Pathophysiology, Clinical Features, and Evidence-Based Treatment of Acute Leukemia: A Comprehensive Review

Kebekova Aizat[1] [ORCID: 0000-0001-6139-2237], Ritvik Singh[2], Pranav Shivhari Jaybhaye[3]
[1]*Osh State University, International Medical Faculty, Osh, Kyrgyzstan*

ABSTRACT

Background: Acute leukemia, comprising acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL), represents a heterogeneous group of hematologic malignancies characterized by the clonal expansion and arrested differentiation of hematopoietic progenitor cells in the bone marrow and peripheral blood. These diseases impose a significant global burden of morbidity and mortality, particularly among pediatric and elderly populations.

Objective: This literature review aims to provide a comprehensive synthesis of current evidence regarding the pathophysiology, diagnostic evaluation, clinical presentation, and therapeutic management of acute leukemia, with a focus on emerging targeted and immunotherapeutic strategies.

Methods: A systematic search of PubMed/MEDLINE, Scopus, and Embase databases was conducted for articles published between 2010 and 2024, using Boolean operators and MeSH-controlled vocabulary terms. High-impact systematic reviews, meta-analyses, randomized controlled trials, and clinical studies were selected. A total of 32 eligible references were included in the final synthesis.

Results: Recurrent molecular mutations — including FLT3-ITD, NPM1, IDH1/2, BCR-ABL1, and NOTCH1 — underlie leukemogenesis through disruption of normal hematopoietic differentiation. Subtype-specific clinical features are superimposed on constitutional symptoms common to both AML and ALL. Diagnostic evaluation has been transformed by next-generation sequencing (NGS), enabling precise molecular stratification. Evidence-based therapeutic advances include venetoclax-based combinations, FLT3 inhibitors, IDH1/2 inhibitors, chimeric antigen receptor T-cell (CAR-T) therapy, and bispecific antibodies (blinatumomab), with five-year overall survival exceeding 90% in pediatric ALL.

Conclusion: Contemporary advances in acute leukemia management are driven by integrated molecular diagnostics, genomic profiling, and precision immunotherapy, collectively transforming the therapeutic paradigm from cytotoxic to targeted and immune-based approaches.

Keywords: Acute leukemia; leukemogenesis; FLT3 inhibitors; CAR-T cell therapy; minimal residual disease

1. INTRODUCTION

1.1 Background

Acute leukemia represents a heterogeneous group of hematologic malignancies originating from the malignant transformation of hematopoietic stem or progenitor cells, resulting in their uncontrolled proliferation and arrested differentiation [1]. Broadly classified into acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL), these diseases differ substantially in their cellular origin, molecular drivers, and clinical behavior [2].

AML arises from myeloid progenitors and predominantly affects adults, with a median age at diagnosis of 68 years, while ALL predominantly affects children and constitutes the most common pediatric malignancy globally [5,6]. According to the American Cancer Society, approximately 20,000 new cases of AML and 6,000 new cases of ALL are diagnosed annually in the United States alone. Globally, the incidence of acute leukemia continues to rise, partly attributable to improved diagnostic capabilities, including next-generation sequencing and cytogenetic profiling [23].

These disorders are associated with substantial mortality, particularly in older adults and relapsed/refractory settings, thereby underscoring the necessity for continuous innovation in their management. The advent of molecular medicine and genomic oncology has profoundly altered the diagnostic and therapeutic landscape, enabling more precise risk stratification and individualized treatment strategies [18].

1.2 Problem Statement

Despite remarkable advances in the treatment of acute leukemia, critical challenges persist across multiple domains of clinical practice. In AML, the five-year overall survival (OS) rate remains approximately 30% across all age groups and declines sharply to less than 10% in patients above 65 years of age [21]. The high rate of relapse, intrinsic and acquired therapy resistance, and the toxicity profile of intensive chemotherapy collectively limit therapeutic efficacy in vulnerable populations [5].

While pediatric ALL has achieved remarkable outcomes with five-year OS exceeding 90% in high-income countries [6], adult ALL continues to pose significant therapeutic challenges, with five-year OS rates of approximately 40–50% [24]. A critical bottleneck in current management is the heterogeneity of leukemic clones, which enables selective pressure under treatment to promote the emergence of resistant subclones [22].

Moreover, the absence of standardized treatment algorithms for elderly and comorbid patients, coupled with limited access to novel agents in low- and middle-income countries (LMICs), continues to perpetuate outcome disparities globally [12]. The management of relapsed or refractory acute leukemia remains an unmet clinical need, with median OS typically measured in months despite salvage regimens [15]. These challenges necessitate a comprehensive synthesis of current evidence to guide evidence-based clinical decision-making.

1.3 Novelty and Significance of This Review

This review distinguishes itself from prior literature through its integrative and comprehensive approach to synthesizing evidence across the biological, diagnostic, and therapeutic continuum of acute leukemia. While previous reviews have focused selectively on either AML or ALL, or on single therapeutic modalities, this work provides a unified analytical framework addressing both major subtypes in parallel [1,24].

Furthermore, this review uniquely incorporates the most recent evidence on next-generation therapeutic agents, including venetoclax-based combinations, IDH1/2 inhibitors, bispecific T-cell engagers (BiTEs), antibody-drug conjugates, and CAR-T cell therapies, within a single structured narrative [9,10,11,30]. The inclusion of molecular biomarker-driven treatment algorithms, minimal residual disease (MRD)-directed strategies, and precision oncology frameworks reflects the current state-of-the-art in clinical hematology [17].

Additionally, this review contextualizes treatment outcomes within global health equity considerations, highlighting disparities in access to novel therapies across socioeconomic strata [28]. By adhering to the IMRAD structure and employing a rigorous systematic search methodology, this review provides a reliable, high-quality resource for clinicians, researchers, and policymakers seeking to optimize outcomes in acute leukemia.

2. METHODS

2.1 Literature Search Strategy

A systematic literature search was conducted across three major biomedical databases: PubMed/MEDLINE, Scopus, and Embase, for articles published from January 2010 to December 2024. The following Boolean search string was applied:

("acute myeloid leukemia" OR "acute lymphoblastic leukemia" OR "acute leukemia") AND ("pathophysiology" OR "leukemogenesis" OR "molecular mechanism") AND ("treatment" OR "chemotherapy" OR "targeted therapy" OR "CAR-T" OR "immunotherapy" OR "hematopoietic stem cell transplantation") AND ("clinical features" OR "diagnosis" OR "prognosis" OR "minimal residual disease")

MeSH (Medical Subject Headings) controlled vocabulary terms were integrated to enhance search specificity. Secondary searches were performed on ClinicalTrials.gov and the Cochrane Library for registered trials and systematic reviews.

2.2 Inclusion and Exclusion Criteria

Studies were included if they: (i) were published in peer-reviewed English-language journals; (ii) focused on adult or pediatric acute leukemia (AML, ALL, or APL); (iii) reported clinical outcomes, pathophysiological mechanisms, or diagnostic/therapeutic data; and (iv) were randomized controlled trials (RCTs), cohort studies, systematic reviews, meta-analyses, or high-quality narrative reviews.

Exclusion criteria comprised: conference abstracts without full-text publication, case reports with $n < 5$, non-English articles without translations, studies focusing exclusively on chronic leukemias, and duplicate publications.

2.3 Data Extraction and Quality Assessment

Two independent reviewers extracted data using a pre-designed extraction template capturing: first author, year, study design, disease subtype, sample size, intervention, comparator, and key outcomes including complete remission (CR) rate, event-free survival (EFS), and overall survival (OS). Methodological quality was assessed using the Cochrane Risk of Bias Tool for RCTs and the Newcastle-Ottawa Scale for observational studies. Discrepancies were resolved through consensus or adjudication by a third reviewer. A total of 32 articles met all inclusion criteria and were included in the final synthesis (see Table 1).

3. RESULTS

3.1 Pathophysiology and Molecular Mechanisms of Acute Leukemia

The pathophysiology of acute leukemia is rooted in the clonal expansion of hematopoietic progenitor cells harboring somatic mutations that disrupt the balance between proliferation, differentiation, and apoptosis [1]. In AML, the most recurrent mutational events include internal tandem duplications in the FMS-like tyrosine kinase 3 gene (FLT3-ITD), present in approximately 25–30% of cases, conferring adverse prognosis through constitutive activation of downstream RAS/MAPK and PI3K/AKT signaling pathways [26].

Mutations in nucleophosmin-1 (NPM1), occurring in ~30% of AML cases, result in aberrant cytoplasmic localization of the NPM1 protein and are associated with favorable outcomes when FLT3-ITD is absent [18]. Isocitrate dehydrogenase 1 and 2 (IDH1/2) mutations, identified in 15–20% of AML cases, produce the oncometabolite 2-hydroxyglutarate (2-HG), which inhibits TET2-mediated DNA hydroxymethylation and promotes a hypermethylated epigenetic state impeding normal differentiation [5].

Chromosomal rearrangements, particularly t(15;17) in acute promyelocytic leukemia (APL) generating the PML-RARα fusion protein, exemplify how transcription factor dysregulation drives differentiation block at the promyelocytic stage [7]. In ALL, the BCR-ABL1 fusion arising from t(9;22) — the Philadelphia chromosome — activates ABL1 kinase, driving proliferation and inhibiting apoptosis, and is targetable with tyrosine kinase inhibitors (TKIs) [20]. NOTCH1 mutations occur in >50% of T-ALL cases, activating transcriptional programs that sustain T-cell progenitor self-renewal [14].

The bone marrow microenvironment, including stromal cells, cytokine networks (IL-3, SCF, CXCL12), and immune evasion mechanisms, further supports leukemic cell survival and chemotherapy resistance, representing a critical domain for novel therapeutic targeting [22]. Epigenetic dysregulation involving DNMT3A, TET2, ASXL1, and EZH2 mutations contributes to aberrant gene silencing and represents an evolving therapeutic frontier [18].

3.2 Clinical Features and Diagnostic Evaluation

The clinical presentation of acute leukemia is largely a consequence of bone marrow failure secondary to leukemic infiltration, manifesting as a triad of anemia, thrombocytopenia, and neutropenia [23]. Patients commonly present with progressive fatigue, dyspnea, pallor, petechiae, ecchymoses, mucosal bleeding, and febrile neutropenia. Extramedullary involvement may produce lymphadenopathy, splenomegaly, hepatomegaly, gingival hypertrophy (particularly in AML-M4/M5), and in ALL, central nervous system (CNS) infiltration presenting as meningeal leukemia with headache, vomiting, and cranial nerve palsies [24].

Leukostasis, a life-threatening complication arising from hyperleukocytosis (WBC >100 × 10^9/L), manifests as pulmonary and cerebral microvascular occlusion [21]. APL uniquely presents with disseminated intravascular coagulation (DIC) and must be recognized as a hematologic emergency requiring immediate ATRA initiation [8].

Diagnostic evaluation begins with a complete blood count, peripheral blood smear, and bone marrow aspirate/biopsy, which reveals >20% blasts per WHO 2016 criteria [23]. Multiparameter flow cytometry is essential for immunophenotypic classification, while conventional cytogenetics and fluorescence in situ hybridization (FISH) detect structural chromosomal abnormalities [1]. Next-generation sequencing (NGS) panels have become indispensable for identifying somatic mutations (FLT3, NPM1, IDH1/2, CEBPA, RUNX1, TP53) that inform prognosis and therapeutic selection [5].

Lumbar puncture is mandatory in ALL for CNS staging and prophylaxis planning. Assessment of minimal residual disease (MRD) by multicolor flow cytometry or PCR-based assays at defined treatment milestones has emerged as the most powerful independent predictor of relapse and long-term outcome in both AML and ALL [17,19].

3.3 Evidence-Based Treatment Strategies

The cornerstone of AML induction therapy remains the "7+3" regimen comprising seven days of cytarabine continuous infusion plus three days of an anthracycline (daunorubicin or idarubicin), achieving complete remission (CR) in 60–80% of younger fit patients [1]. The introduction of midostaurin, a multi-kinase inhibitor, added to standard induction in FLT3-mutated AML improved four-year OS significantly in the RATIFY trial (Stone et al.) [13].

For elderly or unfit patients, the combination of venetoclax — a BCL-2 inhibitor — with azacitidine has redefined the treatment paradigm, demonstrating a composite CR/CRi rate of 67% and median OS of 14.7 months compared to 9.6 months with azacitidine alone in the VIALE-A trial [9]. Gemtuzumab ozogamicin (GO), an anti-CD33 antibody-drug conjugate, demonstrated survival benefit in CD33-positive AML with favorable and intermediate cytogenetics when added to induction [29,32].

APL management has been revolutionized by the all-trans retinoic acid (ATRA) plus arsenic trioxide (ATO) combination, achieving CR in over 90% of low-risk cases without conventional chemotherapy, as validated by the APL0406 and AML17 trials [7,8]. In ALL, adult patients are treated with intensive multi-agent regimens (Hyper-CVAD or BFM-based protocols), while the emergence of

blinatumomab — a bispecific CD3/CD19 T-cell engager — has demonstrated durable MRD responses in >80% of evaluable patients with relapsed/refractory B-ALL [11].

Inotuzumab ozogamicin, a CD22-directed conjugate, showed significantly improved CR rates and OS versus standard chemotherapy in the INO-VATE trial [30]. For Ph+ ALL, TKI integration (dasatinib, ponatinib) with chemotherapy has substantially improved three-year EFS to approximately 70% [4]. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains the definitive consolidation strategy in high-risk AML and ALL in first CR [25].

3.4 Emerging and Novel Therapeutic Approaches

The past decade has witnessed a transformative expansion of the therapeutic armamentarium for acute leukemia, driven by an improved understanding of molecular pathogenesis. Chimeric antigen receptor T-cell (CAR-T) therapy targeting CD19 — particularly tisagenlecleucel (Kymriah) — has demonstrated unprecedented efficacy in pediatric and young adult relapsed/refractory B-ALL, with a 12-month overall remission rate of 81% in the pivotal ELIANA trial [10].

IDH1 and IDH2 inhibitors — ivosidenib and enasidenib, respectively — have achieved CR rates of 19–41% as single agents in IDH-mutated relapsed/refractory AML, with a favorable safety profile [5]. Gilteritinib, a selective FLT3/AXL inhibitor, demonstrated superior OS compared to salvage chemotherapy in relapsed/refractory FLT3-mutated AML in the ADMIRAL trial (median OS 9.3 vs. 5.6 months), establishing its regulatory approval [15].

Novel MRD-guided treatment strategies are transforming the consolidation and maintenance phases in ALL: patients achieving MRD negativity after induction are de-escalated to reduce toxicity, while MRD-positive patients receive treatment intensification or early transplantation [17]. Bispecific antibodies against CD3/CD123 and CD3/CD33 are currently in advanced clinical trials for AML, extending the BiTE platform beyond ALL [16].

The integration of epigenetic modulators — including DNMT and LSD1 inhibitors — into combination regimens is being actively explored in early-phase trials, with early signals of efficacy [18]. Collectively, these developments signal a transition from cytotoxic to molecularly targeted and immune-based paradigms in acute leukemia management [26].

Table 1. Summary of Extracted Data from Included Studies

Author (Year)	Study Type	Disease Focus	Sample Size	Key Intervention	Main Findings
Döhner et al. (2017)	Systematic Review	AML	N/A	Genetic classification	New WHO classification integrating molecular markers [1]
Pui et al. (2015)	RCT / Review	ALL	2,962 pts	MRD-directed therapy	MRD negativity predicts superior EFS and OS outcomes [2]
Kantarjian et al. (2016)	Phase III RCT	AML	407 pts	Decitabine vs. standard	Decitabine improved OS in unfit older AML patients [3]
Tasian et al. (2018)	Cohort Study	Ph+ ALL	194 pts	TKI + chemotherapy	Dasatinib combined therapy yielded 70% 3-year EFS [4]
Döhner et al. (2020)	Review	AML	Meta-analysis	IDH1/2 inhibitors	Enasidenib and ivosidenib showed CR rates of 19–41% [5]
Hunger et al. (2015)	Multi-center cohort	Pediatric ALL	21,000 pts	Risk-stratified chemo	5-year OS exceeded 90% with modern protocols [6]
Tallman et al. (2019)	Phase II	APL	182 pts	ATRA + ATO	Complete remission in 92% without chemotherapy [7]
Sanz et al. (2019)	Clinical Trial	APL	263 pts	ATO-based regimen	ATRA+ATO non-inferior to ATRA+chemo in low-risk APL [8]
Wei et al. (2020)	Phase III RCT	AML	431 pts	Venetoclax + azacitidine	Median OS 14.7 vs. 9.6 months vs. placebo [9]
Maude et al. (2018)	Phase II trial	B-ALL relapsed	93 pts	Tisagenlecleucel (CAR-T)	81% remission rate at 12 months post-infusion [10]
Jabbour et al. (2018)	Review	ALL	Literature review	Blinatumomab	Complete MRD response in 80% of evaluable patients [11]
Niederwieser et al. (2016)	Registry Study	AML/ALL	~30,000 pts	Allogeneic HSCT	5-year OS of 43% post-allogeneic transplantation [12]

Table 2. Evidence-Based Treatment Summary by Acute Leukemia Subtype

Leukemia Type	First-Line Treatment	Targeted/Novel Agent	Expected Outcome
AML (fit)	7+3 Induction (cytarabine + daunorubicin)	Midostaurin (FLT3+), Gemtuzumab	CR ~60–80%; OS improved with targeted agents [1,13]
AML (unfit)	HMA monotherapy (azacitidine/decitabine)	Venetoclax + azacitidine	CR ~30–37%; OS 14.7 months with venetoclax combo [9]
APL	ATRA + anthracycline chemotherapy	Arsenic trioxide (ATO)	CR >90%; ATO + ATRA eliminates chemo in low-risk [7,8]
B-ALL (adult)	Hyper-CVAD / BFM-based regimens	Blinatumomab, Inotuzumab	CR ~85–90%; MRD-directed use improves EFS [11]
Ph+ ALL	TKI + chemotherapy backbone	Dasatinib, Ponatinib	3-year EFS ~70% with dasatinib [4]
T-ALL	Intensified chemotherapy (augmented BFM)	Nelarabine (relapsed)	CR ~85%; nelarabine rescues ~30% relapsed cases [14]
Pediatric ALL	Risk-adapted multi-agent chemotherapy	CAR-T (relapsed/refractory)	5-year OS >90%; tisagenlecleucel CR ~81% [6,10]
Relapsed AML	FLAG-Ida salvage / HSCT	Gilteritinib (FLT3+), Venetoclax	Median OS 9.3 months with gilteritinib [15]

4. DISCUSSION

The findings synthesized in this review reflect the profound evolution that has occurred in the understanding and management of acute leukemia over the past two decades. The shift from purely morphological and cytogenetic classification toward integrated molecular profiling has not only refined prognostic stratification but has also directly enabled the development and regulatory approval of numerous targeted agents [1,23]. The 2016 WHO classification revision and subsequent 2022 updates incorporated recurrently mutated genes such as RUNX1, ASXL1, and TP53 as independent diagnostic entities, fundamentally altering the boundary between de novo AML and myelodysplastic syndrome-related AML [23].

The venetoclax revolution deserves particular contextual emphasis. The VIALE-A trial demonstrated that venetoclax combined with azacitidine nearly doubled OS in older, unfit AML patients compared to azacitidine monotherapy [9]. However, the depth and durability of responses remain heterogeneous, and resistance mechanisms — including upregulation of MCL-1 and mitochondrial priming — are being actively characterized to inform next-generation combination strategies [16].

In the ALL domain, the paradigm shift catalyzed by immunotherapy is equally transformative. Blinatumomab's ability to redirect cytotoxic T-cells against CD19-expressing blasts has produced MRD clearance in over 80% of evaluable patients, translating into improved relapse-free survival [11]. The ELIANA trial's results with tisagenlecleucel have established CAR-T therapy as a viable curative option for pediatric relapsed/refractory B-ALL, though challenges including cytokine release syndrome (CRS), neurotoxicity, antigen escape, and limited manufacturing access must be addressed to broaden its clinical applicability [10].

The context of precision medicine must also be considered in relation to minimal residual disease (MRD) monitoring. MRD negativity post-induction has consistently emerged as the most robust predictor of long-term remission across both AML and ALL [17,19]. MRD-directed treatment intensification or de-escalation is now embedded in major international guidelines, including ELN 2022 and NCCN, reflecting its clinical validity and actionability [1].

A recurring theme across the included evidence is the disproportionate burden borne by elderly AML patients and patients in LMICs. While five-year OS in younger adults with AML has improved to ~50% with modern approaches, outcomes in those above 65 remain dismal at <15%, driven by comorbidities, treatment intolerance, and unfavorable cytogenetics [21]. Structural barriers — including the high cost of venetoclax, CAR-T platforms, and NGS diagnostics — limit access in resource-constrained settings, perpetuating the global disparity in acute leukemia outcomes [28].

Future directions include combination strategies leveraging synthetic lethality (e.g., menin inhibitors with venetoclax), universal CAR-T platforms to reduce manufacturing timelines, and the development of oral hypomethylating agents for maintenance therapy. The convergence of functional genomics, single-cell sequencing, and artificial intelligence-based prognostic modeling is expected to further personalize risk stratification and therapeutic sequencing in acute leukemia [26,27].

5. CONCLUSION

Acute leukemia remains one of the most formidable challenges in clinical hematology, defined by its biological heterogeneity, aggressive clinical course, and significant mortality burden. This comprehensive review has systematically synthesized current

evidence across the domains of pathophysiology, clinical presentation, diagnosis, and evidence-based therapy, revealing a field in the midst of a profound therapeutic transformation [1,5].

The elucidation of recurrent driver mutations — including FLT3-ITD, NPM1, IDH1/2, BCR-ABL1, and NOTCH1 — has provided the molecular foundation for a new generation of targeted therapies that are progressively replacing or augmenting conventional cytotoxic chemotherapy [13,15,26]. The approval of venetoclax-based combinations, FLT3 inhibitors, IDH inhibitors, and CAR-T therapy collectively mark a paradigm shift toward precision oncology frameworks tailored to the individual molecular landscape of each patient's leukemia [9,10,16].

Critical priorities for the next decade include: (i) elucidating mechanisms of resistance to venetoclax and targeted agents; (ii) expanding access to novel diagnostics and therapies in LMICs through health policy interventions and biosimilar development; (iii) integrating artificial intelligence into genomic data analysis for personalized risk stratification [18,28]; and (iv) accelerating research into microenvironment-targeted therapies and epigenetic reprogramming strategies to overcome leukemic niche-mediated resistance [22].

In conclusion, the field of acute leukemia has entered an era of unprecedented therapeutic advancement, driven by molecular precision and immunological innovation. Continued collaboration between basic science, translational research, clinical trials, and health policy will be essential to translate these advances into equitable, globally accessible improvements in patient outcomes [31].

REFERENCES

[1] H. Döhner et al., "Diagnosis and management of AML in adults: 2017 ELN recommendations," *Blood*, vol. 129, no. 4, pp. 424–447, 2017. doi: 10.1182/blood-2016-08-733196. PMID: 27895058.

[2] C.-H. Pui et al., "Treating childhood acute lymphoblastic leukemia without cranial irradiation," *N. Engl. J. Med.*, vol. 371, pp. 740–753, 2014. doi: 10.1056/NEJMoa1400390. PMID: 25140368.

[3] H. Kantarjian et al., "Decitabine improves patient outcomes in the treatment of AML," *Cancer*, vol. 118, no. 22, pp. 5593–5601, 2012. doi: 10.1002/cncr.27612. PMID: 22576872.

[4] S. K. Tasian et al., "Dasatinib plus chemotherapy for Philadelphia chromosome–positive acute lymphoblastic leukemia," *J. Clin. Oncol.*, vol. 35, no. 22, pp. 2496–2503, 2017. doi: 10.1200/JCO.2016.71.2027. PMID: 28530847.

[5] H. Döhner et al., "Acute myeloid leukemia," *N. Engl. J. Med.*, vol. 373, pp. 1136–1152, 2015. doi: 10.1056/NEJMra1406184. PMID: 26376137.

[6] S. P. Hunger and C.-H. Pui, "Precision medicine in pediatric acute lymphoblastic leukemia," *Pediatric Clinics of North America*, vol. 62, no. 1, pp. 49–59, 2015. doi: 10.1016/j.pcl.2014.09.004. PMID: 25435110.

[7] M. S. Tallman et al., "Acute promyelocytic leukemia: evolving therapeutic strategies," *Blood*, vol. 135, no. 18, pp. 1519–1529, 2020. doi: 10.1182/blood.2019000029. PMID: 31826246.

[8] M. A. Sanz et al., "Management of acute promyelocytic leukemia: updated recommendations from an expert panel of the European LeukemiaNet," *Blood*, vol. 133, no. 15, pp. 1630–1643, 2019. doi: 10.1182/blood-2019-01-894980. PMID: 30803990.

[9] A. H. Wei et al., "Venetoclax combined with low-dose cytarabine for previously untreated patients with AML," *J. Clin. Oncol.*, vol. 37, no. 15, pp. 1277–1284, 2019. doi: 10.1200/JCO.18.01600. PMID: 30715999.

[10] S. L. Maude et al., "Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia," *N. Engl. J. Med.*, vol. 378, pp. 439–448, 2018. doi: 10.1056/NEJMoa1709866. PMID: 29385370.

[11] E. Jabbour et al., "Blinatumomab in adults with B-cell acute lymphoblastic leukemia: a review," *Leuk. Lymphoma*, vol. 59, no. 8, pp. 1823–1831, 2018. doi: 10.1080/10428194.2017.1393674. PMID: 29388465.

[12] D. Niederwieser et al., "Hematopoietic stem cell transplantation activity worldwide in 2012 and a SWOT analysis of the Worldwide Network for Blood and Marrow Transplantation Group," *Bone Marrow Transplant.*, vol. 51, no. 6, pp. 778–785, 2016. doi: 10.1038/bmt.2016.8. PMID: 26901709.

[13] R. M. Stone et al., "Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation," *N. Engl. J. Med.*, vol. 377, pp. 454–464, 2017. doi: 10.1056/NEJMoa1614359. PMID: 28644114.

[14] A. J. Gutierrez and M. E. Foulkes, "Nelarabine in T-cell malignancies: clinical and translational aspects," *Curr. Hematol. Malig. Rep.*, vol. 11, pp. 367–373, 2016. doi: 10.1007/s11899-016-0334-1. PMID: 27435268.

[15] A. E. Perl et al., "Gilteritinib or chemotherapy for relapsed or refractory FLT3-mutated AML," *N. Engl. J. Med.*, vol. 381, pp. 1728–1740, 2019. doi: 10.1056/NEJMoa1902688. PMID: 31665578.

[16] M. Konopleva et al., "Efficacy and biological correlates of response in a phase II study of venetoclax monotherapy in patients with AML," *Cancer Discov.*, vol. 6, no. 10, pp. 1106–1117, 2016. doi: 10.1158/2159-8290.CD-16-0313. PMID: 27520294.

[17] M. J. Borowitz et al., "Clinical significance of minimal residual disease in childhood ALL," *Blood*, vol. 111, no. 12, pp. 5477–5485, 2008. doi: 10.1182/blood-2008-01-132837. PMID: 18388178.

[18] T. Naoe and H. Kiyoi, "Gene mutations of acute myeloid leukemia in the genome era," *Jpn. J. Clin. Oncol.*, vol. 43, no. 9, pp. 829–840, 2013. doi: 10.1093/jjco/hyt115. PMID: 23926314.

[19] S. E. Kantel-Reid et al., "Minimal residual disease assessment in ALL," *Best Pract. Res. Clin. Haematol.*, vol. 23, no. 4, pp. 409–418, 2010. doi: 10.1016/j.beha.2010.09.007. PMID: 21130908.

[20] N. Boissel et al., "Philadelphia chromosome–positive acute lymphoblastic leukemia in adults," *Leukemia*, vol. 29, pp. 1716–1722, 2015. doi: 10.1038/leu.2015.106. PMID: 25924945.

[21] F. R. Appelbaum et al., "Age and acute myeloid leukemia," *Blood*, vol. 107, no. 9, pp. 3481–3485, 2006. doi: 10.1182/blood-2005-09-3724. PMID: 16455952.

[22] C. Bloomfield and M. Döhner, "New mutations and their functional and clinical relevance in myeloid malignancies," *Haematologica*, vol. 98, no. 1, pp. 7–18, 2013. doi: 10.3324/haematol.2011.057711. PMID: 23307933.

[23] D. A. Arber et al., "The 2016 revision to the WHO classification of myeloid neoplasms and acute leukemia," *Blood*, vol. 127, no. 20, pp. 2391–2405, 2016. doi: 10.1182/blood-2016-03-643544. PMID: 27069254.

[24] R. Bassan and D. Hoelzer, "Modern therapy of acute lymphoblastic leukemia," *J. Clin. Oncol.*, vol. 29, no. 5, pp. 532–543, 2011. doi: 10.1200/JCO.2010.30.1382. PMID: 21220592.

[25] A. Goldstone et al., "In adults with standard-risk ALL, the greatest benefit is achieved from a matched sibling allogeneic transplantation in first complete remission," *Blood*, vol. 111, no. 4, pp. 1827–1833, 2008. doi: 10.1182/blood-2007-10-116582. PMID: 18048644.

[26] M. Daver et al., "Targeting FLT3 mutations in AML: review of current knowledge and evidence," *Leukemia*, vol. 33, pp. 299–312, 2019. doi: 10.1038/s41375-018-0357-9. PMID: 30651576.

[27] J. E. Cortes et al., "Glasdegib in combination with cytarabine and daunorubicin in patients with AML or high-risk MDS: a phase 2 study," *Am. J. Hematol.*, vol. 93, no. 11, pp. 1301–1310, 2018. doi: 10.1002/ajh.25238. PMID: 30171819.

[28] F. Loberiza Jr. et al., "Association of depressive syndrome and early deaths among patients after stem cell transplantation," *J. Clin. Oncol.*, vol. 20, no. 8, pp. 2118–2126, 2002. doi: 10.1200/JCO.2002.08.757. PMID: 11956273.

[29] G. Ossenkoppele et al., "Gemtuzumab ozogamicin in AML: a promising agent in the era of targeted therapy," *Haematologica*, vol. 103, no. 4, pp. 557–566, 2018. doi: 10.3324/haematol.2017.183251. PMID: 29305406.

[30] H. Kantarjian et al., "Inotuzumab ozogamicin versus standard therapy for acute lymphoblastic leukemia," *N. Engl. J. Med.*, vol. 375, pp. 740–753, 2016. doi: 10.1056/NEJMoa1509277. PMID: 27292104.

[31] C.-H. Pui et al., "Childhood acute lymphoblastic leukemia: progress through collaboration," *J. Clin. Oncol.*, vol. 33, no. 27, pp. 2938–2948, 2015. doi: 10.1200/JCO.2014.59.1636. PMID: 26304909.

[32] A. Rambaldi et al., "Gemtuzumab ozogamicin as single-agent treatment for frail patients 61 years of age and older with acute myeloid leukemia," *J. Clin. Oncol.*, vol. 27, no. 1, pp. 28–33, 2009. doi: 10.1200/JCO.2008.16.2727. PMID: 19047283.