LUMEN ET VIRTUS

Targeted therapies and immunotherapy in the treatment of pediatric Hodgkin Lymphoma: A literature review on advances and challenges

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ABSTRACT

Introduction: Hodgkin's lymphoma is a relatively rare lymphoproliferative neoplasm in children, but common among adolescents and young adults, representing about 6% of pediatric cancer cases in Brazil. Standard treatment with chemotherapy and radiotherapy has a high cure rate, but is associated with significant long-term adverse effects. In recent years, targeted therapies and immunotherapies, such as monoclonal antibodies and immune checkpoint inhibitors, have shown promise for refractory or relapsed pediatric patients. Methodology: The integrative review included studies published between 2020 and 2024, selected from databases such as PubMed, SciELO, and LILACS, using terms such as "pediatric Hodgkin lymphoma" and "immunotherapy". Original studies, systematic reviews, and case reports addressing the use of targeted therapies and immunotherapies in pediatric patients were considered, excluding publications prior to 2020, articles without full text, and non-relevant studies. Results: Targeted therapies, such as brentuximab vedotin, and immunotherapies,

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including the use of CAR-T cells, have been shown to be effective in the treatment of pediatric Hodgkin lymphoma, with reduced toxicity and a higher response rate in refractory cases. The studies highlight the importance of personalization of treatment, long-term monitoring, and equitable access to innovative therapies, especially in developing countries like Brazil. Conclusions: Targeted therapies and immunotherapies represent significant advances in the treatment of pediatric Hodgkin lymphoma, but their implementation faces challenges related to cost, accessibility, and the need for further studies on long-term effects. A coordinated effort is essential to ensure equitable access and safe use of these therapies.

Keywords: Pediatric Hodgkin Lymphoma, Targeted Therapies, Immunotherapy, CAR-T Cells, Immune Checkpoint Inhibitors.

INTRODUCTION

Hodgkin's lymphoma is a lymphoproliferative neoplasm characterized by the presence of Reed-Sternberg cells in a background of reactive inflammatory infiltrate. Although this condition is relatively rare in the pediatric population, it represents one of the most common solid tumors in adolescents and young adults, accounting for about 6% of pediatric cancer cases in Brazil (Souza et al., 2021). Standard treatment for Hodgkin lymphoma includes chemotherapy and radiation therapy, which have a high cure rate but are associated with significant long-term adverse effects, such as cardiovascular and pulmonary toxicity, and an increased risk of second malignancies (Gonçalves et al., 2023).

In recent years, there has been significant advancement in targeted therapies and immunotherapies, which have shown promise in the treatment of Hodgkin's lymphoma, especially in refractory or relapsed pediatric patients. Targeted therapies include drugs that directly target malignant cells or specific components of the tumor microenvironment, reducing damage to healthy tissues and decreasing side effects (Oliveira et al., 2022). Among targeted therapies, the use of monoclonal antibodies, such as brentuximab vedotin, which binds to CD30 in Reed-Sternberg cells, has demonstrated significant efficacy, especially in refractory cases (Ferreira et al., 2023).

Immunotherapy, which takes advantage of the patient's own immune system to fight cancer, has also gained prominence as an innovative therapeutic approach. Immune checkpoint inhibitors, such as nivolumab and pembrolizumab, which block PD-1, a protein that inhibits the antitumor immune response, have shown promising results in the management of pediatric Hodgkin lymphoma (Machado et al., 2021). In addition, the use of CAR-T cells, where the patient's T cells are genetically modified to recognize and destroy tumor cells, represents a new frontier in pediatric cancer treatment (Lima et al., 2024).

In Brazil, the development and application of innovative therapies for Hodgkin's lymphoma in pediatrics face unique challenges. Recent national studies have explored the genetic specificities of the Brazilian population, which may influence the response to treatment and the incidence of adverse effects (Martins et al., 2023). In addition, socioeconomic factors and unequal access to new therapies constitute additional barriers to the widespread implementation of these approaches in the country (Silva et al., 2022).

Despite advances in treatment, there is a growing need for data evaluating the long-term safety and efficacy of these new therapies in the pediatric population. Recent clinical trials have provided promising early evidence, but studies with longer duration and more robust samples are essential to determine the long-term impact on patients' quality of life and survival (Almeida et al., 2021). In addition, the introduction of combination therapies, involving chemotherapy with targeted

therapies or immunotherapy, is being investigated to optimize therapeutic outcomes and minimize toxicity (Ribeiro et al., 2023).

In the global context, immunotherapy and targeted therapies represent an evolution in the management of pediatric Hodgkin lymphoma, offering new treatment possibilities for patients who do not respond to conventional protocols. However, integrating these approaches into clinical practice requires careful considerations of cost, access, and long-term safety monitoring, especially in developing countries such as Brazil (Fernandes et al., 2024).

This article critically reviews the recent literature on the use of targeted therapies and immunotherapies in the treatment of Hodgkin's lymphoma in children, highlighting scientific advances, prospects for clinical use, and knowledge gaps that still need to be addressed. The relevance of this topic lies in the search for more effective and less toxic treatments, which provide better quality of life for pediatric patients (Costa et al., 2022).

Given the current scenario, the incorporation of new therapies in the treatment of pediatric Hodgkin lymphoma represents a significant hope for improving clinical outcomes. However, it is imperative that research efforts remain focused on exploring the best therapeutic combinations, identifying biomarkers of response, and ensuring equity in access to innovative treatments (Pereira et al., 2023).

METHODOLOGY

This integrative literature review was conducted following the methodological criteria for integrative reviews, including experimental and non-experimental studies. The methodological process was composed of several stages: definition of the theme, determination of the inclusion and exclusion criteria, construction of an instrument for collecting relevant data from the selected articles, critical evaluation of the articles, and finalization with the interpretation and discussion of the results found.

The research was carried out based on the selection of articles published between 2020 and 2024 in Portuguese and English, which met the previously established inclusion criteria. Data sources were identified in the electronic databases PubMed, SciELO, and LILACS, using terms such as "pediatric Hodgkin's lymphoma", "targeted therapies", "immunotherapy", "monoclonal antibodies", "immune checkpoint inhibitors", and "CAR-T cells". The search also included systematic review articles, case reports, clinical guidelines, and cohort studies. The inclusion criteria included original studies addressing the use of targeted therapies and immunotherapies in the treatment of Hodgkin's lymphoma in pediatric patients, focusing on clinical outcomes, efficacy, safety, and quality of life. Studies published only in abstract format, articles without full text available, and publications prior to 2020 were excluded from this review.

Article selection followed a rigorous process, in which two independent reviewers initially evaluated titles and abstracts to identify relevant studies. The articles that passed the initial screening were analyzed in full text to confirm their eligibility, resulting in a final sample of fifteen scientific articles. The data were extracted and organized in a summary table, containing information on title, author, year of publication, study objective, methodology used, main results and conclusions. This process sought to ensure the inclusion of predominantly Brazilian sources, representing at least 70% of the selected sample.

The methodological quality of the included studies was assessed using specific criteria for different types of studies, such as the Newcastle-Ottawa scale for cohort and case-control studies, and the PRISMA for systematic reviews. Data analysis followed a descriptive approach, highlighting the main trends and results found in the recent literature on the use of targeted therapies and immunotherapies in pediatric Hodgkin lymphoma.

RESULTS AND DISCUSSION

The analysis of the articles selected for this integrative review evidenced the significant impact of targeted therapies and immunotherapies in the treatment of pediatric Hodgkin lymphoma, especially in patients with refractory or relapsed disease. Recent Brazilian studies have shown that the use of monoclonal antibodies, such as brentuximab vedotin, has provided promising response rates, with a reduction in toxicity compared to conventional treatments. This therapy, by binding to the CD30 antigen present in tumor cells, allows a more selective destruction of malignant cells, minimizing damage to adjacent healthy tissues (Ferreira et al., 2023).

In addition to brentuximab vedotin, immune checkpoint inhibitors such as nivolumab and pembrolizumab have emerged as effective therapeutic options, particularly in cases where Hodgkin lymphoma shows resistance to standard chemotherapy regimens. These inhibitors work by blocking the interaction between PD-1 and PD-L1, proteins that normally suppress the immune response, allowing immune system T cells to attack tumor cells more effectively. Studies conducted in Brazil indicate that combining these inhibitors with other therapeutic modalities can further improve outcomes in pediatric patients (Silva et al., 2022).

CAR-T cell immunotherapy has also been evaluated in the recent literature as an innovative strategy in the management of pediatric Hodgkin lymphoma. This approach involves genetically modifying the patient's own T cells so that they recognize and destroy the malignant cells. Although it is still in the clinical study phase and its large-scale application faces logistical and financial challenges, preliminary results suggest a high rate of complete remission in refractory cases, which represents a significant advance in the treatment of complex pediatric lymphomas (Lima et al., 2024).

The Brazilian studies included in this review highlight the importance of personalizing treatment, taking into account the individual characteristics of each patient, such as genetic profile and immune response to the tumor. This is particularly relevant in the context of Brazil, where the genetic diversity of the population can influence the efficacy of targeted therapies and immunotherapies. Therapeutic personalization aims not only to increase cure rates but also to reduce long-term adverse effects, which are a constant concern in pediatric cancer treatment (Martins et al., 2023).

An important aspect discussed in the literature is the need for continuous monitoring of patients treated with these new therapies, since the long-term effects are not yet fully understood. Checkpoint inhibitors, for example, although effective, are associated with an increased risk of developing immune toxicities, which can affect several organs and systems. Therefore, it is essential that medical teams are prepared to identify and manage these complications, ensuring the safety and well-being of patients throughout the treatment (Machado et al., 2021).

The accessibility and cost of innovative therapies were also recurring themes in the studies analyzed. Despite significant advances, the high cost of targeted therapies and immunotherapies limits access for many patients, especially in developing countries such as Brazil. This raises the need for public policies that promote the inclusion of these therapies in the health system and ensure that all pediatric patients have access to cutting-edge treatments, regardless of their socioeconomic status (Ribeiro et al., 2023).

The combination of therapies, both between different immunotherapies and between immunotherapy and conventional chemotherapy, has shown promise in several studies, pointing to a possible path in optimizing the treatment of pediatric Hodgkin lymphoma. The combined approach seeks to maximize therapeutic efficacy while simultaneously reducing the required dose of chemotherapy drugs, which could lead to a decrease in long-term side effects (Oliveira et al., 2022).

In conclusion, targeted therapies and immunotherapies represent a significant evolution in the treatment of pediatric Hodgkin lymphoma, offering new hope for patients who previously had few therapeutic options. However, the implementation of these therapies in clinical practice still faces significant challenges, including the need for more long-term studies, the development of strategies for the management of toxicities, and the Thus, as these new therapeutic approaches continue to evolve, it is crucial that research efforts and public health policies work together to maximize benefits for all patients (Fernandes et al., 2024).

CONCLUSION

The literature review on the use of targeted therapies and immunotherapies in the treatment of pediatric Hodgkin lymphoma reveals significant advances in pediatric oncology, especially for

patients with refractory or relapsed disease. The introduction of targeted agents, such as monoclonal antibodies (e.g., brentuximab vedotin) and immune checkpoint inhibitors (such as nivolumab and pembrolizumab), has offered new therapeutic perspectives, enabling a more selective and effective treatment, reducing the toxicity associated with conventional approaches. These drugs emerge as viable and effective options, particularly in cases that do not respond to standard chemotherapy protocols, expanding the possibilities of cure with lower morbidity (Ferreira et al., 2023; Silva et al., 2022).

Immunotherapy, especially through the use of CAR-T cells, represents a significant advance, although it still faces challenges in terms of costs, application logistics, and monitoring of long-term adverse effects. Recent studies suggest a high positive response rate, including complete remission in complex cases, which emphasizes the transformative potential of this approach in the treatment of pediatric lymphomas (Lima et al., 2024). However, it is crucial that the use of these therapies be accompanied by rigorous monitoring and complication management strategies, given the risk of severe immune toxicities, as seen in immune checkpoint inhibitors (Machado et al., 2021).

Despite promising advances, widespread implementation of these new therapies faces significant obstacles, especially in resource-limited settings such as Brazil. The accessibility and high cost of innovative therapies represent barriers that require urgent attention from public health policies. The inclusion of these therapies in the Brazilian health system and the promotion of their equitable access to all pediatric patients should be a priority to ensure that the benefits of these advances are widely shared (Ribeiro et al., 2023).

In conclusion, targeted therapies and immunotherapies are redefining the landscape of pediatric Hodgkin lymphoma treatment, providing new opportunities for cure with fewer adverse effects. However, maximizing the benefits of these therapies requires a coordinated effort among researchers, healthcare professionals, and policymakers to overcome the challenges associated with their implementation. Additional long-term studies, the development of therapeutic combination strategies, and ensuring equitable access to treatments emerge as priority areas for the continuation of the positive evolution in the therapeutic approach to this disease (Fernandes et al., 2024).

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