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EDITORIAL

Global advances in adult acute lymphoblastic leukemia: when access defines the prognosis

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B or T precursor cell leukemia/lymphoma is a clonal disorder characterized by the uncontrolled proliferation of immature lymphoid cells that block hematopoiesis, affecting the bone marrow and peripheral blood[1]. Although most cases occur in the pediatric population, they are increasingly diagnosed in adolescents and young adults, whose biology differs from that of pediatric patients, which explains a more unfavorable prognosis[2]. Except for Down syndrome, most cases occur in previously healthy individuals, where genetic susceptibility or exposure to environmental factors may play a key role[3]. In adults, some factors associated with an increased risk of relapse include age over 35 years, an elevated white blood cell count (> 30 × 10^3/μL in B precursor leukemia and > 100 × 10^3/μL in T precursor leukemia), as well as extramedullary invasion, which most often affects the central nervous system, the skin, and gonads[4]. Together with clinical and laboratory data, molecular alterations are essential for correct classification.

The measurement of minimal residual disease (MRD) at diagnosis is the main dynamic factor in predicting relapses in acute lymphoblastic leukemia (ALL). Thanks to technologies such as next-generation sequencing and next-generation flow cytometry, it is now possible to detect extremely low leukemic loads, allowing for more precise risk stratification and avoiding intensive treatments in patients with better prognosis[5].

Both risk stratification and MRD measurement allow for a more accurate assessment of the prognosis of patients with ALL. The integration of these factors makes it possible, as far as possible, to individualize the treatment. In cases with specific genetic alterations, such as the presence of the Philadelphia chromosome (breakpoint cluster region [BCR]: Abelson murine leukemia [ABL1]), the addition of tyrosine kinase inhibitors (TKI) to the conventional chemotherapy regimen improves the proportion of overall responses as well as long-term survival[6,7].

The selection of treatment depends largely on age (especially for patients considered adolescents and young adults), the presence of specific mutations such as the Philadelphia chromosome, and the expression of surface markers such as CD20 that allow the use of monoclonal antibodies such as rituximab or ofatumumab[8]. Adolescents and young adults (15-39 years) benefit from the use of therapeutic regimens inspired by pediatric protocols, characterized by increased exposure to asparaginase, intensive steroid use, and shorter, more intensive cycles. In contrast, treatment in older adults is adjusted according to functional status and the presence of comorbidities, prioritizing tolerance and adherence[9].

Older adults continue to be a population of complex management, in which treatment is individualized according to their functionality, comorbidities, tolerance

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to therapeutic schemes, and, in some cases, the presence of relevant genetic alterations. Among them, the Philadelphia chromosome (BCR: ABL1) stands out, whose expression is more frequent in this age group and conditions the use of TKI as part of treatment[10]. The addition of TKIs radically transformed the prognosis of chronic myeloid leukemia. In Philadelphia chromosome ALL, its combination with chemotherapy has significantly improved complete remission rates and raised 5-year survival to more than 50%[11].

The response to treatment in Philadelphia-positive (Ph+-ALL) depends largely on the potency of the TKI used, with dasatinib and ponatinib being the options that have shown the best results. Its incorporation into chemotherapy regimens or even into chemotherapy-free regimens combined with blinatumomab has significantly increased complete molecular remission rates, improved long-term survival, and, in many cases, reduced the need for hematopoietic progenitor cell transplantation[12].

The efficacy of these treatments has rewritten the prognosis of patients with Ph+-ALL, allowing not only to improve remission and survival rates but also to question the need for allogeneic transplantation in all cases. The emergence of even more potent combinations, such as ponatinib and blinatumomab, has made it possible to achieve sustained deep molecular remissions, allowing the development of chemotherapy-free regimens that achieve similar responses in the pediatric population[13,14].

Beyond chemotherapy, immunotherapy has established itself as a key tool in the treatment of ALL. Blinatumomab is a bi-specific antibody Bi-specific T-cell engager that directs cytotoxic T cells against CD19+ B cells, promoting their targeted destruction. In clinical trials in patients with relapsed or refractory B-cell ALL (R/R B-ALL), blinatumomab as monotherapy has demonstrated superior clinical and molecular remission rates to salvage chemotherapy[15]. In a meta-analysis, an analysis of 18 studies with 1,373 patients showed a complete remission rate of 54% and a molecular response of 43%, with better results in patients with < 50% blasts in the bone marrow. The median overall survival was 8.16 months, and the median relapse-free survival was 6.02 months. Although the incidence of serious adverse events was high (80%), neurological toxicities and grade ≥ 3 cytokine release syndrome were relatively low (7% and 3%, respectively)[16].

In conjunction with bi-specific drugs and immunoconjugates, this is an antibody directed against the CD22 receptor bound to a cytotoxic toxin derived from calicheamicin[17]. Its indication now is in refractory or relapsed patients. The phase 3 INO-VATE study demonstrated significantly higher rates of remission and greater access to hematopoietic transplantation, although with an increased risk of hepatic venoocclusive disease[18]. The future of treatment includes the use of chimeric antigen receptor (CAR-T) cells, and these cells are genetically modified to recognize and destroy cancer cells that express a specific antigen, such as CD19 in B-cell ALL, the most recognized CAR-T cell therapies include tisagenlecleucel, approved for pediatric and young adult patients, and brexucabtagene autoleucel, approved for adults, both directed against the CD19 antigen[19].

When comparing anti-CD19 CAR-T cell therapy and blinatumomab in patients with relapsed or refractory ALL, CAR-T therapy achieved higher rates of complete remission, overall survival, and relapse-free, although with greater toxicity; on the other hand, blinatumomab showed a more favorable safety profile and utility as a bridge treatment before allogeneic transplantation. Both strategies share specific adverse events such as cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome, the severity of which depends largely on the selection of the CAR-T type[20]. Now, the main indication for bi-specific drugs, immunoconjugates, and CAR-T cells are relapsed or refractory patients, but more and more patients are benefiting in earlier lines and even as a bypass before transplantation of hematopoietic progenitors or CAR-T cells. Figure 1 presents the main therapeutic strategies in the treatment of adult ALL.

Recently, blinatumomab has been approved as part of the consolidation schedule, even with measurable negative residual disease[21]. Unfortunately, in our region, the implementation of strategies based on redirecting the immune system remains limited due to restricted access and high costs, which forces the use of highly toxic chemotherapy schemes or the use of other agents, such as proteasome inhibitors[22]. In this context, our group has evaluated the incorporation of bortezomib, a first-generation proteasome inhibitor, in different lines of treatment with the aim of improving the efficacy of chemotherapy. Figure 2 describes the major events that have impacted the prognosis of adult ALL.

Finally, despite global advances in the treatment of ALL, Latin American countries face serious limitations that negatively affect clinical outcomes, especially in pediatric and adult populations. The main barriers include limited access to diagnostic tests, innovative therapies, and immunotherapies, high dropout rates,

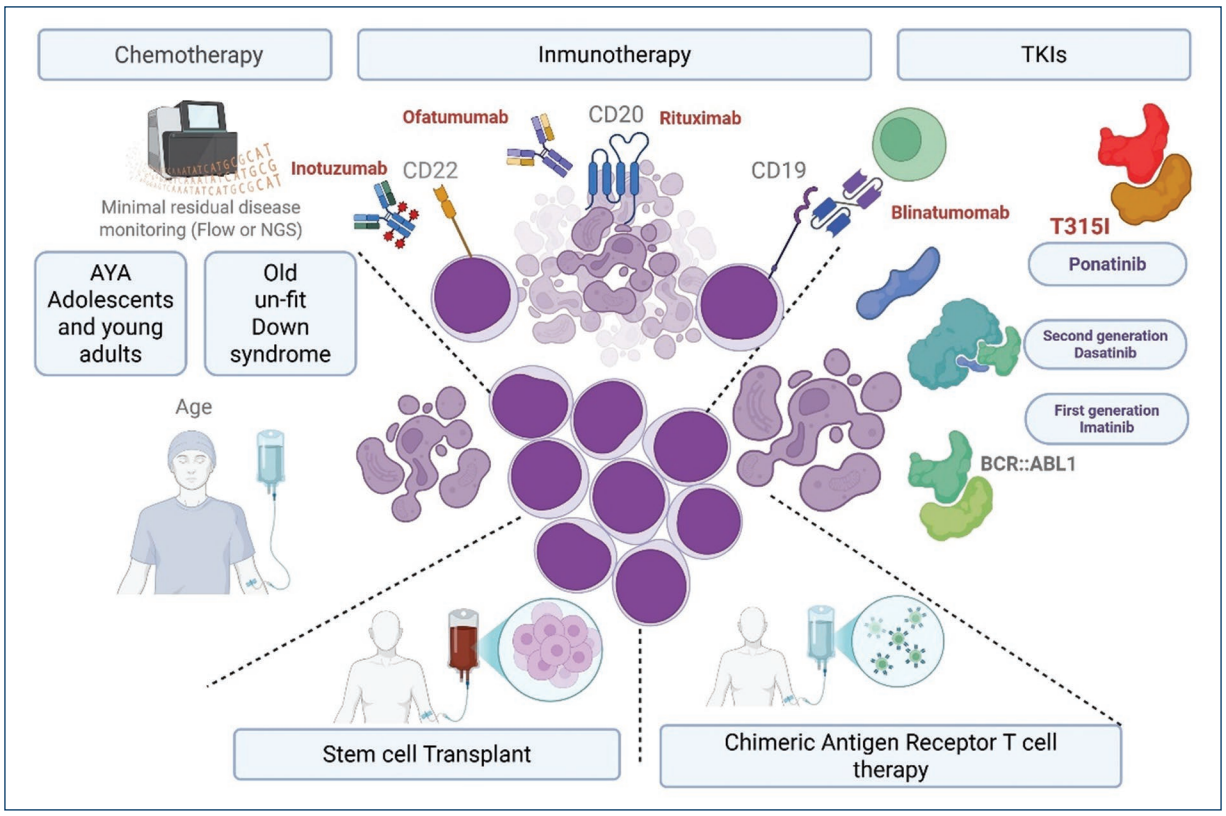

Figure 1. Therapeutic combinations in adult patients with acute lymphoblastic leukemia (chemotherapy, immunotherapy, molecular targets, progenitor cell transplantation and CAR-T).

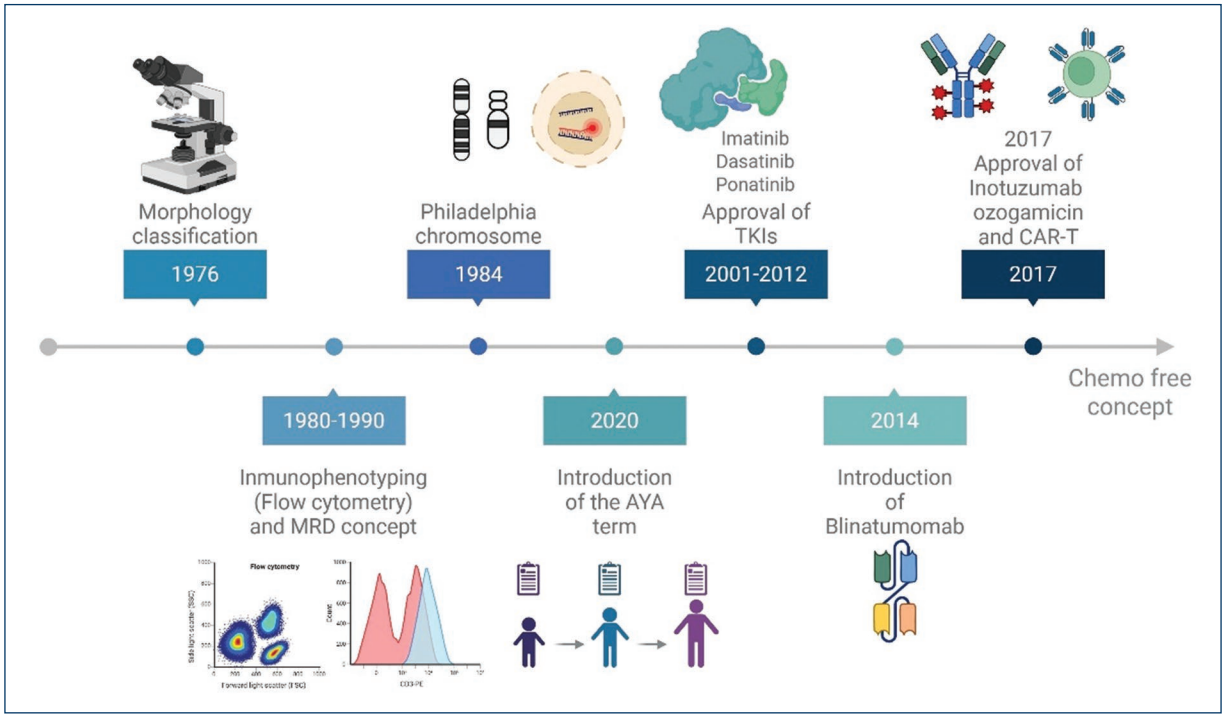

Figure 2. Historical aspects in the treatment of adult acute lymphoblastic leukemia.

treatment-related toxicity, and deficiencies in clinical support strategies[23]. In developing countries, adapting treatments to available resources and working collaboratively has helped improve both survival and quality of life for patients with acute lymphoblastic leukemia.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

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