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Editorial

Chemotherapy-free approaches in acute lymphoblastic leukemia: A new paradigm in precision oncology

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Over the past two decades, the treatment of acute lymphoblastic leukemia (ALL) has witnessed a remarkable transformation. With a growing understanding of leukemogenesis and molecular profiling, there has been a decisive shift away from traditional, highly toxic chemotherapeutic regimens, especially in older adults or those with comorbidities toward targeted and immunotherapeutic approaches. The goal of these newer strategies is not only disease eradication but also improved tolerability, quality of life, and achieving more personalization. Cure rates in pediatric ALL are now exceeding 90%, but in adults, particularly those over 60 years, the outcomes remain dismal, with long-term survival ranging from 20 to 40% despite intensive chemotherapy. The outcomes in adolescent and young adult are intermediate, although at the cost of variable tolerance and considerable toxicity. This gap is mainly driven by poor tolerability and adverse disease biology.[1]

Ph-POSITIVE ALL

Combining tyrosine kinase inhibitors (TKIs) with chemotherapy in Ph-positive ALL did improve 5-year overall survival (OS) markedly from about 20% with conventional chemotherapy to 50% with second-generation TKIs and chemotherapy in adults and even to about 70% with ponatinib (third-generation TKI with BCR-ABL1 activity) alongside conventional chemotherapy with double the rate of measurable residual disease (MRD) negativity.[2] Still, these protocols have considerable amounts of chemotherapy and carry consequent toxicity risks.

Notably, in India, chemotherapy-induced myelosuppression and neutropenia are a more significant infection risk than in the West, and prolonged treatment duration with myelotoxic agents is also a cause for socioeconomic fatigue and treatment abandonment.

Recently, it has been shown that various combinations of TKIs, bispecific T-cell engagers (BiTEs) like blinatumomab,[3] antibody drug conjugates (ADC) like inotuzumab ozogamicin,[4] and allosteric inhibitors like asciminib in appropriate subsets without or with minimal conventional chemotherapy can achieve high complete remission (CR) rates and deep molecular responses (DMR) while minimizing toxicity and treatment-related mortality substantially.

The dasatinib plus alternating blinatumomab and chemotherapy trial combined dasatinib with blinatumomab, achieving a 3-year OS of 80.7% and event-free survival (EFS) of 74.6% at a median follow-up of 53 months. This regimen not only eliminated the need for chemotherapy but also dramatically reduced treatment-related toxicity in patients with a median age in their 60s. The concern for the emergence of T315I clones, which is high when using first/second-

generation TKI-chemotherapy, is significantly lower when blinatumomab is combined with even second-generation TKIs as it can eliminate such resistant and treatment-emergent clones better.[5]

Going a step further, a phase II study at MD Anderson Cancer Center combined ponatinib with blinatumomab. The results were striking, with CR/CRi in 100% of patients and a complete molecular response (CMR) in 87%, with 1-year OS and EFS rates of 100% in newly diagnosed Ph+ ALL patients. Such results underscore the synergistic potential of targeting surface antigens and intracellular kinase pathways. These figures represent a massive improvement over historical outcomes with conventional chemotherapy alone or even those with TKI-chemotherapy at least in terms of initial impressions.[6]

Resistance mutations, especially T315I, have long plagued TKI-chemotherapy strategies. Asciminib, the first-in-class allosteric sequential TKI and minimal chemotherapy platform inhibitor, offers a novel mechanism by targeting the myristoyl pocket of ABL1 rather than the ATP-binding site. In a phase I trial combining asciminib with dasatinib and prednisone in newly diagnosed Ph+ ALL, all evaluable patients achieved CR within one month, and 71% showed a 3-log BCR-ABL1 transcript reduction by three months .[7]

Ph-NEGATIVE ALL

Inotuzumab ozogamicin, an anti-CD22 ADC, has demonstrated great utility in minimal toxicity approaches for Ph-negative ALL. In the EWALL-INO trial, which combined fractionated inotuzumab with low-intensity chemotherapy in older adults with newly diagnosed CD22+ B-ALL, CR rates reached 100%. Flow cytometry (FCM) showed MRD negativity in 95% and next-generation sequencing (NGS) in 73%. The estimated 3-year OS was an impressive 89%. These results underscore the potential of inotuzumab to induce rapid apoptosis in CD22-expressing blasts and achieve DMR.[8]

Dr. Kantarjian and Dr. Nitin Jain's group at MD Anderson has extensively studied lower doses of inotuzumab and Hyper CVAD (Ino-MiniHCVD) and its various modifications in young and elderly and combinations with sequential blinatumomab followed by maintenance in Ph-negative ALL with reduced toxicity and promising survival. The elderly population (median age–68 years) has shown a remarkable 5-year progression free survival (PFS) of 44% in Ph-negative ALL.[9]

Further supporting this approach, a US intergroup pilot trial led by the Alliance Cooperative Group treated 23 older adults with CD22+ B-ALL using inotuzumab for cytoreduction followed by blinatumomab. With a median age of 71 years, the cumulative CR rate was 97%, and at a 22-month median follow-up, the 1-year OS and EFS rates were 84% and 75%, respectively.[10]

The EWALL-BOLD trial from the GMALL group applied blinatumomab in a phased approach for Ph-negative ALL in patients aged 56–76 years. After one chemotherapy cycle, patients received multiple cycles of blinatumomab alternating with age-adapted chemotherapy. The hematologic CR rate rose from 76 to 85%, and the molecular CR rate increased from 18% post-chemotherapy to 82% after blinatumomab. The 3-year OS reached 67%, compared to 49% in historical chemotherapy cohorts.[11]

Similarly, the Southwest Oncology Group (now part of SWOG Cancer Research Network) 1318 study in older patients utilizing blinatumomab 1–2 cycles in induction and 3 in consolidation followed by POMP (6-Mercaptopurine + Vincristine + Methotrexate + Prednisone) maintenance for 18 months demonstrated 3-year OS and DFS rates approaching 85% and 80%, respectively.[12]

The boldest evolution is the integration of upfront CAR-T cell therapy. The MD Anderson group explores the feasibility and efficacy of CD19-directed CAR-T cells as frontline therapy in adult B-ALL. Although data remains early, the rationale lies in bypassing chemotherapy entirely in favor of a one time curative immune-based modality.

While these chemotherapy-free approaches offer unprecedented depth and durability of response, several issues warrant attention:

Central nervous system (CNS) prophylaxis

Despite deep systemic remissions, isolated CNS relapses remain a concern due to poor blood-brain barrier penetration of most TKIs and antibodies. Even with rigorous CNS prophylaxis (often through multiple intrathecal chemotherapy doses), isolated CNS relapses are observed in approximately 10–15% of patients.

MRD-guided strategies

Next-generation FCM and NGS-based MRD monitoring are essential to tailor therapy intensity and duration while escalating and de-escalating protocols and predicting relapse risk.

Prospective randomized trials

Direct comparisons with conventional regimens are limited. Trials comparing chemotherapy-free versus standard induction approaches are crucial.

Patient selection

Older or comorbid patients may benefit most, but biomarkers to predict responders are urgently needed, especially for

those with high-risk genetic features.

Chemotherapy-free regimens in ALL are no longer aspirational – they are evidence-based, feasible, and increasingly becoming standard in defined populations. From TKIs and BiTEs to ADCs and CAR-T, we are witnessing a convergence of precision tools that strike leukemia at its core while preserving patient function. The integration of blinatumomab with second- and third-generation TKIs has already transformed the management of Ph+ ALL, yielding CR rates of 95–100%, CMR rates between 60% and 87%, and 3 to 5-year OS rates exceeding 70–80% in several studies. Meanwhile, asciminib and inotuzumab ozogamicin are adding further prowess to our therapeutic arsenal. Although long-term follow-up is still needed and challenges such as CNS relapse persist, these data signal that chemotherapy-free regimens may soon redefine the standard of care, particularly for patients who historically fared poorly with conventional chemotherapy. Ongoing trials and real-world data will be critical in refining these strategies, but the message is loud and clear: The era of chemotherapy-dominant ALL treatment is giving way to one of intelligent, individualized precision oncology with cutting-edge science at the forefront.

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