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MANAGEMENT OF PEDIATRIC LEUKEMIA: INDUCTION, CONSOLIDATION, AND MAINTENANCE PHASES

MANEJO DA LEUCEMIA PEDIÁTRICA: FASES DE INDUÇÃO, CONSOLIDAÇÃO E MANUTENÇÃO

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ABSTRACT

Acute leukemias represent the most prevalent neoplasm in childhood, with Acute Lymphoblastic Leukemia (ALL) accounting for the majority of cases. Contemporary treatment is structured into risk-stratified protocols and organized into sequential phases: remission induction, consolidation, and maintenance. Induction aims to eradicate most of the leukemic burden to achieve complete remission (CR), while consolidation focuses on eliminating Minimal Residual Disease (MRD), which is the main prognostic predictor. Maintenance, which is long-term, aims to prevent late relapse through low-intensity chemotherapy. Recent advances have enabled the progressive integration of targeted and immunological therapies (such as blinatumomab, daratumumab, and BCL-2 and menin inhibitors) into traditional regimens, contributing to increased cure rates and improved long-term prognosis. Current management requires the integration of structured protocols with precise biological stratification and continuous multidisciplinary support, aiming to maximize cure and reduce toxicity for the child.

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Keywords: Pediatric Leukemia. Induction. Consolidation. Maintenance. Minimal Residual Disease (MRD). Immunotherapy.

RESUMO
As leucemias agudas representam a neoplasia mais prevalente na infância, sendo a Leucemia Linfoblástica Aguda (LLA) responsável pela maioria dos casos. O tratamento contemporâneo é estruturado em protocolos de estratificação de risco e se organiza em fases sequenciais: indução da remissão, consolidação e manutenção. A indução tem como objetivo a erradicação da maior parte da carga leucêmica para alcançar a remissão completa (RC), enquanto a consolidação foca na eliminação da Doença Residual Mínima (MRD), que é o principal preditor prognóstico. A manutenção, de longa duração, visa prevenir a recidiva tardia através de quimioterapia de baixa intensidade. Avanços recentes têm permitido a integração progressiva de terapias direcionadas e imunológicas (como blinatumomab, daratumumab, e inibidores de BCL-2 e menina) aos esquemas tradicionais, o que tem contribuído para o aumento das taxas de cura e para a melhoria do prognóstico a longo prazo. O manejo atual exige a integração de protocolos estruturados com a estratificação biológica precisa e o suporte multiprofissional contínuo, buscando maximizar a cura e reduzir a toxicidade para a criança.

Palavras-chave: Leucemia Pediátrica. Indução. Consolidação. Manutenção. Doença Residual Mínima (MRD). Imunoterapia.

RESUMEN
Las leucemias agudas representan la neoplasia más prevalente en la infancia, siendo la Leucemia Linfoblástica Aguda (LLA) responsable de la mayoría de los casos. El tratamiento contemporáneo se estructura en protocolos de estratificación de riesgo y se organiza en fases secuenciales: inducción de la remisión, consolidación y mantenimiento. La inducción tiene como objetivo erradicar la mayor parte de la carga leucémica para alcanzar la remisión completa (RC), mientras que la consolidación se centra en la eliminación de la Enfermedad Residual Mínima (MRD), que es el principal predictor pronóstico. El mantenimiento, de larga duración, tiene como objetivo prevenir la recaída tardía mediante quimioterapia de baja intensidad. Los avances recientes han permitido la integración progresiva de terapias dirigidas e inmunológicas (como blinatumomab, daratumumab, e inhibidores de BCL-2 y menina) en los esquemas tradicionales, lo que ha contribuido al aumento de las tasas de curación y a la mejora del pronóstico a largo plazo. El manejo actual requiere la integración de protocolos estructurados con una estratificación biológica precisa y un soporte multidisciplinario continuo, con el objetivo de maximizar la curación y reducir la toxicidad en el niño.

Palabras clave: Leucemia Pediátrica. Inducción. Consolidación. Mantenimiento. Enfermedad Residual Mínima (MRD). Inmunoterapia.

1 INTRODUCTION

Acute leukemia represents the most prevalent neoplasm in childhood, with Acute Lymphoblastic Leukemia (ALL) accounting for most cases, followed by Acute Myeloid Leukemia (AML) (Rubnitz and Kaspers, 2021; Kulczycka et al., 2024). These hematological neoplasms are characterized by clonal proliferation of immature hematopoietic precursors in the bone marrow, leading to the replacement of normal hematopoiesis and systemic impairment resulting from cytopenias and leukemic infiltration in different organs and tissues (KULCZYCKA et al., 2024). Contemporary treatment is grounded in highly refined risk stratification protocols, which aim to maximize the cure rate and minimize long-term toxicities (Gupta et al., 2025; Summers et al., 2023). These protocols incorporate clinical, immunophenotypic, cytogenetic, and molecular factors, in addition to the initial response to treatment, allowing a progressively more individualized therapeutic approach adapted to each patient's risk of relapse (SUMMERS; TEACHEY; HUNGER, 2023; RUBNITZ; KASPERS, 2021).

The classic therapeutic structure is organized into sequential phases: induction of remission, consolidation (or intensification), and maintenance, each with specific biological objectives (Teachey et al., 2022; Gupta et al., 2025). The induction phase aims to eradicate most of the leukemic load and restore normal hematopoiesis, while consolidation focuses on the elimination of minimal residual disease (MRD), a factor that has been consolidated as the main prognostic predictor in pediatric management (Summers et al., 2023; Teachey et al., 2022). The longer maintenance phase aims to prevent late recurrence through low-intensity chemotherapy (Gupta et al., 2025).

In recent decades, significant advances in the understanding of the molecular biology of pediatric leukemia have enabled the development of more targeted therapeutic approaches, especially in higher-risk subtypes or in contexts of relapsed or refractory disease (KULCZYCKA et al., 2024). Among these strategies, immunological therapies based on monoclonal antibodies and target-molecular agents that act on specific pathways of leukemogenesis stand out, expanding the therapeutic possibilities for pediatric patients with different biological profiles (GUPTA et al., 2025). The incorporation of immunotherapies such as blinatumomab and targeted therapies such as girl inhibitors and BCL-2 have transformed the scenario for high-risk subtypes and relapsing cases (Gupta et al., 2025; Rubnitz and Kaspers, 2021; Kulczycka et al., 2024). In addition, new immunotherapeutic approaches continue to be investigated in relapse or refractoriness

scenarios, such as the use of the anti-CD38 monoclonal antibody daratumumab, evaluated in the DELPHINUS study in pediatric patients with acute lymphoblastic leukemia or relapsed or refractory lymphoblastic lymphoma (BHATLA et al., 2024).

Even in the face of these therapeutic innovations, contemporary treatment protocols continue to be organized based on the classic phases of induction, consolidation, and maintenance, which remain the structural basis of pediatric leukemia management. Recent evidence indicates that the response obtained during induction and the evaluation of minimal residual disease throughout consolidation play a decisive role in defining the risk of relapse and in the adequacy of therapeutic intensity in current protocols (SUMMERS; TEACHEY; HUNGER, 2023; TEACHEY et al., 2022). In addition, emerging therapeutic strategies have been progressively incorporated or investigated within these stages of treatment, highlighting the importance of understanding how each phase contributes to the clinical outcomes observed in the contemporary management of pediatric leukemia (GUPTA et al., 2025; BHATLA et al., 2024). In this context, international clinical trials have played a crucial role in validating both modifications to classical protocols and the introduction of innovative agents. Studies such as AALL1231, which evaluated bortezomib in ALL/T Lymphoma, have demonstrated the feasibility of reducing the prophylactic use of cranial radiotherapy without compromising overall survival (TEACHEY et al., 2022). Similarly, DELPHINUS investigated the monoclonal antibody daratumumab in pediatric patients with ALL or relapsed lymphoblastic lymphoma, evidencing relevant response rates and viability as a bridge to allogeneic transplantation (BHATLA et al., 2024). These results reinforce that the future of the treatment of acute leukemia in childhood depends on the integration of conventional chemotherapy, immunotherapy, and targeted therapies, in protocols adapted to the biological and clinical risk of each patient.

In view of this scenario, the contemporary management of pediatric leukemia involves not only the application of traditional chemotherapy regimens organized into well-defined therapeutic phases, but also the progressive integration of targeted and immunological therapies, which has contributed to increased cure rates and improved long-term prognosis (GUPTA et al., 2025; RUBNITZ; KASPERS, 2021). In this context, understanding the characteristics and objectives of the induction, consolidation, and maintenance phases becomes essential for optimizing treatment and developing increasingly effective therapeutic strategies.

2 METHODOLOGY

The present study is characterized as a narrative literature review, developed with the objective of synthesizing and analyzing the most recent scientific evidence related to the Management of Pediatric Leukemia: Induction, Consolidation and Maintenance Phases. The search was carried out in the PubMed database, using the descriptors "Leukemia", "Child", "Treatment" and "Diagnosis", combined using the Boolean operators AND and OR, according to the Medical Subject Headings (MeSH) terminology. Articles published in the last five years, available in full and written in Portuguese or English, that directly addressed the topic, were included. Studies that did not have a direct relationship with the central theme, duplicate publications, narrative reviews with low methodological rigor, and articles not indexed in the database used were excluded. The selection of studies was conducted in two stages: screening of titles and abstracts, followed by the evaluation of full texts to confirm relevance. The information extracted was organized in a descriptive way.

3 RESULTS AND DISCUSSION

3.1 INDUCTION OF REMISSION AND RISK STRATIFICATION

The primary goal of induction is to achieve complete remission (CR), defined by the absence of morphological blasts in peripheral blood and less than 5% in bone marrow. In T-cell ALL, the addition of bortezomib to the intensive chemotherapy regimen (protocol AALL1231) has been shown to be safe and effective, improving event-free survival in patients with lymphoblastic lymphoma, although without overall statistical benefit for all cases of T-ALL (Teachey et al., 2022). In AML, induction is significantly more intensive and often associated with severe toxicities, requiring close clinical support (Rubnitz and Kaspers, 2021). The response to induction, measured by the MRD at the end of this phase, dictates the intensity of subsequent steps (Summers et al., 2023).

Minimal residual disease (MRD) assessment currently represents one of the main prognostic markers in the management of pediatric leukemia. Highly sensitive techniques, such as multiparametric flow cytometry and molecular methods based on PCR or next-generation sequencing, make it possible to detect extremely low levels of persistent leukemia cells after the induction phase. Negative MRD has been associated with longer event-free survival and lower risk of relapse, whereas persistence of residual disease indicates the need for therapeutic intensification or early consideration of

hematopoietic stem cell transplantation in certain risk subgroups (SUMMERS; TEACHEY; HUNGER, 2023; RUBNITZ; KASPERS, 2021).

3.2 CONSOLIDATION AND THE ROLE OF IMMUNOTHERAPY

The consolidation phase uses different combinations of chemotherapy drugs to eradicate persistent leukemia cells. For standard-risk B-lineage ALL, the introduction of blinatumomab—a bispecific T-cell activating antibody (BiTE)—during consolidation resulted in superior event-free survival (91.1%) compared with conventional chemotherapy (Gupta et al., 2025). In addition to improving efficacy, blinatumomab had a favorable safety profile, with a lower incidence of serious infections and mucositis (Gupta et al., 2025). In cases of ALL with rearrangements in the KMT2A gene (common in infants), new therapeutic opportunities with girl inhibitors are being explored to overcome resistance to conventional chemotherapy (Kulczycka et al., 2024).

Aiming beyond the use of bispecifics, different immunotherapeutic strategies have been investigated in the treatment of acute lymphoblastic leukemia. Among them, we can highlight the approach of therapy with CAR-T cells directed at the CD19 antigen. Based on the genetic modification of the patient's own T lymphocytes, where it aims at the recognition and destruction of leukemia cells. Recent studies have pointed out that this strategy has been able to promote deep readmissions, including minimal residual disease negative, especially in patients with relapsed or refractory disease (KULCZYCKA et al., 2024). However, despite the great promising results, there are still challenges related to clinical application, such as the occurrence of immunological toxicities and also the possibility of relapse associated with the loss of the target antigen by leukemia cells (SUMMERS et al., 2025). In view of the above, immunotherapy has been consolidating itself as a complementary tool to more conventional therapeutic regimens, contributing to the expansion of treatment actions and improving the prognosis of patients with ALL. Despite the advances promoted by immunotherapies, the consolidation phase continues to play a central role in the eradication of minimal residual disease and the prevention of early relapses. Contemporary protocols have sought to integrate immunological agents and targeted therapies into traditional chemotherapy regimens, with the aim of increasing therapeutic efficacy without significantly increasing toxicity. In this context, the adaptation of therapeutic intensity based on the patient's individual biological response has become a fundamental strategy, allowing greater personalization of treatment and better clinical

outcomes in pediatric patients with acute leukemia (GUPTA et al., 2025; KULCZYCKA et al., 2024; RUBNITZ; KASPERS, 2021).

The phase II DELPHINUS clinical study investigated the use of the anti-CD38 monoclonal antibody daratumumab in addition to chemotherapy in children and young adults with acute lymphoblastic leukemia or lymphoblastic lymphoma in a setting of relapse or refractoriness. The results showed slightly higher overall response rates of 80% among patients with T-lineage ALL. In addition, a relevant proportion of the participants could be referred for allogeneic hematopoietic stem cell transplantation, suggesting that daratumumab can act as an effective therapeutic rescue strategy and as a bridge to transplantation in this group of patients (Bhatla et al., 2022).

In addition to the approaches in the B lineage, the optimization of the consolidation phase in T lineage Acute Lymphoblastic Leukemia (T-ALL) has advanced with the incorporation of targeted therapies. In the phase III clinical study AALL1231, the addition of the proteasome inhibitor bortezomib to the intensive chemotherapy regimen was shown to be a safe and effective strategy, resulting in a significant improvement in event-free survival, especially in patients with T-lymphoblastic lymphoma (Teachey et al., 2022). In scenarios of relapsed or refractory disease, the anti-CD38 monoclonal antibody, daratumumab, revealed robust results in the DELPHINUS study, where its combination with chemotherapy allowed 83.3% of patients to achieve complete response, serving as a key bridge to stem cell transplantation (Bhatla et al., 2022). For the early T-cell precursors subtype (ETP-ALL), which often presents resistance to standard protocols, BCL-2 protein inhibition with venetoclax emerges as a biological alternative to rescue patients with persistent minimal residual disease (Summers et al., 2025; Rubnitz & Kaspers, 2021). In addition, in infants with *KMT2A* rearrangements, epigenetic priming strategies with azacitidine are being evaluated prior to consolidation to sensitize leukemia cells and overcome the intrinsic chemoresistance of this group (Kulczycka et al., 2024).

3.3 MANAGEMENT OF HIGH-RISK SUBTYPES: ETP-ALL AND AML

Early T-cell precursor ALL-IL (ETP-ALL) has historically been associated with a dismal prognosis. However, recent data suggest that contemporary chemotherapy regimens have attenuated this disparity, although the persistence of positive MRD remains a wake-up call for the need for first-remission hematopoietic stem cell transplantation (HSCT) (Summers et al., 2023). In AML, the integration of targeted

therapies, such as venetoclax (BCL-2 inhibitor), has shown promising results, especially when combined with standard chemotherapy, by potentiating blast cell apoptosis (Rubnitz and Kaspers, 2021).

In addition to chemotherapy support, genomic characterization has revealed new therapeutic vulnerabilities in these subtypes. In ETP-ALL, the high expression of CD38 in blasts from pediatric patients paves the way for the use of daratumumab, which in recent studies has been shown to be able to convert cases of positive residual disease into negativity before HSCT (Bhatla et al., 2022). In the field of pediatric AML, the precision medicine approach expands with the use of girl inhibitors for patients who have rearrangements in the *KMT2A gene or* NPM1 *mutations*, aiming to reverse the cell differentiation blockade characteristic of these alterations (Rubnitz & Kaspers, 2021). Additionally, the intensification of treatment for patients with high-risk AML has incorporated the use of hypomethylating agents, such as azacitidine, which acts as an epigenetic sensitizer for subsequent chemotherapy, seeking to overcome mechanisms of intrinsic resistance (Kulczycka et al., 2024). The decision for consolidation with bone marrow transplantation in these patients is now guided more strictly by the kinetic response of the disease, where only those who fail to achieve deep molecular remission after the first few cycles are directed early to cell therapy (Summers et al., 2025).

3.4 MAINTENANCE AND PERSPECTIVES ON RELAPSES

Maintenance is the longest phase, essential to sustain remission in ALL. In cases of recurrence or refractoriness, the use of monoclonal antibodies such as daratumumab (anti-CD38) has been investigated. The DELPHINUS study demonstrated that daratumumab in combination with chemotherapy achieved complete remission rates in about 50% of patients with relapsed T-ALL, allowing many to progress to consolidative HSCT. Many factors contribute to the successful transition to hematopoietic stem cell transplantation (HSCT), in the DELPHINUS study, 75% of children and 60% of young adults with T-cell acute lymphoblastic leukemia (T-ALL) successfully underwent RCRH, with hematopoietic reconstitution rates of 89% and 100%, respectively. (Bhatla et al., 2024). These advances reinforce the transition to precision pediatric oncology, where molecular genetics and immunotherapy complement the skeleton of classical chemotherapy (Kulczycka et al., 2024; Rubnitz and Kaspers, 2021).

4 CONCLUSION

The therapeutic approach to pediatric leukemia has evolved significantly in recent decades, resulting in a significant increase in survival rates and improved quality of life of patients. In this context, treatment structured in sequential phases — induction, consolidation, and maintenance — constitutes the basis of contemporary management, allowing progressive control of tumor burden and reduction of the risk of relapse.

The main objective of the induction phase is to achieve complete remission through intensive chemotherapy regimens, requiring strict surveillance due to the high toxicity and the risk of infectious and metabolic complications. Consolidation acts in the eradication of minimal residual disease, a crucial step to prevent early recurrences, while maintenance promotes prolonged suppression of leukemic clonal proliferation with less cumulative toxicity, favoring hematological recovery and outpatient follow-up.

Therapeutic success depends not only on the appropriate choice of chemotherapy protocols, such as those established by international cooperative groups, such as the Children's Oncology Group and the Brazilian Society of Pediatric Oncology, but also on risk stratification based on clinical, cytogenetic, and molecular criteria. The incorporation of sensitive monitoring methods, such as the assessment of minimal residual disease, has allowed individualized therapeutic adjustments and greater prognostic accuracy.

In addition, adequate management requires continuous multidisciplinary support, including control of adverse effects, prevention of opportunistic infections, transfusion support, nutritional follow-up, and psychosocial care for children and families. Recent strategies, such as molecular targeted therapies and immunotherapy, broaden future perspectives by offering greater therapeutic specificity and potential reduction of systemic toxicities.

Therefore, it is concluded that the management of pediatric leukemia should be understood as a dynamic process, which combines structured chemotherapy protocols with modern tools for biological stratification and response monitoring. More than following traditional stages of induction, consolidation, and maintenance, contemporary treatment requires integration with innovative therapies and continuous multidisciplinary support, ensuring not only a higher cure rate, but also a reduction in toxicities and a better quality of life in the long term.

In addition, recent evidence reinforces that the future of pediatric leukemia treatment will be marked by the integration between traditional chemotherapy protocols

and innovative therapies. Clinical trials such as AALL1231 have shown that the incorporation of bortezomib in ALL/T Lymphoma can improve survival without the need for prophylactic cranial radiotherapy, reducing late effects (TEACHEY et al., 2022). Similarly, the DELPHINUS study evaluated the anti-CD38 monoclonal antibody daratumumab in pediatric patients with ALL or relapsed lymphoblastic lymphoma, evidencing relevant response rates and viability as a bridge to allogeneic transplantation (BHATLA et al., 2024). In addition, advances in cell therapies, such as CAR-T targeting CD19 or CD7, and molecular-targeted agents, such as menin inhibitors and BCL-2, have broadened the prospects for higher-risk or refractory subgroups (SUMMERS; TEACHEY; HUNGER, 2025; KULCZYCKA et al., 2024; RUBNITZ; KASPERS, 2021). In this sense, the consolidation of therapeutic strategies based on precise biological stratification and international collaboration will be decisive to maximize cure rates, reduce toxicities, and ensure a better long-term quality of life for children and adolescents affected by acute leukemias.

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