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Perspective

The Role of Antibody Dependent Cellular Cytotoxicity in Leukemia Management

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DESCRIPTION

Leukemia, a heterogeneous group of hematologic malignancies, arises from the uncontrolled proliferation of abnormal white blood cells in the bone marrow and peripheral blood. Despite advancements in chemotherapy, radiotherapy and hematopoietic stem cell transplantation, many forms of leukemia remain challenging to treat due to their molecular complexity, chemoresistance and high relapse rates. In recent years, Monoclonal Antibodies (mAbs) have emerged as a promising therapeutic modality, offering targeted and highly specific treatment strategies that minimize off-target toxicity while exploiting unique cellular antigens expressed by leukemic cells. The development and clinical integration of mAbs represent a paradigm shift in leukemia therapy, underscoring the growing importance of precision medicine in hematologic oncology.

Monoclonal antibodies are laboratory produced molecules designed to bind with high specificity to antigens expressed on the surface of target cells. In leukemia, these antigens are often lineage specific or aberrantly expressed on malignant cells, making them ideal targets for selective therapy. The mechanism of action of mAbs can induce direct cytotoxicity through apoptosis or growth inhibition, others recruit immune effector functions *via* Antibody Dependent Cellular Cytotoxicity (ADCC) or Complement Dependent Cytotoxicity (CDC), and a subset serves as vehicles for delivering cytotoxic payloads, such as toxins, radioactive isotopes, or chemotherapeutic agents, directly to leukemic cells. This versatility allows monoclonal antibodies to be used both as stand-alone therapies and in combination with conventional treatments to enhance efficacy.

In the treatment of B-cell malignancies, which include Acute Lymphoblastic Leukemia (ALL) and Chronic Lymphocytic Leukemia (CLL) the CD20 antigen has been extensively exploited. Rituximab, a chimeric anti-CD20 monoclonal antibody, revolutionized B-cell leukemia management by targeting malignant B-cells while sparing most normal tissues. Rituximab's efficacy stems from its ability to induce apoptosis, mediate ADCC, and trigger complement activation, resulting in selective depletion of CD20-positive leukemic cells. Clinical trials have demonstrated that combining rituximab with standard chemotherapy regimens significantly improves overall survival and progression-free survival in both newly diagnosed and relapsed B-cell leukemia patients. Furthermore, the development of second- and third-generation anti-CD20 antibodies, such as ofatumumab and obinutuzumab, has expanded therapeutic options by enhancing binding affinity, improving immune effector recruitment, and overcoming resistance mechanisms associated with rituximab.

Antibody-drug conjugates represent another transformative application of monoclonal antibodies in leukemia treatment. Inotuzumab ozogamicin, an anti-CD22 ADC, links a cytotoxic agent, calicheamicin, to a monoclonal antibody specific for CD22-expressing leukemic cells. Upon binding and internalization, the conjugated drug is released intracellularly, inducing DNA double-strand breaks and cell death. This targeted delivery allows for the selective killing of malignant cells while minimizing systemic toxicity, a major limitation of conventional chemotherapy. Clinical trials in relapsed or refractory B-cell ALL have demonstrated higher complete remission rates and improved progression-free survival compared to standard salvage chemotherapy, validating the clinical utility of ADCs in hematologic malignancies.

The advent of bispecific and multispecific antibodies has further enhanced the therapeutic landscape of leukemia. By simultaneously engaging multiple antigens or linking immune effector cells to malignant cells, these agents overcome limitations of conventional monoclonal antibodies, including antigen escape and insufficient immune activation. Ongoing research focuses on optimizing pharmacokinetics, reducing immunogenicity, and mitigating adverse events associated with immune overactivation. These innovations underscore the dynamic evolution of antibody-based therapies, bridging immunology and oncology to achieve more durable remissions.

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