigated in a large cohort study involving nearly 5000 patients. Rituximab was administered to treat malignancies, autoimmune or hematologic disorders, or autoimmune conditions in patients with primary immunodeficiency. In the entire group, approximately 30% developed a serious infection requiring hospitalization within 18 months of the first treatment with rituximab, most within the first 6 months. Pretreatment IgG levels were measured in only 15%, almost half of whom had a history of hypogammaglobulinemia suggesting that this finding is not uncommon. In this subgroup, immunoglobulin levels generally continued to decline during treatment, and the incidence of serious infections remained high after rituximab was stopped. This high-risk group appeared to benefit from immunoglobulin replacement therapy.(7).

Finally, Mark Ballow's study mentions that IgG levels before treatment with rituximab and persistent hypogammaglobulinemia after treatment were associated with serious infections in another study of patients with autoimmune disease. This has been resolved in a consensus statement recommending that patients who need to receive treatment with rituximab should have their IgG levels measured before treatment and before adding Rituximab.(7).

Speaking of specific infections, Mark Ballow indicates that when rituximab causes hypogammaglobulinemia, pulmonary infections are the most common manifestation. However, rituximab therapy has been associated with severe cytomegalovirus infections associated with progressive multifocal leukoencephalopathy, reactivation of latent hepatitis B infection, and hypogammaglobulinemia associated with severe and fatal infections. This may be the result of impaired antigen presentation, decreased B cell uptake by T cells, and impaired interaction with other immune effector cells.(7).

According to Kanti Rai, patients with lymphocytic leukemia present abnormal cell-mediated immune responses due to quantitative and qualitative effects on immune effector cells, which may be due to the underlying disease process or the therapy used for treatment. This is consistent with research mentioning that there are reactions in patients treated with rituximab that make them more susceptible to infection. This author argues that the spectrum of infections in these patients has changed in recent decades with the introduction of new treatments that have a specific action on immune function, especially cell-mediated immunity.(8.9)

On the other hand, Vicki A Morrison highlights that untreated patients have a higher risk of bacterial infections caused by common pathogens, such as staphylococcus aureus, streptococcus pneumoniae, haemophilus influenza, escherichia coli, klebsiella pneumonia and even pseudomona aeruginosa. Recurrent bacterial infections of mucosal or respiratory origin are the most common. However, when using rituximab, grade 3 or 4 infections and opportunistic infections are uncommon when receiving anti-CD20 therapy, but hepatitis B reactivation and multifocal leukoencephalopathy are complications that appear or reappear in a higher percentage when using this drug, especially in patients positive for the hepatitis B surface antigen.(12,13).

Infections play a major role in the clinical course of patients with lymphocytic leukemia, since they have inherent immune defects in humoral and cell-mediated immunity that are related to the primary disease process, including hypogammaglobulinemia, T-cell abnormalities, and defects in complement activity. In cases of specific therapies that cause immune defects with subsequent infectious complications, prophylaxis is recommended, which varies depending on the type of therapy used.(12,13).

The use of vaccines is very important for patients with lymphocytic leukemia, but we must remember that they should not be administered during periods of immunosuppression caused by immunotherapy because, at those times, they may not be effective and live vaccines can cause infections derived from the vaccine itself.(11). See Chart 2

Finally, in a study on low doses of rituximab in children, Julia Esther carried out a retrospective investigation analyzing 78 patients, diagnosed with CD-20 B-cell acute lymphoblastic leukemia who agreed to participate in the protocol, highlighting the use of rituximab in the remission induction phase on day 8 and on day 22 at a dose of 100 mg of rituximab. During the intensification phase, rituximab was applied again on days 8 and 22 of the protocol again at a dose of 100 mg. Some of them presented adverse effects such as rash, chills and fever.(11). See Table 2.

Board2 Antimicrobial prophylaxis recommended according to the CLL treatment regimen

Regime	Antibacterial	Antifungal
Alkylating agents (e.g. chloracrylamide)	No	No
Bendamustine	No	No
Monotherapy with purine analogs (e.g., fludarabine)	No	No
Purine analog: anti-CD20 monoclonal antibody	No	No
Chlorambucyte – monotional anti-CD20 antibody	No	No

Table 2 Antimicrobial prophylaxis recommended according to the CLL treatment regimen (continued)

Regime	Antibacterial	Antifungal
Purine analogue - cycloflostamide	No*	No
Purine analogue - cycloflostamide - monoclonal antibody anti-CD20	No*	No
Monotional anti-CD20 antibody (e.g., Rituximab, ofatumamab, obnutuzumb)	No	No
Alemtuzumab	No*	Without
Lenalidomide	No	No
Ibrutinib, acalabrutinib	No	No
Idelasibid, duvelisib	No	No
Venetoclax	No	No

As a result of the study, it is concluded that including reduced doses of rituximab in the chemotherapy regimen in children suffering from acute lymphoblastic leukemia does not demonstrate improvements in the response rate, nor in the overall survival rate. Despite not being a study with a large number of patients, the data obtained support the

administration of full doses of rituximab in neoplastic diseases, taking into account the side effects such as the risk of contracting infections.(2)

Conclusion

- Generally speaking, biological therapies that suppress the immune system have a high potential to cause serious side effects, such as an increased risk of infections or the development of malignant or even autoimmune diseases. Of course, this depends on the specific agent used, its dose and duration, as well as patient-specific factors such as the underlying disease, functional status and medical frailty.
- Rituximab, as we have argued in this research, is a monoclonal antibody that acts against B cells and decreases their presence in peripheral blood over a period of months. When possible, vaccines should be administered before rituximab therapy because it can cause hypogammaglobulinemia, which would represent an increased risk of infections.
- In cases where there are patients with recurrent infections after rituximab therapy, antibiotic prophylaxis or even immunoglobulin replacement is suggested.

Conflict of interest

The authors declare that they have no conflicts of interest that could compromise, in whole or in part, the results of this work or its publication.

Authors' contribution statement

JLI and KGP conceived the research idea, defined the problem and conducted an initial information search.

MAVL and KALR conducted the non-systematic search to construct the article database and designed the first draft under the supervision of JLI and KGP.

KGP supervised the development of the second draft by AIQS and MAVL.

KALR applied corrections to the second and third drafts.

JLI and KGP approved the final manuscript.

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