Journal of Leukemia
ISSN: 2329-6917
OPEN ACCESS Freely available online
Commentary

Leukemia in the Aging Population: Navigating Therapeutic Challenges and Opportunities

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DESCRIPTION

The intersection of leukemia and aging represents a significant and growing challenge in hematologic oncology. As the global population ages, the incidence of leukemia in older adults continues to rise, with individuals over 65 accounting for the majority of new cases across most leukemia subtypes. This demographic shift has profound implications for clinical practice, research priorities, and healthcare resource allocation. Older adults with leukemia present unique challenges that extend beyond the disease itself, including age-related physiological changes, comorbidities, functional limitations, and social considerations. Navigating these complexities requires an integrated approach that balances disease control with quality of life and acknowledges the heterogeneity of the older population.

The biology of leukemia in older adults differs significantly from that observed in younger patients, reflecting both age-related changes in hematopoiesis and distinct disease pathogenesis. Aging is associated with clonal hematopoiesis, decreased hematopoietic reserve, and alterations in the bone marrow microenvironment that may influence disease development and therapeutic response. Acute Myeloid Leukemia (AML) in older adults more frequently exhibits adverse cytogenetic features, secondary disease arising from prior myelodysplasia or exposure to cytotoxic therapy, and mutations in genes such as *ASXL1*, *RUNX1*, and *TP53* that confer poor prognosis. Similarly, Chronic Lymphocytic Leukemia (CLL) in the elderly more commonly presents with unfavorable prognostic markers such as unmutated *IGHV* status and complex karyotype. These biological differences contribute to the generally poorer outcomes observed in older adults with leukemia and necessitate age-specific therapeutic approaches.

Traditional clinical trials have often excluded or underrepresented older adults, particularly those with comorbidities or functional limitations. This exclusion has created an evidence gap that complicates treatment decision-making for the majority of patients seen in clinical practice. The generalizability of trial results derived from younger, fitter populations to older adults with multiple comorbidities remains questionable, and extrapolation may lead to inappropriate treatment selections with unfavorable risk-benefit profiles. Recent efforts to design trials specifically for older adults or to include broader eligibility criteria in conventional trials represent important steps toward addressing this evidence gap, but significant work remains to be done in generating relevant data for this population.

Comprehensive Geriatric Assessment (CGA) has emerged as a valuable tool for evaluating older adults with leukemia and guiding treatment decisions. This multidimensional assessment encompasses physical function, comorbidities, cognition, psychological state, social support, nutritional status, and medication review, providing a more holistic view of the patient than chronological age or performance status alone. CGA can identify vulnerabilities that may increase the risk of treatment complications, guide interventions to address these vulnerabilities, and inform decisions regarding treatment intensity and goals of care. The integration of CGA into routine clinical practice for older adults with leukemia represents a paradigm shift from age-based to function-based treatment selection.

Older adults exhibit significant heterogeneity in their physiological reserve, functional status, and preferences, necessitating individualized approaches to leukemia management. Some older patients may tolerate and benefit from intensive therapies comparable to those administered to younger patients, while others may experience prohibitive toxicity without meaningful clinical benefit from such approaches. Tools such as CGA, biomarkers of physiological age, and predictive models for treatment-related mortality can help identify which older patients are likely to tolerate intensive therapy and which may benefit from alternative approaches. This risk-stratified approach represents a more nuanced alternative to chronological age-based cutoffs for treatment selection.

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Received: 03-Mar-2025, Manuscript No. JLU-25-38101; **Editor assigned:** 05-Mar-2025, PreQC No. JLU-25-38101 (PQ); **Reviewed:** 18-Mar-2025, QC No. JLU-25-38101; **Revised:** 25-Mar-2025, Manuscript No. JLU-25-38101 (R); **Published:** 01-Apr-2025, DOI: 10.35248/2329-6917-25.13.430

Citation: Scholz A (2025). Leukemia in the Aging Population: Navigating Therapeutic Challenges and Opportunities. J Leuk. 13:430.