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Difficult Leukemias in the Geriatric Population: Bridging Gaps in Diagnosis, Access and Survival

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Abstract

Leukemia in the elderly poses a distinct clinical challenge, characterized by atypical presentations, diagnostic delays, and poor treatment tolerance. Difficult leukemias—including chemoresistant acute myeloid leukemia (AML), high-risk chronic lymphocytic leukemia (CLL), and therapy-related myeloid neoplasms—are increasingly prevalent among older adults due to both immunosenescence and cumulative genetic insults over time. However, diagnosis in this population is often delayed due to overlapping comorbidities, subtle symptomatology, and underutilization of confirmatory diagnostics like bone marrow biopsy and cytogenetic profiling. Treatment decisions in geriatric patients are complicated by a high prevalence of frailty, polypharmacy, cognitive decline, and limited social support. Additionally, systemic barriers such as age bias, lack of clinical trial representation, and restricted access to hematology-oncology services further diminish treatment equity. Many elderly patients are excluded from intensive therapies and emerging treatments due to concerns over toxicity, despite some being biologically fit. As a result, survival outcomes remain dismal, with significantly higher mortality rates compared to younger cohorts. This review underscores the urgent need for geriatric-focused strategies to improve outcomes in difficult leukemias. These include implementing comprehensive geriatric assessments in routine care, expanding access to hypomethylating agents and targeted therapies, and increasing enrollment of older adults in clinical trials. Policy-level interventions, education on age-inclusive oncology, and integration of supportive care services are pivotal to bridging the gaps in diagnosis, access, and survival in this vulnerable population.

Keywords: Geriatric leukemia, diagnosis delay, treatment access, survival outcomes, healthcare disparities

Abbreviations

Abbreviation	Meaning
AML	Acute Myeloid Leukemia
CAR-T	Chimeric Antigen Receptor T-cell
CHIP	Clonal Hematopoiesis of Indeterminate Potential
CLL	Chronic Lymphocytic Leukemia
DNA	Deoxyribonucleic Acid
HSC	Hematopoietic Stem Cell
MDS	Myelodysplastic Syndromes

Introduction

The burden of leukemia is rapidly shifting with global demographic transitions, particularly as the proportion of elderly individuals continues to rise. Leukemia is no longer predominantly a disease of the young; it increasingly affects older adults, with the median age at diagnosis for most leukemia subtypes—especially acute myeloid leukemia (AML) and chronic lymphocytic leukemia (CLL)—being over 65 years. As populations age worldwide, geriatric hematologic malignancies are becoming a major public health concern, underscoring the urgent need for age-tailored diagnostic and treatment strategies [1-2].Leukemias in the elderly are inherently more complex, both biologically and clinically. Older patients frequently present with unfavorable cytogenetics, secondary leukemias related to prior therapies, and comorbid conditions that limit the feasibility of intensive interventions. Additionally, immune senescence and age-associated clonal hematopoiesis contribute to the emergence of more aggressive disease phenotypes. These factors not only reduce survival rates but also complicate the development of standardized care protocols applicable to the elderly [3-4].

The diagnostic process in geriatric leukemia is often hindered by atypical or non-specific presentations such as fatigue, weight loss, or cognitive decline. These symptoms are frequently misattributed to aging or existing comorbidities, delaying definitive investigations. Furthermore, invasive diagnostic procedures like bone marrow biopsy may be deferred in frail individuals, leading to underdiagnosis or misclassification of leukemia subtypes. As a result, many elderly patients are diagnosed at advanced stages, when the therapeutic window has already narrowed [5-6].Even when diagnosis is achieved, access to appropriate care remains uneven. Ageism within the healthcare system, geographic disparities, socioeconomic factors, and lack of geriatric-specific oncology infrastructure contribute to substantial inequities. Many older adults lack proximity to specialized centers or are underinsured, limiting their ability to receive optimal treatment. These barriers disproportionately affect patients in low-resource settings and contribute to stark differences in outcomes across populations [6].

Treatment challenges are amplified by age-related declines in organ function, frailty, and increased sensitivity to chemotherapy toxicities. Traditional cytotoxic regimens often prove intolerable, and supportive care measures are inconsistently implemented. Moreover, despite the availability of less toxic targeted therapies such as hypomethylating agents and BCL-2 inhibitors, many elderly patients remain undertreated due to rigid eligibility criteria and limited real-world application of newer regimens. This therapeutic gap contributes significantly to the poor survival outcomes seen in this age group [7-8].Compounding these issues is the historical underrepresentation of older adults in clinical trials. Most pivotal leukemia studies exclude patients above a certain age or with comorbidities, leading to a lack of robust evidence for guiding treatment decisions in the elderly. This evidence gap perpetuates therapeutic nihilism and prevents

oncologists from offering more personalized, risk-adapted strategies. Bridging this divide requires deliberate efforts to design trials that accommodate the clinical realities of older adults with leukemia [9-10].

Aim of the Review:

To explore the clinical, diagnostic, therapeutic, and systemic challenges surrounding difficult leukemias in older adults, and to highlight evidence-based strategies and policy-level interventions needed to improve outcomes and equity in care for the aging population.

Diagnostic Challenges in the Elderly

The diagnosis of leukemia in older adults is often delayed or missed entirely due to the complex interplay of age-related physiological changes, comorbidities, and atypical symptomatology. Unlike younger patients, geriatric individuals may present with subtle, non-specific signs such as fatigue, malaise, anorexia, or cognitive decline—symptoms commonly attributed to the aging process or existing chronic illnesses. As a result, there is a tendency to overlook hematologic malignancies as part of the differential diagnosis in elderly patients, especially in primary care or non-specialist settings [11-12].One major barrier to timely diagnosis is the high burden of comorbidities in this age group. Conditions such as chronic kidney disease, heart failure, diabetes, or anemia of chronic disease can mask or mimic the laboratory abnormalities typically seen in leukemia. For instance, persistent cytopenias may be ascribed to nutritional deficiencies or bone marrow suppression from medications, delaying further hematological workup. Moreover, polypharmacy—common among elderly patients—can confound laboratory interpretation and obscure the underlying malignant process [13].

Another significant challenge lies in the underutilization or avoidance of invasive diagnostic procedures. Bone marrow aspiration and biopsy, essential for confirming leukemia diagnosis and guiding risk stratification, may be deemed too burdensome or risky for frail or immobile patients. This reluctance, whether patient- or provider-driven, leads to diagnostic uncertainty and often results in empiric management or supportive care without a clear diagnosis. Furthermore, logistical difficulties—such as transportation to specialized centers or lack of caregiver support—can further hinder diagnostic evaluation [12].Cognitive impairment, often underrecognized, poses an additional barrier to diagnosis. Patients with early dementia or delirium may struggle to articulate their symptoms, adhere to follow-up appointments, or provide an accurate medical history. This not only affects clinical assessment but also delays shared decision-making regarding further investigations. In some cases, family members or caregivers may misinterpret subtle behavioral or functional changes as “normal aging,” further reducing the likelihood of timely medical evaluation [14-15].Compounding these challenges is the limited awareness among healthcare providers regarding age-specific manifestations of leukemia. In resource-constrained or rural settings, a lack of access to hematology expertise and diagnostic infrastructure contributes to underdiagnosis. Even when basic tests such as complete blood counts are performed, the absence of immediate follow-up with peripheral smear evaluation, flow cytometry, or cytogenetic studies can lead to missed opportunities for early detection [16-17].

Difficult Leukemias in Focus

Leukemia in the geriatric population is not only more prevalent but also more biologically aggressive and resistant to standard therapies. Among the most challenging leukemias affecting older adults are AML, high-risk chronic lymphocytic leukemia (CLL), and therapy-related myeloid neoplasms. These subtypes are often characterized by adverse cytogenetic profiles, poor treatment responses, and a high likelihood of relapse, making them particularly difficult to manage in the context of age-related vulnerabilities [18].**AML** is the prototypical difficult leukemia in the elderly, with a median age at diagnosis of around 68–70 years. Older adults with AML frequently present with complex karyotypes, secondary AML (evolving from prior myelodysplastic syndromes or therapy-related

etiologies), and mutations such as TP53, which confer chemoresistance and poor outcomes. Furthermore, age-related decline in bone marrow reserve, increased prevalence of comorbidities, and frailty significantly limit the use of intensive induction chemotherapy, traditionally the mainstay of treatment. Even with hypomethylating agents or venetoclax-based regimens, response durability remains limited, especially in those with adverse molecular risk factors [19-20].

CLL is another challenging entity in elderly patients, particularly those harboring high-risk genetic abnormalities such as del(17p), TP53 mutations, and unmutated IGHV. These patients often fail to respond to conventional chemoimmunotherapy and require targeted agents such as Bruton's tyrosine kinase (BTK) inhibitors or BCL-2 antagonists. However, the chronic nature of CLL necessitates long-term therapy, which may not be well-tolerated in older adults with competing health issues. Additionally, CLL-associated immune dysfunction predisposes geriatric patients to recurrent infections, autoimmune cytopenias, and second malignancies, further complicating management [21-22].**Therapy-Related Myeloid Neoplasms,** including therapy-related AML (t-AML) and therapy-related myelodysplastic syndromes (t-MDS), are particularly aggressive and commonly occur in older adults who have previously undergone chemotherapy or radiation for other malignancies. These neoplasms are associated with complex cytogenetics, multilineage dysplasia, and rapid disease progression. Their pathogenesis is thought to be linked to cumulative DNA damage and impaired DNA repair mechanisms that become more pronounced with aging. Unfortunately, these leukemias are often resistant to both standard and novel therapies, and their prognosis remains dismal, with median survival often measured in months [23].

In addition to these subtypes, **acute lymphoblastic leukemia (ALL)**in older adults, although less common, presents its own challenges. Older patients with ALL are more likely to harbor the Philadelphia chromosome (Ph+), necessitating the use of tyrosine kinase inhibitors in combination with less intensive chemotherapy. However, the risk of treatment-related toxicity remains high, and achieving minimal residual disease (MRD) negativity is more difficult in this age group [24-25].Another entity worth noting is **myelodysplastic syndromes (MDS)**, which frequently progress to AML in the elderly. High-risk MDS with excess blasts poses a diagnostic and therapeutic challenge due to its overlap with AML and poor response to existing therapies. The decision to initiate treatment versus supportive care becomes particularly complex when life expectancy and quality of life are factored into the equation(Figure 1) [26].

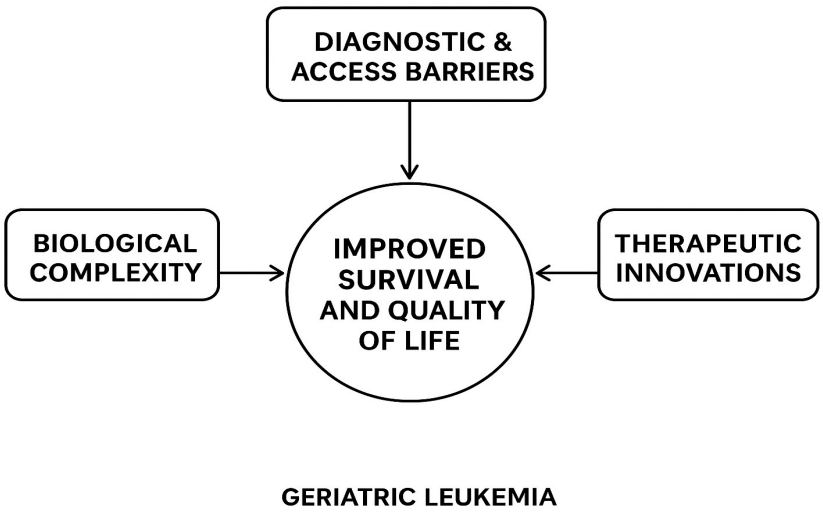


Figure 1: Conceptual Framework of Challenges and Interventions in Geriatric Leukemia

Barriers to Access and Treatment

Despite advances in the understanding and management of leukemia, older adults continue to face significant obstacles in accessing timely and appropriate treatment. These barriers are multifactorial, encompassing patient-level, provider-level, and systemic challenges that collectively result in undertreatment and worse outcomes in this vulnerable population. Ageism, limited geriatric oncology infrastructure, and economic constraints disproportionately impact elderly leukemia patients, especially those in low-resource or rural settings [27].At the patient level, frailty, cognitive decline, and a high burden of comorbidities often preclude aggressive therapies or participation in clinical trials. Many elderly patients are deemed ineligible for standard treatment protocols based solely on chronological age, despite evidence suggesting that physiological age and functional status are more appropriate determinants of treatment suitability. In addition, some patients or families may choose to forgo treatment due to fears of toxicity, loss of independence, or a perceived futility of care—decisions that are often shaped by insufficient counseling or lack of access to comprehensive geriatric assessment tools [27].

Healthcare provider attitudes also play a role in treatment disparities. Oncologists may exhibit therapeutic nihilism, underestimating the potential benefits of leukemia treatment in older adults. Time constraints and lack of training in geriatrics can hinder proper evaluation of treatment fitness. Furthermore, the underrepresentation of older adults in clinical trials leaves providers without clear evidence-based guidelines to manage this population, prompting default to conservative or palliative approaches even when more active treatments may be appropriate [28].System-level barriers compound these challenges. Limited access to hematology specialists, geographic distance from tertiary care centers, and inadequate transportation or caregiver support frequently delay care or prevent follow-up. Insurance limitations, particularly in underfunded healthcare systems, can restrict access to newer therapies such as hypomethylating agents, targeted oral drugs (e.g., BTK or BCL-2 inhibitors), and supportive interventions like transfusions or prophylactic antimicrobials. Even in high-income countries, disparities persist due to socioeconomic status, racial or ethnic background, and digital illiteracy that inhibits engagement with telemedicine or health portals [29].

In many parts of the world, particularly low- and middle-income countries, diagnostic and therapeutic resources for leukemia are scarce. Access to essential tests such as flow cytometry, cytogenetics, or molecular diagnostics may be limited, making accurate diagnosis and risk stratification challenging. In these settings, expensive therapies are often out of reach, and treatment is typically limited to basic supportive care or outdated chemotherapies with limited efficacy. These global disparities in access create an unacceptable survival gap between older leukemia patients in well-resourced versus under-resourced regions [30].Psychosocial factors, including isolation, depression, and limited social support, further hinder treatment adherence and follow-through. Many older adults live alone or rely on aging spouses or children with competing responsibilities. Without adequate support systems, patients may miss appointments, fail to take medications consistently, or become noncompliant with complex regimens. This is especially problematic in oral chemotherapy or maintenance therapy, which requires sustained self-management and vigilance over months or years (Table 1) [31].

Table 1: Common Biological and Clinical Challenges in Geriatric Leukemia

Category	Challenges	Implications
Biological	Hematopoietic stem cell aging, clonal hematopoiesis, mutation accumulation	Poor treatment response, aggressive disease
Clinical	Atypical presentation, comorbidities, frailty	Delayed diagnosis, limited treatment options
Systemic	Underrepresentation in trials, poor healthcare access	Data gaps, inequitable outcomes

Therapeutic Landscape and Innovations

The treatment landscape for leukemias in older adults has undergone significant transformation over the past decade, driven by a better understanding of disease biology, aging physiology, and the development of novel agents with improved tolerability. Traditional chemotherapeutic regimens—often poorly tolerated by elderly patients—are gradually being supplemented or replaced by targeted therapies, hypomethylating agents, and low-intensity combinations tailored to individual risk profiles. These innovations are redefining survival expectations and improving quality of life in selected patients who were once considered unfit for therapy [32-33].In **AML**, the emergence of hypomethylating agents such as azacitidine and decitabine offered the first glimmer of hope for elderly patients unable to tolerate intensive chemotherapy. More recently, combinations of hypomethylating agents with venetoclax, a BCL-2 inhibitor, have demonstrated remarkable efficacy in older AML patients, including those with poor-risk cytogenetics. This low-intensity, outpatient-friendly regimen has become the standard of care for many unfit patients, achieving complete remission rates previously seen only with high-dose chemotherapy. However, optimizing dose schedules, managing cytopenia-associated infections, and identifying predictors of durable response remain areas of ongoing research [34].

In **CLL**, the shift from chemoimmunotherapy to targeted oral agents has dramatically improved outcomes, particularly in the elderly. Bruton's tyrosine kinase (BTK) inhibitors (e.g., ibrutinib, acalabrutinib) and BCL-2 inhibitors (e.g., venetoclax) offer effective, often chemotherapy-free regimens with manageable toxicity profiles. These agents are especially beneficial in older patients with high-risk molecular features such as TP53 disruption or unmutated IGHV. However, long-term use is associated with atrial fibrillation, hypertension, and bleeding risks—factors that require careful consideration in the geriatric population. Fixed-duration therapy protocols and second-generation agents with fewer cardiovascular side effects are helping to mitigate some of these concerns [35].For **Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL)** in older adults, tyrosine kinase inhibitors (TKIs) such as imatinib and dasatinib have enabled less-intensive treatment protocols with significant survival benefits. When combined with reduced-intensity chemotherapy or corticosteroids, these regimens offer a viable therapeutic pathway for older patients who are ineligible for stem cell transplantation. The incorporation of novel agents such as blinatumomab, a bispecific T-cell engager, has further improved outcomes, particularly in patients with minimal residual disease. However, the neurotoxicity and immune-related side effects associated with some immunotherapies demand vigilant monitoring in elderly patients [36].

MDS, particularly high-risk cases with excess blasts, remain a therapeutic challenge in the elderly. While hypomethylating agents continue to serve as first-line therapy, new agents such as luspatercept (for anemia in MDS with ring sideroblasts) and experimental therapies targeting splicing mutations are under active investigation. Allogeneic hematopoietic stem cell transplantation (HSCT), once rarely considered for elderly patients, is increasingly being offered in selected fit individuals up to age 75, thanks to reduced-intensity conditioning regimens and improved supportive care [37].Personalized medicine is now at the forefront of geriatric leukemia management. Next-generation sequencing (NGS) allows for comprehensive molecular profiling, enabling risk-adapted therapy even in older patients. Geriatric assessment tools are being integrated into treatment algorithms to better predict treatment tolerance, guide supportive care needs, and optimize therapy selection. Additionally, machine learning models are being explored to anticipate complications and customize care pathways [38].

Strategies for Bridging the Gaps

Bridging the diagnostic, therapeutic, and survival gaps in the management of difficult leukemias among the geriatric population requires a multidimensional strategy rooted in equity, personalization, and systemic reform. Older adults represent a highly heterogeneous group in terms

of biological age, functional reserve, comorbidity burden, and psychosocial needs. Therefore, strategies must extend beyond conventional oncologic care to include comprehensive geriatric assessment, multidisciplinary collaboration, and targeted health policy interventions [39].**Early and accurate diagnosis** is foundational to improving outcomes. This requires expanding access to diagnostic technologies such as immunophenotyping, cytogenetics, and next-generation sequencing, particularly in resource-limited settings. Mobile diagnostic units, telehematology platforms, and partnerships with regional diagnostic hubs can decentralize services and bring early detection closer to rural and underserved communities. Equally important is educating primary care providers and community health workers to recognize early signs of hematologic malignancies in older adults, reducing diagnostic delays [40].

Integrating geriatric oncology services into hematologic care is a critical yet often overlooked step. Tools like the Comprehensive Geriatric Assessment (CGA) can help stratify patients based on frailty, cognition, nutritional status, and social support, thereby informing individualized treatment plans. Institutions should embed geriatricians within leukemia care teams to balance curative intent with patient-centric goals, especially when navigating the complexities of aggressive therapies, comorbid conditions, and polypharmacy [41].**Expanding treatment access and affordability** is paramount. Governments and global health agencies must work collaboratively to include novel leukemia therapies in essential drug lists, negotiate price reductions, and implement subsidized treatment schemes. Public–private partnerships could support the rollout of oral agents and supportive therapies in remote areas. Additionally, encouraging pharmaceutical companies to conduct clinical trials in diverse and low-resource populations can help ensure that therapeutic advances are applicable to the elderly worldwide [42].

Enhancing clinical trial inclusion is another key strategy. Historically, older adults have been underrepresented in leukemia trials due to stringent eligibility criteria. This exclusion skews therapeutic evidence and limits our understanding of treatment outcomes in the real-world geriatric population. Trials should adopt more flexible criteria, incorporate geriatric assessments, and evaluate endpoints meaningful to older patients—such as quality of life, functional independence, and caregiver burden [43].**Patient and caregiver support mechanisms** must also be strengthened. Effective communication about prognosis, treatment options, and potential toxicities is essential for shared decision-making. Psychological support, transportation services, home-based care programs, and financial counseling are critical enablers of treatment adherence and follow-up. Digital health tools—such as telemedicine platforms, medication reminders, and remote monitoring devices—can empower elderly patients to manage their illness more effectively, especially those living alone or far from treatment centers [43].**Research and policy innovation**should focus on addressing the social determinants of health that disproportionately affect elderly leukemia patients. National cancer control plans should prioritize geriatric leukemia care through dedicated funding, workforce training, and registry development. Additionally, more investment is needed in implementation science to study how best to scale proven interventions—like hypomethylating agent-venetoclax combinations or BTK inhibitors—across diverse healthcare systems (Table 2) [44].

Table 2: Strategies to Improve Leukemia Care in the Elderly

Intervention Area	Proposed Strategy	Expected Benefit
Diagnosis	Early screening, molecular testing, telepathology	Timely and accurate diagnosis
Treatment	Geriatric-adapted regimens, targeted therapy	Reduced toxicity, improved tolerance
Access	Insurance support, outreach programs	Enhanced treatment equity
Research	Inclusive clinical trials	Evidence-based geriatric care

Conclusion

Difficult leukemias in the geriatric population pose a formidable challenge at the intersection of biology, clinical care, and health equity. While remarkable therapeutic advancements have redefined treatment possibilities in recent years, their full impact remains out of reach for many older adults due to persistent gaps in diagnosis, access, and individualized care. Chronological age alone should no longer dictate therapeutic limitations; rather, a nuanced, multidimensional understanding of each patient's physiological reserve, comorbid burden, and social context must guide clinical decisions.

Bridging these gaps requires a paradigm shift—one that integrates geriatric principles into hematologic oncology, promotes early and equitable access to diagnostic and therapeutic tools, and amplifies the voices of elderly patients in clinical research and policy-making. Ensuring that elderly patients are not merely surviving but living with dignity and quality should be central to all efforts in leukemia care. This includes strengthening supportive infrastructure, enhancing caregiver engagement, and adopting metrics of success that resonate with the values and preferences of older adults.

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