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Opinion Article

Immunotherapy in Acute Leukemia: Harnessing the Immune System Beyond Allogeneic Transplantation

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DESCRIPTION

The therapeutic landscape for acute leukemias has been revolutionized by novel immunotherapeutic approaches that harness the immune system's inherent capacity to recognize and eliminate malignant cells. While allogeneic Hematopoietic Stem Cell Transplantation (HSCT) has long represented the original form of immunotherapy for leukemia through the graft-*versus*-leukemia effect, recent advances have expanded immunotherapeutic options beyond transplantation. These innovations offer the potential for targeted immune activation with reduced toxicity compared to traditional approaches and provide much-needed options for patients with relapsed/refractory disease or those ineligible for intensive therapy.

Bispecific T-cell Engagers (BiTEs) have emerged as a transformative modality in Acute Lymphoblastic Leukemia (ALL), with blinatumomab targeting CD19 representing the prototype of this class. By simultaneously engaging CD3 on T cells and CD19 on B-ALL blasts, blinatumomab facilitates formation of an immunological synapse and redirected T-cell cytotoxicity. The phase 3 TOWER study demonstrated superior survival with blinatumomab compared to conventional chemotherapy in adults with relapsed/refractory B-ALL, leading to FDA approval in this setting. Subsequent studies have demonstrated particular efficacy in the Minimal Residual Disease (MRD) positive setting, with 78-80% of patients achieving MRD negativity after blinatumomab monotherapy. This remarkable activity has prompted integration of blinatumomab earlier in treatment sequences, including frontline approaches for older adults and combination with conventional chemotherapy in newly diagnosed patients. The ECOG-ACRIN E1910 trial combining blinatumomab with chemotherapy in newly diagnosed CD19-positive B-ALL demonstrated significantly improved survival compared to chemotherapy alone, potentially establishing a new standard of care.

The success of blinatumomab has stimulated development of BiTEs targeting additional antigens relevant to acute leukemias. Bispecific antibodies targeting CD20, CD22, and CD123 have shown promising activity in early-phase trials. Particularly notable is the development of dual-targeting molecules such as CD19/CD22 bispecifics, which may reduce the risk of antigen escape observed with CD19-directed therapies. This approach appears especially relevant in pediatric ALL, where CD19 loss represents a common mechanism of resistance to immunotherapy. Similar approaches are being explored in Acute Myeloid Leukemia (AML) with flotetuzumab (CD123×CD3) demonstrating activity in relapsed/refractory disease with an overall response rate of 30% in a phase 1/2 study.

The remarkable efficacy of Chimeric Antigen Receptor (CAR) T-cell therapy in B-lymphoid malignancies has transformed the treatment paradigm for relapsed/refractory B-ALL. Tisagenlecleucel, the first FDA-approved CAR T-cell product for B-ALL, demonstrated complete remission rates of 81% in the pivotal ELIANA trial of pediatric and young adult patients with heavily pretreated disease. The durability of these responses is particularly impressive, with approximately 60% remaining leukemia-free at 12 months. This transformative efficacy has prompted investigation of CAR T-cell therapy in earlier treatment lines, including as consolidation after initial therapy in high-risk patients or as an alternative to HSCT in second remission. The randomized CASSIOPEIA trial comparing CD19 CAR T-cells to standard HSCT in children and young adults with high-risk B-ALL in first complete remission represents a paradigm-shifting study that may fundamentally alter the role of transplantation in ALL therapy.

Immune Checkpoint Inhibitors (ICIs) have demonstrated more modest activity in acute leukemias compared to solid tumors, with response rates of 15-20% as monotherapy in relapsed/refractory disease. However, several patterns have emerged suggesting specific contexts with enhanced efficacy. Hypermutated leukemias, including those arising in the setting of DNA repair defects or prior mutagen exposure, appear more responsive to PD-1/PD-L1 blockade. Additionally, specific genetic subtypes including early T-cell precursor ALL and RUNX1-mutated AML demonstrate increased PD-L1 expression

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and potential sensitivity to checkpoint inhibition. Perhaps most promisingly, combination approaches integrating ICIs with hypomethylating agents, targeted therapies, or conventional chemotherapy have shown enhanced activity compared to monotherapy, with several phase 3 trials ongoing in AML.