Relapsed acute lymphoblastic leukemia: back to the drawing board

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Although the majority of children with acute lymphoblastic leukemia (ALL) are cured with combination chemotherapy and corticosteroids, the immunotherapy revolution in the past decade is re-shaping therapeutic paradigms for this disease. Blinatumomab, a bispecific T-cell engager, has been approved as consolidative treatment for relapsed B-cell precursor (BCP)-ALL based on two multicenter clinical trials from the Children's Oncology Group (COG), the ALLL1331 trial,[1,2] and the IntReALL[3] collaborative group. In both studies, randomization to blinatumomab was performed only on a subset of patients reaching consolidative blocks, leaving out many patients in whom outcomes are unknown.

The article by Hogan *et al*.[4] published in this issue of *Haematologica* reports the outcomes of the entire cohort with relapsed ALL enrolled on the COG AALL1331 trial, making this the largest prospective trial reported on relapsed BCP-ALL. This report includes many patients who did not reach later randomizations, reflecting real-life challenges in relapsed ALL, the first being how to re-induce patients to achieve remission.

The backbone therapy used for relapsed ALL induction is in many ways similar to the induction used in upfront settings, consisting of corticosteroids, anthracyclines, asparaginase, vincristine and intrathecal chemotherapy. In first relapse of ALL, the mitoxantrone-based induction block of the UK-ALL R3[5] demonstrated superior outcomes compared to idarubicin-based induction, and long-term results seemed better than those with other relapse-oriented regimens. Thus, the UK-ALL R3 induction block was incorporated into many relapsed ALL protocols, including the AALL1331 study, in which it is termed 'Block 1'.

One of the aims of the study by Hogan *et al*.[4] was to report on the toxicity of the UK-ALL R3 induction regimen, as well as its rate of failure to induce remission. In 661 enrolled patients on AALL1331, the rate of induction failure was 6.4%, and the rate of induction death was 3.6%, similar to the rates in the original UK-ALL R3 report[5] (7.6% and 3.3%, respectively). Only 80.3% of patients achieved remission, most being positive for minimal residual disease (MRD). Beyond the toxicity and failure rates, this large study confirms several risk factors for relapsed BCP-ALL.

First, the time of relapse matters. Patients with a late relapse had an event-free survival of 62%, similar to that in the groups treated with UK-ALL R3 induction[6] or BFM-REZ induction.[7] In contrast, the report by Hogan *et al*. highlights that patients who relapsed very early, within 18 months of the initial diagnosis of ALL, did extremely poorly, having a high rate of treatment failure (54%), poor MRD response and a 4-year event-free survival of less than 10%.

Second, the value of MRD in the relapsed setting was further validated in the study by Hogan *et al*. The post-induction rate of MRD-negativity (defined as <0.01% by flow-cytometry) in the entire cohort was 40%. Moreover, post-induction MRD levels were associated with outcomes in patients with very early, early and late relapses, confirming findings in other studies.[6,7]

In addition to MRD and timing of response, high-risk cytogenetics have a prognostic value in relapse. Only a handful of cytogenetic aberrations were reported in the AALL1331 study, limiting the value of any analyses. Still, the high abundance of *KMT2A*-rearranged leukemia in the early relapse groups is important. Additional high-risk cytogenetics such as *TCF3::HLF*, *TCF3::PBX1*, iAMP21,[8] *TP53* alterations[7] and others should be incorporated in studies of relapsed ALL.

The large relapsed cohort described by Hogan *et al*.[4] clearly demonstrates that despite reported advantages, adding consolidative blinatumomab to the treatment backbone is not sufficient for many patients. In addition, the high failure rates warrant better re-induction regimens. Clearly, there is a need for new roadmaps for relapsed ALL. In the high-risk and especially very-high risk group (relapsing <18 months from diagnosis), current studies are already testing inotuzumab, an anti-CD22 antibody-drug conjugate that has shown good response rates in second relapses or beyond.[9]

Chimeric antigen receptor T cells targeting CD19 or other antigens may also be of benefit in first relapse, although studies in this setting are scarce.

In June 2024, the Food and Drug Administration approved blinatumomab as a consolidative cycle for both pediatric and adult patients with B-cell ALL in the upfront setting, further changing the paradigm of leukemia treatment. Utilization of immunotherapy in upfront protocols may not only reduce altogether the incidence of relapsed leukemia, but may substantially alter the phenotype, risk factors and therapeutic landscape of relapsed disease.[10] Thus, the roadmaps for relapsed ALL are likely to change yet again in the near future, incorporating more immunotherapeutic strategies and therapies targeting biological vulnerabilities of leukemic blasts. In addition to eliciting better response rates and survival rates, these therapies may improve long-term quality of life, critical for the future of children surviving relapsed ALL.

Disclosures

No conflicts of interest to disclose.

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