Treatment of Relapse in Pediatric Patients with Acute Lymphoblastic Leukemia in Argentina: Results from a Clinical Trial and a Prospective Cohort

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Acute leukemias represent the most frequent oncological disease in pediatrics. According to the Argentine Pediatric Oncology Hospital Registry (ROHA), they account for 36% of childhood neoplasms; of these, 75% are acute lymphoblastic leukemias (ALL) and 25% are acute myeloblastic leukemias (AML)[1].

Rates of cure of ALL in developed countries can reach 90%; however, in Argentina, they are approximately 70%[2]. The most frequent cause of treatment failure is disease relapse[3].

Relapses represent 15% in more developed countries and 25-30% in Argentina. The prognostic factors for relapses are the time elapsed since the initial diagnosis, the site of relapse, the immunophenotype, the previously instituted treatment, and minimal residual disease (MRD)[4], i.e., the response to the administered treatment. According to the BFM group (Berlin-Frankfurt-Münster Study Group)[5], taking these parameters into account, high-risk (HR) relapses are those that occur before 30 months from the diagnosis (very early before 18 months and early between 18 and 30 months from the initial diagnosis), in bone marrow (BM) or combined (cBM), with B-cell immunophenotype, with HR also including T-cell immunophenotype marrow relapses regardless of the time elapsed since the initial diagnosis. The COG[6] classifies relapses using the minimal residual disease (MRD) value determined by flow cytometry (FC). For low-risk (LR) relapses: late medullary and extramedullary relapses with an MRD of < 0.1% intermediate risk (IR) at the end of the first block); medullary and extramedullary relapses with an MRD of ≥ 1% at the end of the first block; and for HR relapses: early precursor B marrow and extramedullary relapses and T-cell immunophenotype relapses, regardless of the time since the diagnosis of the initial disease. In recent decades, the prognosis for patients who relapsed within 30 months from diagnosis has not exceeded an event-free survival of 50%[5], and it is even lower for second and third relapses[7].

Regarding the subpopulations analyzed in the article by Makiya et al.8, it is worth noting that they are two different subpopulations; some patients were exposed to laclofarabine, though possible biases have been corrected. Treatment with this was initially adopted in the prospective cohort, according to the treating physician's criteria, which remain unknown. Additionally, the sample size in both populations is limited. These variables could bias the obtained results, and it would be valuable to evaluate all patients who underwent transplantation and those who did not to consider transplant-related mortality[9] in both groups, regardless of the treatment received. Considering the mentioned situation, clofarabine could be introduced in very well-defined cases, such as in patients with a diagnosis of high-risk relapsed ALL who, after a first cycle of chemotherapy based on the BFM strategy, do not respond or do not achieve MRD negativity, or in those high-risk relapses of patients who were initially treated as high-risk ALL at diagnosis, or in patients with second relapses/refractory disease[10], provided that adequate clinical support measures are available and that there is the possibility of performing a hematopoietic progenitor cell transplant if the patient achieves a second complete remission. Otherwise, referral to a more complex center would be mandatory.

Relapsed ALL continues to be a problem, especially in our setting. New therapeutic strategies such as blinatumomab[11], inotuzumab[12], nelarabine[13], and CAR-T cells[14] could be effective, though not all centers in the country have the resources to use them, and it is still necessary to define their efficacy to apply them in our setting, minimizing the cost of administering expensive therapies without definitively proven efficacy.

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It is essential to adequately administer first-line treatment promptly, in the correct form, and according to the complete therapeutic regimen to reduce the risk of relapses and to continue investigating possible treatment lines for relapsed ALL according to the social and economic realities of Argentina and other low-resource countries.

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