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Opinion Article

Pediatric Leukemia Treatment: Balancing Cure Rates with Long-term Quality of Life

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DESCRIPTION

The treatment of pediatric leukemia represents one of the most remarkable success stories in modern medicine. Over the past five decades, survival rates for childhood Acute Lymphoblastic Leukemia (ALL) have improved from less than 10% to more than 90% in developed countries. This dramatic progress has transformed a once uniformly fatal disease into a largely curable condition, establishing a paradigm for successful translational research in oncology. However, this success has come with significant costs, as survivors often face a lifetime of treatment-related complications. The field now stands at a critical juncture, seeking to maintain or improve cure rates while reducing the burden of therapy and its long-term consequences.

Risk-adapted therapy has been a cornerstone of pediatric leukemia treatment, allowing for treatment intensification in high-risk patients while sparing those with favorable features from unnecessary toxicity. The evolution of risk stratification systems has paralleled advances in our understanding of leukemia biology, moving from primarily clinical factors to increasingly sophisticated molecular classifications. Cytogenetics, Minimal Residual Disease (MRD) assessment, and comprehensive genomic profiling now guide treatment intensity decisions with unprecedented precision. This approach has not only improved outcomes but has also begun to address the historical problem of overtreatment in substantial subsets of patients.

The identification of targetable molecular lesions has further refined the therapeutic landscape. The addition of tyrosine kinase inhibitors to conventional chemotherapy for Philadelphia chromosome-positive ALL represents an early success story in targeted therapy for pediatric leukemia, dramatically improving outcomes in this historically poor-prognosis subset. More recently, the targeting of other kinase alterations, such as ABL-class fusions, JAK pathway mutations, and *FLT3* aberrations, has shown promise in specific molecular subgroups. These approaches exemplify the potential of precision medicine to enhance efficacy while potentially reducing toxicity. Immunotherapeutic strategies have emerged as another transformative approach for pediatric leukemia. The approval of CD19-directed Chimeric Antigen Receptor (CAR) T-cell therapy for relapsed/refractory B-cell ALL has provided a potentially curative option for patients who previously faced dismal prognoses. Bispecific T-cell engagers, such as blinatumomab, have similarly demonstrated impressive activity in relapsed disease and are being evaluated in frontline settings. These immunotherapeutic approaches offer the potential to reduce reliance on conventional cytotoxic agents and their associated toxicities, although they introduce new challenges related to unique adverse events, long-term immune effects, and implementation in resource-limited settings.

Despite these advances, significant challenges remain in certain subsets of pediatric leukemia. Infants with *KMT2A*-rearranged ALL continue to have poor outcomes despite intensive therapy, highlighting the need for novel approaches for this biologically distinct entity. Similarly, T-cell ALL, particularly early T-cell precursor ALL, remains challenging, with higher relapse rates than B-cell ALL. In Acute Myeloid Leukemia (AML), despite significant improvements, overall survival rates remain substantially lower than those for ALL, and the intensity of therapy required for cure carries substantial acute toxicity and long-term consequences.

Efforts to reduce treatment intensity while maintaining efficacy represent a major focus of current research. The identification of patients who can be effectively treated with reduced therapy based on early response assessment and molecular features has already allowed for significant de-escalation in certain subgroups. For instance, the elimination of cranial radiation in most patients with ALL has reduced neurocognitive sequelae without compromising central nervous system control. Similarly, reductions in anthracycline exposure in selected patients have aimed to mitigate cardiotoxicity. Ongoing trials are exploring further opportunities for de-escalation, including shortened duration of maintenance therapy in selected populations.

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