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Advances in the Molecular Pathogenesis of Acute Myeloid Leukemia

Rusul Ahmed Mohammed[1,*], Nada Khazal K. Hindi[2], Mustafa Hussein Mohammed[3], Zahraa I. J. Shubber[4], Abdolmajid Ghasemian[5]

[1] *Department of Pharmacology and Toxicology, College of Pharmacy, Al-Mustaqbal University, Babylon, Hillah 51001, Iraq.*
[2] *Department of Basic and Medical Sciences, College of Nursing, University of Babylon, and College of Pharmacy, Al-Mustaqbal University, Babylon, Hillah 51001, Iraq.*
[3] *Computer Techniques Engineering Department, Al-Mustaqbal University, Babylon, Hillah 51001, Iraq.*
[4] *College of Pharmacy, Al-Mustaqbal University, Babylon, Hillah 51001, Iraq.*
[5] *Fasa University of Medical Sciences, Fasa 7461686688, Iran.*

Corresponding Author Email:
rusul.ahmed.mohammed@uomus.edu.iq

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ABSTRACT

Acute Myeloid Leukemia comprises a heterogeneous group of clonal disorders that result from the abnormal accumulation of immature myeloid cells within the bone marrow and peripheral blood. This study aims to detect Advances in the Molecular Pathogenesis of Acute Myeloid Leukemia. This has been elucidated by recent molecular studies that identified crucial mutations in FLT3, NPM1, and DNMT3A genes and epigenetic changes that contribute to leukemogenesis. Deregulated pathways besides PI3K/AKT and MAPK have also asserted themselves in disease progression and resistance to therapy. Hence, the review presents an extensive discussion of contemporary molecular perspectives of AML pathogenesis and their relevance to diagnosis and treatment. The rise in targeted therapies and precision medicine thus paints a promising clinical picture for a better prognosis. Knowledge of the biological compromise unleashed by mutations in genes and their interplay with the bone marrow microenvironment is key to forging newer therapies.

Keywords: AML, molecular pathogenesis, genetic mutations, hematology, targeted therapy.

1. Introduction

Acute myeloid leukemia (AML) is a very aggressive illness of the blood stem progenitors marked by an exalted clonal proliferation, with resultant hematopoietic dysfunction [1]. Treating elderly set of patients is usually poor in prognosis because multiple genetic aberrations with complicated treatment processes often come together [2]. The patient will be subjected to treatment on the basis of age,

cytogenetic risk factors, LD cytarabine or anthracyclines (or HMAs), or intensive regimens of HD Teusah or 3 + 7, with further consolidation therapy [3].

Indeed, the field is moving toward incorporation of agents directed at mutations, such as FLT3 and IDH1/2, into these regimens and into approaches to increase efficacy or overcome resistance [4]. Omics is being integrated with regard to clonal evolution and molecular heterogeneity in AML. Network approaches combined with proteomics, transcriptomics, and metabolomics have demonstrated pathways activated in resistant cells, which are being explored for therapeutic intervention. Because tumor-immune co-evolution mechanisms have various clinical implications, chemotherapy-resistant cases are examined [5].

Meanwhile, drugs that confer intense stealth with targeted dosages are in the making. Promising developments include the design and implementation of liquid biopsy systems for blood collection with non-invasive methods, with studies currently being held that compare circulating DNA and RNA from plasma with bone marrow samples [6].

2. Overview of Acute Myeloid Leukemia

The complex region of hematological disorders is caused by genetic and epigenetic changes in hematopoietic progenitor cells, occurring as the most common acute leukemia in adults, thereby imposing a great healthcare burden [7]. While targeted therapies have improved outcomes for some patients, the majority of patients continue to be treated with conventional cytotoxic chemotherapy, hence the urgent need for improved therapies [8].

AML develops in patients with prior myelodysplastic syndromes or chronic myelomonocytic leukemia, involving mutations such as SF3B1 and SRSF2. Important mutations in AML include FLT3, NPM1, RUNX1, and many others, together with chromosomal aberrations [9]. Genetically, these subjects belong to the 2017 ELN guidelines but exclude phenotypes for which there are no implications for interventions. Secondary mutations, those involved in transcription regulation and signaling pathways, contribute to the fully developed malignant phenotype [10].

Table 1. Synthesizing the advances in molecular pathogenesis of Acute Myeloid Leukemia (AML) and their applications may be of interest [11].

Advances in Molecular Pathogenesis	Details	Applications
Genetic Mutations Identified	Mutations in genes like FLT3, NPM1, CEBPA, IDH1/2, RUNX1, TP53.	Personalized treatment based on mutation profile.
Understanding Clonal Evolution	AML arises from pre-leukemic stem cells, clonal heterogeneity.	Targeted drugs and combination therapies to prevent relapse.
Role of Epigenetics	Changes in DNA methylation, histone modification, chromatin remodeling.	Mutations used for prognosis and therapy guidance.
Microenvironment Influence	Bone marrow microenvironment (stromal cells, cytokines) supports AML.	Sensitive monitoring to detect minimal residual disease (MRD).
Targeted Therapies Emergence	Drugs targeting mutations like FLT3, IDH1/2; combination therapies.	Gene editing tools like CRISPR may correct mutations.

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3. Molecular Genetics of AML

Acute myeloid leukemia (AML) is a violent hematological cancer with high relapse rates despite good initial response to chemotherapy. With cytogenetic abnormalities, clonal expansion of the hematopoietic progenitor cells is seen. Molecular biology updates opened an insight into the pathways involved in AML oncogenesis and will influence diagnosis and treatment [12]. Mutations in epigenetic genes such as TET2 and IDH1/IDH2 are quite frequent, but current genetic tests probably overlook factors that have to do with transcriptional effects. Mutations tend to cluster near the transcription start sites, indicating possible targets for therapy, regardless of the particular mutations [13]. Now, on the basis of mutation profiles, an integrated approach of drug selection was initiated, which predicted recurring epigenetic variations. The new systems of classification will try to throw light on molecular mechanisms in AML. The recent advances also cover the aspects of targeting missense mutations in the most frequently mutated genes, dealing with applications and limitations of existing approaches [14].

3.1. Key Genetic Mutations

Acute myeloid leukemia (AML) is the most common acute leukemia in adults and rising incidence attributed to the aging population. It entails different genetic alterations, chromosomal abnormalities, and point mutations that interfere with the routine hematopoietic function and push tumorigenesis [15]. Pre-leukemic mutations in precursor cells are alleged to be the initial occurrences of leukaemogenesis [16]. Famous ones like NPM1 and FLT3 mutations cause more malignant leukemia. Using advanced technology, next-generation sequencing (NGS) has identified smaller genetic alterations frequently overlooked by typical methodologies and has elucidated genetic differences that can exist between diagnosis and relapse. Knowledge of these changes is very important for prognosis and treatment [17].

3.2. Epigenetic Modifications

Epigenetic changes, like DNA methylation and histone modifications, generally control gene expression, with the respective epigenetic enzymes being called "writers," "erasers," and "readers." Being dysregulated, these modifications could cause altered expressions of the genes and hence cause several disorders, including cancer. With the recent sequencing of cancer samples, mutations have been detected in genes important in the epigenetic modulation machinery, particularly in AML, which is characterized by uncontrolled cell growth and differentiation arrest [18].

Epigenetic changes in AML have been associated with mutations in DNMT3A, TET2, EZH2, and IDH1/IDH2 genes that can reprogram gene expression to sustain cell proliferation and block differentiation, a vital step in leukemia development. The evolution of their inhibitors and their administration therapeutically constitutes a novel therapeutic approach for AML, and studies at present evaluate their use as monotherapies and in combination therapies [19].

3.2. Epigenetic Modifications

Epigenetic changes like DNA methylation and histone modification regulate gene expression and are formed by enzymes called "writers," "erasers," and "readers." When these modifications get dysregulated, gene expression is affected and it causes different diseases, including cancers [19]. Cancer sample sequencing of recent times has identified mutations in epigenetic modulator genes, mainly in

AML, characterized by unchecked cell proliferation and impaired differentiation [20].

Epigenetic changes to genes such as DNMT3A, TET2, EZH2, and IDH1/IDH2 are associated with AML. These changes reprogram gene expression to foster cell proliferation and block differentiation, which is key in leukemia formation. Thus, inhibitors that specifically target epigenetic modifiers are now seen as a new treatment option for AML, and their application in both monotherapy and combination remains under investigation [21].

4. Cellular Microenvironment in AML

The rapid proliferation of immature myeloid cells and the arising heterogeneity from gene mutation and interaction with the bone marrow microenvironment constitute AML [22]. This extracellular environment, in essence imperatively comprising extracellular matrix proteins, growth factors, and other nonmalignant cells, sustains the pathogenesis for AML. Chemotherapeutic treatments are administered for eliminating malignant cells, but they usually ignore the changes occurring in stromal and immune cells [23].

The main source of glial influence is germlined hematopoietic cells and maintenance growth for leukemic cells. Interactions in this environment inhibit stemness and the existence of resistance from drugs through mechanisms such as soluble factors and exosomes [21]. Comprehensive knowledge about these interactions will shed light on novel therapeutic targets and on ways to improve existing treatment modalities with the aim of ultimately improving the outcome [22].

4.1. Role of Bone Marrow Niche

Recent studies have shed more light on the molecular mechanisms involved in the development of acute myeloid leukemia (AML), especially regarding the bone marrow niche [23]. In the mouse, general conducive microenvironments provide sites for leukemic growth. Several key observations are: there is an increase in ECs and MSCs in AML, and they have noted that proliferation of ECs and activation of ECs are influenced by AML blasts.

The AML-MSCs are hypermethylated, suggesting that early mutation events affect MSC function. Both the AML blasts and the bone marrow niche undergo changes that favor disease progression. However, very often the studies do not distinguish whether the mutations are stable or whether the epigenetic changes are reversible. Loss of differentiation without mutation probably further enhances the competitive behaviour of AML blasts [24].

4.2. Interactions with Stromal Cells

The bone marrow (BM) microenvironment consists of various cell types that interact with hematopoietic stem cells (HSCs) to maintain their quiescence and self-renewal. Aberrant signals from the stroma can lead to hematopoietic disorders, including leukemias. In AML, a collagen-rich stroma protects leukemic blasts from chemotherapy, with signaling through CXCR4 contributing to chemoresistance. This raises the potential for pharmacological interventions targeting the stroma [25]. While several candidates have shown promise in mouse models, none have yet translated into clinical use. These include compounds like SCM and anti-IL-22.

The role of the hypoxic stroma in protecting leukemic cells from treatment remains poorly understood, as its characteristics do not uniformly confer resistance to all chemotherapeutics [26]. Understanding the interactions between endothelial cells and the stroma may reveal insights into chemoresistance mechanisms. Drawing on strategies from solid tumors, such as re-engaging immune cells, could inspire new approaches for AML. Identifying differences in immune cell populations may also yield promising therapeutic candidates for further investigation [27].

5. Signaling Pathways in AML Pathogenesis

Different signaling pathways are involved in the pathogenesis of AML; those related to hematopoiesis include receptor tyrosine kinases, MAP kinases, and the PI3K/Akt/mTOR signaling pathways [7]. Genetic and epigenetic mechanisms of regulation in these pathways lead to the initiation, sustenance, and resistance to therapy in AML.

Downstream signaling by phosphorylation of the PI3K/Akt/mTOR pathway is one of the most frequently dysregulated signalling pathways in AML, i.e., mutations of its components such as PTEN activation lead to overproliferation of cells and resistance to treatment. This pathway was activated through mutations in about half of AML patients [29]. Although the targeted therapies have been developed for which FDA approval has been granted, still there are many patients who cannot be treated successfully. Further knowledge of these signaling pathways could help in providing better treatment for AML [28].

5.1. FLT3 Signaling

5.2 FLT3: AUGMENTED PROLIFERATION AND SURVIVAL

Flt3 (Florin T-eighty-eight) is a receptor-type tyrosine kinase that becomes activated upon binding to its ligand, Flt3L, leading to autophosphorylation and activation of signaling pathways that promote cell proliferation and survival [12]. While Flt3L is normally expressed in early hematopoietic environments, aberrant Flt3 expression is common in de novo acute myeloid leukemia (AML), often without the presence of its ligand.

This dysregulation is implicated in AML pathogenesis. Flt3 is crucial for the development of hematopoietic progenitor and dendritic cells, and its activation influences various pathways, including Ras-MAPK and PI3K. Activating mutations in the Flt3 receptor are found in 23%–30% of AML cases, making it one of the most frequently detected mutations in the disease. Understanding these mutations has significantly advanced cancer genetics research in the past decad [30].

5.2. Ras Pathway Activation

Ras is a GTP-binding protein crucial for controlling the cell cycle and promoting oncogenesis through various downstream pathways, including Raf/MAPK and PI3K. Ras proteins signal to multiple effectors, primarily activating RAF kinases in hematological malignancies. Activating mutations in Ras, such as K-Ras and N-Ras, contribute to AML heterogeneity, with N-Ras mutant cells arrested in the G0/G1 phase and K-Ras mutant cells more prevalent in the G2/M phase [31].

The phosphatidylinositol 3-kinase subunit PIK3CA is the second most frequently mutated downstream activator of the Ras pathway, influencing metabolism, proliferation, and survival. Mutations in tumor suppressor genes like PIK3R1 and others (e.g., TET2, IDH, ASXL1, DNMT3A) are also observed, often correlating with patient outcomes [32].

The activation of Ras pathways leads to diverse effects, showing significant mutation heterogeneity between different age groups. Overall, alterations in these pathways, combined with early Ras signaling changes, suggest complex mechanisms of cancer escape and coexistence of mutations within AML [33].

5.3. JAK-STAT Pathway

Approximately 75% of AML patients have epigenetic alterations, with unclear mechanisms. Notably, mutations in NPM1 and IDH1/2 lead to genetic hypermethylation and the oncometabolite 2-

hydroxyglutarate (2HG), impacting DNA methylation [34]. The JAK-STAT pathway is commonly dysregulated in AML, especially through JAK2 and FLT3 mutations, promoting excessive cell survival and proliferation.

The tumor microenvironment significantly influences these changes, altering the epigenome and contributing to leukemogenesis. FLT3 mutations are present in 30%-40% of de novo AML cases and correlate with poor prognosis. They are also frequently observed in leukemic transformations from myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPNs), highlighting their importance as therapeutic targets [33].

6. Role of Stem Cells in AML

Acute Myeloid Leukemia (AML) is a complex hematological malignancy with a heterogeneous disease course and variable clinical outcomes. Most patients receive intensive chemotherapy, including induction and consolidation therapy, aiming for a complete response (CR). However, even when CR is achieved, minimal residual disease (MRD) may remain, leading to relapse in approximately 75% of cases. This relapse indicates the presence of a leukemic cell population responsible for ongoing disease.

Research has identified leukemic stem cells (LSCs) as a rare but crucial subpopulation that can engraft in immunocompromised mouse models and sustain AML. LSCs typically express surface markers associated with hematopoietic stem and progenitor cells (HSPCs), such as CD34 and CD38, facilitating their identification and characterization [16].

The recognition of LSCs is beginning to influence the development of new therapeutic strategies and risk stratification for AML patients. Particularly striking is the variability in outcomes for cytogenetically normal acute myeloid leukemia (CN-AML), where some patients achieve effective cures while others face poor prognoses [34].

6.1. Cancer Stem Cell Hypothesis

Cancer stem cells (CSCs) are crucial in the metastasis of acute myeloid leukemia (AML) and pose significant challenges for treatment. Targeting these immune-competent stem-like cells could improve therapeutic outcomes. In solid tumors, CSCs can be effectively targeted using a combination of monoclonal antibodies and toxins.

However, efforts to target CSCs in hematologic malignancies, such as with CD44, have not succeeded, possibly due to the ineffectiveness of anti-human CD44 antibodies that do not cross-react, limiting their efficacy. Alternative strategies may involve indirect targeting of the hematopoietic stem cell (HSC) niche and cytokines like IL-3, GM-CSF, SDF-1, and IL-6 to selectively eliminate CSCs in AML.

Additionally, in wild-type FLT3 AML, interferon gamma (IFN-γ) signaling pathways are silenced through epigenetic mechanisms, correlating with poor patient prognosis. In FLT3-ITD mutant mice, the deposition of H3K27me3 leads to transcriptional silencing of IFN-γ pathways, causing delayed transformation linked to the sequential activation of the FLT3-ITD mutation. Early epigenetic changes occur without concurrent mutations, suggesting a convergence of mutated kinases, paralleling human AML. Studies have revealed aberrant DNA methylation at early leukemogenic stages, highlighting the role of epigenetic modifications in AML progression [35].

6.2. Therapeutic Implications

Despite advances in chemotherapy, the prognosis for acute myeloid leukemia (AML) patients remains poor, with the "3 + 7" regimen (anthracycline and cytarabine) as the standard treatment. There is a pressing need for new therapeutic strategies, as AML is a clonal malignancy characterized by various genetic alterations that impact prognosis and treatment response.

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Recent attempts are made to hit intracellular processes specific to abnormal proteins, giving rise to four emerging strategies for therapy suited for different AML subtypes.

Molecular targeting can go hand in hand with conventional chemotherapy, wherein applications would become more personalized and with lesser systemic toxicity. However, compared to B-cell lymphomas and acute lymphoblastic leukemia (ALL), AML is behind when it comes to the best strategies. In many relapsed or refractory settings, patients find few options and resort to high-dose chemotherapy that gives temporary respite. The complexity of the molecular landscape of AML also renders it difficult to select targets.

Some mutations such as CEBPA and NPM1 might be inappropriate for targeted therapy owing to their differing sets of signaling pathways. Further difficulty lies in the question of whether one ought to target the mutations that initiate the malignancy or the downstream pathways. Then, some chromosomal abnormalities, such as p53 R175H and MLL rearrangements, make it impossible to develop effective therapies. Overall, while there has been progress in other malignancies, the search for effective AML targets continues to be a significant challenge [36].

7. Immune Microenvironment in AML

Acute myeloid leukemia (AML) engages a complex immune microenvironment that often promotes disease progression rather than eradication. Cancer cells in AML can dampen T cell immunity while increasing suppressive immune elements like myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs). Although chemotherapy reduces leukemic burden, long-term disease-free survival will likely require combined treatment strategies. Two main immunotherapy strategies are being explored for newly diagnosed AML patients.

The first involves enhancing T cell function through checkpoint blockade therapies targeting PD-1 and CTLA-4, though initial response rates have been suboptimal. The second strategy focuses on agents that promote myeloid maturation, such as all-trans retinoic acid (ATRA), IDO inhibitors, and CSF1R-targeting monoclonal antibodies, which aim to improve immune responses. Integrating research on the cancer immunity cycle is crucial for advancing T cell immunity in AML [37].

7.1. Immune Evasion Mechanisms

Recent advances in cancer immunotherapy show promise for treating myeloid leukemias, including chronic myeloid leukemia (CML) and acute myeloid leukemia (AML). CML's only curative option is allogeneic hematopoietic stem cell transplantation (HSCT), which is limited to a few patients. While tyrosine kinase inhibitors (TKIs) can target the BCR-ABL1 fusion protein effectively, they are not curative, as many patients relapse.

Immunotherapy, such as CAR T-cell therapy, is still relevant for CML due to the presence of numerous mutations in leukemic cells that may encode neoantigens. The BCR-ABL1 protein can also stimulate anti-CML immunity. In AML, genetic mutations disrupt normal hematopoiesis, leading to immune evasion strategies that promote tumor progression. Recent findings indicate that macrophages play an immunosuppressive role in AML, contributing to a dysfunctional immune environment [38].

7.2. Potential for Immunotherapy

Immunotherapy has significantly improved outcomes in many cancers, but its success in acute myeloid leukemia (AML) has been limited. Myeloid blasts have low immunogenicity, and the difficulty in identifying AML-specific antigens may hamper the efficacious implementation of immune checkpoint blockade therapies. On the contrary, epigenetic manipulation holds promise for improving immunotherapy responses by neoantigen formation and better antigen presentation. Clinical trials

combining non-specific epigenetic drugs with checkpoint inhibitors have returned modest outcomes in relapsed/refractory (R/R) AML.

Promising response rates have appeared in particular under magrolimab, an anti-CD47 antibody, in combination with azacitidine. CAR-NK cell therapies could offer an excellent safety profile, with transient hematopoiesis toxicity. Gaining a deeper understanding of immune mechanisms in AML, allowing for antitumor and protumor activity, will help maximize immunotherapy efficacies while minimizing adverse effects [21]. An increasing number of ongoing trials in AML are concentrated on ICIs, seeking to offer another approach to traditional cytotoxic therapies with less toxicity [39].

8. Current Therapeutic Approaches

Cytotoxic agents constitute the treatment of newly diagnosed and relapsed acute myeloid leukemia (AML), with extensive guideline assistance. Standard induction regimens combine cytarabine (AraC) with an anthracycline (daunorubicin or idarubicin), with midostaurin or hypomethylating agent (HMA) added as deemed suitable. These agents offer a CR rate of greater than 70% in patients up to 65 years of age. Despite this, only about one-third of patients survive five years, and many face significant side effects. Relapses with therapy-resistant disease (TRD) are common, and standard treatments often fail during therapy-free intervals. Recent studies suggest that AML cell membranes could be targeted by complementary agents to enhance treatment efficacy. Transcriptomic analyses indicate that while standard therapies impact downstream pathways, few changes in mRNA are observed. This underscores the need to investigate factors that can therapeutically modify these pathways [40].

8.1. Chemotherapy

Acute myeloid leukemia (AML) involves the clonal expansion of immature myeloid cells and constitutes 10% of global leukemia cases [22]. These malignant cells accumulate in the bone marrow and blood, impairing normal blood cell production and leading to marrow failure. The standard treatment for AML has been a combination of cytarabine and anthracyclines for the past 50 years, achieving complete remission in fewer than 45% of patients. Many patients experience treatment-related mortality and relapse due to chemoresistance.

Cytarabine, an anti-metabolite, is central to therapy but faces challenges from drug resistance mechanisms in leukemic cells. Recent FDA-approved treatments have had limited success, showing no significant improvement in overall survival compared to traditional therapies. Targeted therapies typically offer minimal benefit to newly diagnosed patients, who mainly receive standard chemotherapy. Since 2017, new agents have been approved, allowing for potential sequential treatments. Understanding the mechanisms of drug resistance is vital for enhancing management strategies. The heterogeneous nature of AML necessitates more effective and less toxic treatment approaches, focusing on key molecules related to drug resistance and strategies to sensitize leukemic cells to cytarabine [41].

8.2. Targeted Therapy

In the last decade, significant strides have been made in understanding acute myeloid leukemia (AML) through improved molecular profiling and biomarker-guided clinical trials. New agents for therapy are now focusing on malignant signaling, cellular vulnerabilities, and immune evasion, moving precision medicine one step ahead with new small-molecule drugs and biologics. Genomic and epigenomic bases for many mutations may be increasingly characterized, but clinical meaning may still lack for many recently identified mutations.

Cell-free DNA sequencing technologies hold promise for the determination of appropriate therapy and non-invasive assessment of minimal residual disease (MRD). Thus, a thorough grasp of genomic

hierarchies in AML will have to go hand-in-hand with the broad profiling of the transcriptomes and proteomes to improve therapy and overcome issues of AML heterogeneity [42].

9. Emerging Therapies

With a more targeted process, the recent advances in the molecular basis of AML have introduced therapeutic modalities beyond the traditional cytotoxic treatments. With NGS incorporated into the clinico-pathological workflows for AML diagnosis and treatment selection, the survival of AML patients has been enhanced [1]. This is evident with small-molecule inhibitors being developed against specific mutations such as IDH1/2 and FLT3ITD. Chromatin biology is currently providing emerging evidence and therefore the inhibition of the epigenetic machinery is treated as one interesting way of treatment, especially in FLT3ITD AML.

Downstream effectors such as RND3 have been targeted with much promise [18]. New regimens for patients refusing standard treatments appear promising in early developmental stages (18). Given the multifactorial nature of AML, combinatorial therapies targeting epigenetic, transcriptional, and protein translation processes are key; these "global"-acting therapies hope for broad responses and potentially to turn resistance around [43].

9.1. Novel Targeted Agents

The prognosis for acute myeloid leukemia remains poor despite advances in chemotherapy. The "3 + 7" regimen has been the standard treatment for over 40 years, achieving low complete remission rates, particularly in older patients, which underscores the urgent need for new therapies [18]. AML is characterized by various genetic alterations, leading to a focus on targeting the intracellular events driven by these abnormal proteins. Many of these protein alterations are druggable, resulting in the development of novel agents like spliceosome inhibitors, CD33 and FLT3 antibodies, and kinase inhibitors [44].

While promising results have emerged from these agents, few have gained approval or led to significant changes in clinical practice. This review highlights the latest novel agents and their potential roles in AML management, shifting the focus from merely identifying genetic mutations to targeted therapies. Molecular targeting offers a more personalized approach, potentially complementing traditional chemotherapy. The success of targeted therapies in other malignancies, like imatinib in chronic myeloid leukemia (CML), suggests that similar strategies may enhance the eradication of malignant clones in AML [45].

9.2. Combination Therapies

The impact of mutations in acute myeloid leukemia (AML), especially DNMT3A, is sparking interest in combination therapies that target epigenetic regulators with DNA-damaging agent [46]. Idelalisib and venetoclax have been used together for the first time in older patients and those with multiple comorbidities who typically cannot undergo chemotherapy. However, challenges like resistance to vincristine and increased Aurora B kinase expression have been noted. In FLT3-ITD AML, the unique MAPK pathway suggests a lower likelihood of resistance, and combining FLT3 inhibitors with second-generation agents like quizartinib has shown significant antiproliferative effects. Research on transcriptional activation domains (TAD) and 3D genome architecture mediators is limited, despite evidence linking ASXL1 and KMT2A mutations with TET2 loss [46].

Recent advances in molecular understanding have identified actionable mutations and compound dependencies, aiding prognosis and treatment strategies [24]. Targeting FLT3 with new inhibitors is a key example, although these therapies have not yet replaced conventional chemotherapy due to their inability to penetrate the blood-brain barrier. Emerging advances in virology may allow for novel combinations that could benefit malignancies with limited progress. Target discovery through drug library screening

and biological profiling may lead to new therapies for challenging cancers [47].

10. Clinical Trials and Research Advances

The recent advancements in therapies for acute myeloid leukemia (AML) demonstrate a remarkable shift for a disease once considered untreatable, thanks to the collaborative efforts of researchers, the biopharmaceutical industry, and organizations like the US National Institutes of Health [48]. Rapid discoveries in AML pathogenesis have outpaced publication efforts, resulting in competing studies that can confuse the landscape. Nonetheless, insights into mutations and signaling pathways have formed a solid foundation for targeted therapies.

Organizing advancements into clear categories—such as basic research versus drug development—could enhance understanding, though it may require acknowledging collaborative efforts. The identification of actionable target genes in AML has significantly boosted drug development. Integrating academic research with pharmaceutical initiatives has accelerated progress, while insights from small molecule development are proving applicable to antibody therapies. The current drug development landscape in AML is dynamic, with validated screening platforms aiding future research and potentially avoiding previous setbacks. However, the complexity of compound interactions suggests ongoing challenges in navigating this evolving field [49].

10.1. Recent Clinical Trials

Recent studies have significantly impacted the treatment of acute myeloid leukemia (AML). In addition to standard cytarabine/anthracycline regimens, incorporating targeted treatments like FLT3, IDH1/2, and BCL2 inhibitors has improved outcomes for newly diagnosed patients. The successful integration of gemtuzumab ozogamicin and inotuzumab ozogamicin into treatment protocols marks over a decade of development [50].

However, challenges remain, including therapy resistance, cytotoxicity, and pan-resistance, particularly in elderly AML patients. Loss-of-function mutations in Cohesin complex genes (e.g., STAG2) are linked to poor prognosis, and understanding the molecular pathogenesis of these novel AML subtypes could lead to future theranostic advancements. While subtypes like M0, M3, and M7 have been well-studied, less is known about driver mutations in M1/M4 subtypes.

The feasibility of developing NSG mouse models for these subtypes and establishing spheroid cell lines for pharmacogenomic and epigenomic studies remains uncertain. Pilot studies show parallels between aberrant DNA methylation and gene expression in AML clinical samples, focusing on novel therapeutic targets related to del(5q), OS, NPM1, and FLT3-ITD. AML remains a heterogeneous and complex cancer, and ongoing efforts are essential to fully understand it and develop novel targeted therapies, ultimately translating research findings into clinical applications to help patients combat this deadly disease [51].

10.2. Future Directions in Research

Recent studies have significantly impacted the treatment of acute myeloid leukemia (AML). In addition to standard cytarabine/anthracycline regimens, incorporating targeted treatments like FLT3, IDH1/2, and BCL2 inhibitors has improved outcomes for newly diagnosed patients. The successful integration of gemtuzumab ozogamicin and inotuzumab ozogamicin into treatment protocols marks over a decade of development [52].

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11. Challenges in AML Treatment

Acute myeloid leukemia (AML) is a malignant disorder characterized by rapid cell proliferation and impaired differentiation of leukemic blasts, driven by various genetic and epigenetic abnormalities. Advances in molecular technologies like whole genome next-generation sequencing (NGS) have enhanced the identification of relevant mutations and introduced MLFS risk stratification systems to guide therapy. While treatment outcomes have improved for patients with favorable and intermediate risk, older patients with p53 mutations or adverse karyotypes still face poor prognoses [54]. New strategies are needed, including targeted compounds and hematopoietic stem cell transplantation (alloHSCT) in complete remission [52].

The development of additional targeted agents is expanding treatment options. Present biomedical research is focused on compounds targeting apoptotic, epigenetic, and microenvironmental pathways and immune modulators. New developments in computational drug design and the identification of cell-type-specific proteasome substrates may expose further vulnerabilities in AML. Yet, problems such as cardiac toxicities, drug interactions, and resistance mechanisms should be more deeply studied to realize a wider application of precision medicine in AML [55].

11.1. Drug Resistance Mechanisms

In AML, abnormal cancerous transformations occur in myeloid cells with adverse consequences such as infections, hemorrhages, and anemia [56]. Treatment modalities target genetic aberrations; however, abdominal areas where chemoresistance develops in blast compartments during therapy keep the overall patient survival still low. Elucidating the molecular basis of drug resistance is therefore important in the design of effective therapies.

Targeting such resistance foci may shift the tumor dynamics and start exhibiting effects on clones heretofore left unexploited therapeutically. This review, therefore, intends to cover drug resistance issues in AML with special reference to Ara-C, which is among the drugs mostly widely used for chemotherapy. By analyzing the key molecules and pathways involved in Ara-C resistance, the review highlights current strategies to overcome this resistance and underscores the importance of understanding these mechanisms to develop next-generation therapies that enhance treatment efficacy [57].

11.2. Patient Heterogeneity

Acute myeloid leukemia (AML) is a heterogeneous group of hematologic malignancies marked by significant genetic and epigenetic regulation. Recent studies indicate that certain compounds can decrease key transcription factors like MEIS1 while restoring BMP4 expression, leading to cell cycle arrest and apoptosis [58]. Combining drugs that target the epigenetic landscape and transcription factors such as MYC shows promise in treatment. However, translating extensive genomic data into effective therapies remains challenging.

While some targeted drugs have led to successful clinical trials, many genetic alterations have been

studied more thoroughly than their epigenetic counterparts. The loss of epigenetic information is a hallmark of cancer, particularly in AML, where genetic and epigenetic changes collaborate in tumorigenesis. Distinct clonal evolution patterns for these alterations emphasize the need for advanced sequencing techniques to explore epigenetic dynamics in AML further [59].

12. Conclusion

The updated European Leukemia, Net recommendations on AML molecular profiling highlight new insights into secondary-type mutations in AML. These mutations can lead to diverse cellular abnormalities and disrupt pathways involved in normal myeloid differentiation through chromatin remodeling proteins. Understanding these mechanisms may pave the way for selective therapeutic strategies in preclinical studies.

Recent laboratory and patient-based studies have enhanced our understanding of the mutational landscape, supporting the development of targeted therapies. Current treatments focus on specific genetic lesions, and advancements in molecular profiling are expected to refine approaches to targeting AML cells. New mutations alongside NPM1, TET2, SRSF2, U2AF1, ZRSR2, ASXL1, IDH1/2, PDGFRA, FLT3, and CBL provide insights into clonal evolution within cytogenetically defined groups. While hopes for curing AML have evolved, the complexity of genetic, epigenetic, and transcriptomic data presents new challenges. Comprehensive data may lead to effective detection tests for early disease onset, and ongoing collaborative research across global therapeutic cohorts will be crucial for success.

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