Proceedings of ICBioMed 2025 Symposium: AI for Healthcare: Advanced Medical Data Analytics and Smart Rehabilitation
DOI: 10.54254/2753-8818/2025.AU27356

Molecular Pathogenesis and Evolving Precision Medicine in Leukemia

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Abstract. Leukemia is a complex and heterogeneous group of malignancies that arise within the hematological system, originating in the bone marrow. It is fundamentally characterized by the uncontrolled proliferation and accumulation of immature, non-functional white blood cells, which disrupt normal hematopoiesis and leads to classic symptoms of infection, anemia, and bleeding. This overview examines the molecular mechanism of disease, diagnostic evolution, and therapeutic advancements. The pathogenesis is not driven by a single genetic mutation but rather by a collaborative genetic lesion that affect cellular growth, differentiation, and cell death. Diagnostically, the field has progressed from traditional morphology and cytogenetics to incorporate advanced molecular profiling. The adoption of (Next-generation Sequencing) NGS allows for the comprehensive identification of driver mutations and prognostic markers, while digital PCR and flow cytometry provide effective and sensitive tools for monitoring minimal residual disease (MRD). The therapeutic ways have evolved significantly, shifting from conventional chemotherapy and radiation towards the modern management which guided by the individual genetic profile of a patient's leukemia. The future of leukemia treatment lies in the deeper integration of continuous, non-invasive monitoring tools like liquid biopsy, which analyzes circulating tumour DNA from a simple blood draw. By combining this dynamic data with multi-omics analyses and artificial intelligence, clinicians aim to formulate highly dynamic and adaptable treatment strategies. The goal is to overcome drug resistance, prevent relapse, and to cure all subtype of leukemia.

Keywords: Leukemia, Molecular Pathogenesis, Diagnosis, Therapies

1. Introduction

Leukemia is not a single disease, but rather a complex and heterogenous group of malignant disorders that originate in the hematopoietic system, primarily targeting the bone marrow [1,2]. This disease begins when the genetic material in an immature blood cell or blast, become damage, triggering a cascade of uncontrolled proliferation. This results a mass production of abnormal, non-functional white blood cells that overcrowd the limited space of bone marrow which disrupt normal hematopoiesis. Consequently, patients often present with a classic symptom because of disease. Overwhelming fatigue and a characteristically pale complexion are directly caused by anemia, which is a critical shortage of oxygen-carrying red blood cells. It also causes increased susceptibility

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to infections from neutropenia, leaving patients vulnerable to frequent and serve infections. More seriously aspect is that a lack of platelets which is thrombocytopenia can manifest as easy bruising, prolonged bleeding from small wounds. In many cases, these signs of bone marrow failure are compounded by symptoms of organ infiltration, as the cancerous cells spill into the bloodstream and invade other tissue, potentially causing swelling in the lymph nodes, liver, or spleen. The treatment of leukemia is an extremely complex process, requiring the detailed treatment plans based on the specific subtype of the disease, its unique genetic and molecular profile, and key characteristics of the patient, such as age and overall health. Traditionally, chemotherapy and radiation function as important tool which aim at inducing remission and eradicating residual disease. Advances in precision medicine have introduced targeted therapies, such as tyrosine kinase inhibitors, which designed to precisely block the function of abnormal proteins that drive the uncontrolled growth of certain leukemia, offering a more effective and less toxic alternative to traditional chemotherapy. Immunotherapeutic approaches that harness the body's own immune system to fight cancer, such as monoclonal antibodies and chimeric antigen receptor (CAR) T-cell therapy, effectively reprogram immune cells to attack leukemic cells. This essay will investigate the mechanism underlying leukemia, explore its diagnostic tools that allow for its precise classification, and critically describe and examine therapeutic interventions with its evolving landscape.

2. Mechanism

Leukemia is traditionally classified into four subtypes based on disease tempo (acute or chronic) and cell lineage (myeloid or lymphoid) (Table 1): Acute Lymphoblastic Leukemia (ALL), Acute Myelogenous Leukemia (AML), Chronic Lymphocytic Leukemia (CLL) and Chronic Myelogenous Leukemia (CML). Despite this clinical variation, all leukemias share a common molecular origin: genetic mutations that disrupt normal life cycle of a single hematopoietic stem or progenitor cell within the bone marrow. These mutations interfere with fundamental processes such as cell division, differentiation, and apoptosis. However, modern molecular research has refined this review, showing that leukemia does not usually result from a single mutation, but rather through the collaboration between at least two functional classes of genetic lesions [3].

Class I mutations drive uncontrolled proliferative and enhance cell survival by constitutively activating signal transduction pathways. For example, the BCR-ABL fusion oncoprotein in CML, resulting from the t(9;22) translocation [3]. This chimeric oncogene exhibits unregulated tyrosine kinase activity, leading to the continuous activation of downstream effectors like RAS, JAK-STAT, and PI3K. This led to growth factor-independent cell cycle progression and reduced apoptosis. Similarly, internal tandem duplication (ITD) in the FLT3 gene, frequently found in AML, cause ligand-independent dimerization and autophosphorylation of this receptor tyrosine kinase, triggering identical pro-survival and proliferative signals [3].

However, Class I mutation are insufficient alone to cause acute leukemia. They require cooperation with Class II mutations, which primarily impair normal hematopoietic differentiation and apoptosis. For instance, the t(8;21) translocation in AML generates the AML-ETO (RUNX1-RUNX1T1) fusion. This abnormal transcription factor acts in a dominant-negative manner, interfering with the native core-binding factor (CBF) complex and altering the expression of genes vital for myeloid maturation [3]. When hematopoietic progenitor cells acquire both types of mutations simultaneously, a powerful carcinogenic effect is produced. The Class I lesion provides continuous proliferation signals, promoting cell expansion, while Class II lesion impose stop signals during cell maturation. This combination leads to the rapid accumulation of cell clones that not only proliferate uncontrollably but also fail to differentiate, which is the hallmark of acute leukemia.

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Table 1. Four subtypes of Leukemia

Subtype	Key Features	Typical Patient Demographics	Common Symptoms
Acute Lymphoblastic Leukemia (ALL)	Aggressive cancer of immature lymphocytes. Most common childhood leukemia [1].	Peak in children (3-5 years old); smaller peak in adults >50.	Fever, fatigue, bleeding, bone pain, frequent infections [1].
Acute Myelogenous Leukemia (AML)	Cancer of immature myeloid cells (blasts). Leads to bone marrow failure [1].	Most common acute leukemia in adults [4]; incidence increase with age.	Fatigue, weakness, easy bruising, mucosal bleeding, fever, infections [1,4].
Chronic Lymphocytic Leukemia (CLL)	Slow accumulation of mature but dysfunctional lymphocytes [1]. Often asymptomatic early on.	Primarily affects older adults; median age at diagnosis around 70.	Often asymptomatic; found incidentally. Lymphadenopathy, splenomegaly, fatigue [1].
Chronic Myelogenous Leukemia (CML)	Progresses through chronic, accelerated, and blast phases. Defined by the Philadelphia chromosome (BCR-ABL1 fusion gene) [1].	Affect adults; median age at diagnosis around 65.	Fatigue, weight loss, night swears, splenomegaly [1].

3. Diagnosis and therapeutics

The diagnosis of leukemia has evolved into a sophisticated, multi-step process that integrates classical techniques with innovative technology (Table 2). Traditionally, it begins with a complete blood count (CBC) and microscopic examination of peripheral blood and bone marrow smears to identify blast cells and assess morphology, serving as the initial trigger for further analysis [5]. This is followed by the immunophenotyping via flow cytometry to detect specific cell surface makers (CD antigens), which is essential for the lineage (myeloid or lymphoid) and stage of differentiation of the leukemic cells. Cytogenetic analysis, including karyotyping, identifies gross chromosomal abnormalities such as the Phiadelphia chromosome in CML. Additionally, molecular genetic test such as polymerase chain reaction (PCR) and fluorescence in situ hybridization (FISH) are essential for detecting mutations and fusion genes, such as BCR-ABL1 fusion gene, enabling the identification of submicroscopic genetic lesions critical for classification and prognosis [6].

In recent years, modern methods have further refined leukemia diagnostics. Next-generation sequencing (NGS) allows for high-throughput profiling of mutations across multiple genes simultaneously, providing a comprehensive genetic landscape that guides risk stratification and targeted therapy. Digital PCR and droplet digital PCR (ddPCR) offer ultrasensitive quantification of minimal residual disease (MRD), enabling early detection of relapse. Furthermore, machine learning (ML) applications are revolutionizing the diagnostic pipeline by introducing unprecedented levels of automation and precision [5]. Deep learning algorithms, particularly convolutional neural networks (CNNs), are now deployed to automate the classification and counting of blast cells in digital blood and bone marrow smear images, significantly reducing interobserver variability and diagnostic turnaround time. In flow cytometry, ML-based clustering and pattern recognition tools enhance the objectivity and reproducibility of identifying aberrant immunophenotypes. Beyond morphology and immunophenotyping, premedicine ML models are being developed to infer genetic alterations from routine diagnostic data and to integrate multi-omics information for comprehensive disease

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subtyping and prognosis prediction. The integration of these advanced technologies with conventional approaches ensures a precise, personalized diagnosis, improving further treatment and patient care.

Table 2. The evolution of diagnosis of Leukemia

Era	Primary Diagnostic Method	Key advancement
19th Century	Gross Autopsy Pathology	First description of "leukemia"
Early 20th Century	Microscopy and Staining	First in-vivo (living) diagnoses; Basic cell typing (lymphocytic and myelogenous) [2]
Mid 20th Century	Bone marrow aspiration	Direct analysis of the disease source
1970s-1980s	French-American-British (FAB) System	Standardized classification for acute leukemias (FAB L1-L3 for ALL and FAB M0-M7 for AML) [1,2]
1980s-1990s	Cytogenetics (Karyotyping)	Identification of chromosomal abnormalities
1980s-1990s	Immunophenotyping (Flow Cytometry)	Precise identification of cell lineage
1990s-2000s	Molecular Biology (PCR, FISH)	Detection of specific genetic lesions; minimal residual disease (MRD) monitoring [2]
2000s-Present	Genomics (NGS), WHO Classification	Precision medicine: diagnosis integrates genetics to guide targeted therapy

Traditionally, treatment for leukemia has relied on systemic chemotherapy and radiation, which are designed to target rapidly dividing cells but lack specificity for malignant cells alone. It involves intensive, multi-agent chemotherapeutic regimens that aimed at inducing remission by eradicating visibly detectable cancer cells in the bone marrow and blood [7]. This is often followed by consolidation therapy which is additional cycles of chemotherapy or allogeneic hematopoietic stem cell transplantation (HSCT) for high-risk patient to eliminate residual disease and prevent relapse [7]. While these treatments are effective and cured many patients for decades, they are associated with significant toxicities, such as prolonged myelosuppression, organ damage, and increased susceptibility to infections.

However, treatment for leukemia have revolutionized in recent years. Targeted therapies, particularly tyrosine kinase inhibitors (TKIs), work by competitively blocking the adenosine triphosphate (ATP)-binding site of constitutively active mutant kinase, thereby suppressing abnormal downstream pro-survival and proliferative cascades such as MAPK/ERK, JAK-STAT pathways, which leads to induced apoptosis and a significant reduction in leukemic cell burden. For example, in AML, drugs like midostaurin and gilteritinib target FMS-like tyrosine kinase 3 (FLT3) mutations, especially an internal tandem duplication (FLT3-ITD) [8]. Besides, Ivosidenib and enasidenib inhibit mutant Isocitrate dehydrogenase (IDH) 1 and 2 respectively, reducing the production of the oncometabolite 2-hydroxyglutarate (2-HG), which allows the blocked process of differentiation to resume [8]. In addition, in CML, TKIs like imatinib and nilotinib serve as first-line treatment by specifically targeting the BCR-ABL fusion protein, which results from the Philadelphia chromosome and exhibits constitutive tyrosine kinase activity.

Immunotherapy such as chimeric antigen receptor (CAR) T-cell therapy and monoclonal antibody (mAb)-based therapeutics which boosts the body's own immune system to recognize and kill cancer cells have revolutionized the treatment of leukemia by leveraging highly specific mechanisms to target and eliminate malignant cells. CAR T-cell therapy involves genetically engineering a patient's

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own T-cells to express synthetic receptors that combine an antigen-binding domain with intracellular T-cell signaling domains. These engineered CAR T-cells are then expanded ex vivo and reinfused into the patient, where they recognize and eliminates cells expressing the target antigen, such as CD19 or CD22 on B-cell malignancies [9]. For example, tisagenlecleuc and axicabtagene ciloleucel which target CD19 have demonstrated remarkable efficacy in ALL [9]. As for mAb-based therapeutics, they work through several complementary pathways to induce cell death. Certain mAbs such as alemtuzumab work through direct action. By targeting CD52 antigen on the surface of leukemic cells, it directly inhibits crucial survival pathways simply by binding to its target, thereby triggering apoptosis in cancer cells. However, the primary mechanism for most mAbs is not direct killing but rather work by immune-mediated destruction that the antibody bridges cancer cells to the patient's own immune effectors [10]. For instance, rituximab, an anti-CD20 antibody that binding to its target on B-cells, facilitates antibodies-dependent cellular cytotoxicity (ADCC) by engaging natural killer cells. Concurrently, it activates the complement cascade, leading to complement-dependent cytotoxicity (CDC), which punctures the cell membrane of CD20-positive leukemias and lymphomas, causing them to lyse [10]. Furthermore, the versatility of mAbs allows them to be engineered into precision-guided delivery systems for potent cytotoxic agents. For example, Gemtuzumab ozogamicin direct the highly toxic antibiotic calicheamicin specifically to CD33-expressing AML cells. Similarly, radioimmunoconjugates like ibritumomab tiuxetan utilize an anti-CD20 antibody with a radioactive isotope, yttrium-90, enabling localized irradiation and destruction of specific B-cell malignancies [10]. Together, the specific modern therapies have fundamentally transformed leukemia treatment, enabling more precise and effective approaches for further treatment.

4. Future direction

In the future, the diagnosis of leukemia will undergo a radical transformation, shifting towards a paradigm that is not only less invasive but also more frequent and more informative. Liquid biopsies which detect circulating tumor DNA (ctDNA) from routine blood samples, promises to revolutionize treatment monitoring by allowing frequent, real-time assessment of disease. Its most important impact may lie in the ultra-sensitive detection of minimal residual disease (MRD), with the potential to identify relapse risks at thresholds far below the detection thresholds of current methods such as flow cytometry or bone marrow biopsies, thereby acting as an early warning system long before clinical symptoms reappear. In addition, the diagnostic evaluation will expand to incorporate multi-omics profiling. By integrating genomic, transcriptomic, epigenomic and proteomic data, a holistic, systems-level view of each leukemia can be gained. The extreme complexity of these datasets will require the use of advanced artificial Intelligence (AI) and machine learning algorithms, which will be improved and essential to identify novel subtypes, predict disease behavior for cancer. Furthermore, innovative tools like single-cell sequencing will transition from research to clinical application, allowing to analyze the heterogeneity of patient leukemia cell populations, thereby revealing and guiding combined therapies to prevent disease recurrence. Therapeutically, strategies will focus on addressing the two most formidable challenges in current treatments: therapy resistance and disease recurrence. This will drive the development of next-generation targeted agents engineered with enhanced potency to specifically overcoming resistance mutations, particularly in kinases like FLT3. In advanced Immunotherapy, the development of next-generation CAR T-cells are already being designed with sophisticated features such as dual-targeting mechanisms to eliminate the possibility of antigen escape and are being engineered to secrete cytokines that remodel and overcome the immunosuppressive tumor microenvironment. Furthermore, more novel

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immunomodulators like bispecific T-cell engagers (BiTEs) and antibody-drug conjugates (ADCs) will be improved and target a broader spectrum of leukemia-specific antigens with greater precision and reduced off-target effects. Treatment will no longer be a static protocol but a dynamic, adaptive strategy. Future diagnosis and therapies can be switched and combined for better treatment for patients.

5. Conclusion

Leukemia management has improved and evolved from a reliance on non-specific cytotoxic agents to a sophisticated precision medicine. This review has detailed the fundamental molecular mechanisms that drive the development of leukemia, with a specific focus on the collaboration of Class I and Class II mutations that disrupt normal cellular proliferation and differentiation. The diagnosis pathways have similarly advanced, integrating classic morphological methods with innovative genomic technologies. Techniques like next-generation sequencing provide a deep genetic portrait of an individual's disease, while artificial intelligence algorithms enhance the precision of classification and the sensitivity of residual disease monitoring. Therapeutically, the advent of targeted inhibitors that designed to block specific molecules critical to cancer cell survival, and immunotherapies, which harness the patient's own immune system to destroy leukemic cells, has revolutionized and provided alternatives to conventional treatment, offering more effective and less toxic alternatives. In the future, the continued improvement and integration of non-invasion liquid biopsies for dynamic monitoring, the development of next-generation cellular therapies such as improved CAR T-cells and allogeneic products, and the application of AI-driven predictive analytics promise to a more adaptive and personalized treatment. This indicate that the treatment for leukemia in future will not only be more precise, but also may involve early intervention, thus getting closer to achieving the goal of providing lasting cures for all patients.

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