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Acute Myeloid Leukemia Overview With Focus On Small Molecules Treatment

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Abstract. Acute myeloid leukemia (AML) is the most prevalent subtype of acute leukemia in adults, posing crucial challenges in terms of prognosis, treatment, and relapse. This is particularly evident in elderly patients, who frequently present with comorbidities that complicate their clinical management. This paper examines small molecule therapies that have demonstrated promise in improving AML treatment outcomes, and explores the mechanisms and clinical advancements associated with targeted therapies, including IDH inhibitors, BCL-2 antagonists, FLT3 inhibitors, menin antagonists, and E-selectin inhibitors. Highlighting the potential of combination therapies, it discusses the challenge of treatment resistance, noting that innovative combinations can significantly improve therapeutic efficacy and patient response rates. The result indicates that IDH inhibitors can achieve response rates exceeding 40%, while FLT3 inhibitors have been associated with improved overall survival by approximately 30% when used in conjunction with standard chemotherapy regimens. This paper ultimately contributes to a deeper comprehension of the role of small molecule therapies in AML, thus, underscoring their therapeutic value to improve patient outcomes significantly and provide insights for future research directions in the field.

Keywords: Acute Myeloid Leukemia, IDH Inhibitors, FLT3 Inhibitors, TP53 Mutations, Small Molecule Therapies.

1. Introduction

AML is a clinical heterogeneous cancer with characters of expansion and clonal proliferation of abnormally differentiated myeloid progenitor cells infiltrating bone marrow (BM), blood and other tissues, resulting hematopoietic function failure [1]. While significant advances have been made since introducing cytarabine plus anthracycline in the 1970s, challenges remain, particularly in developing targeted treatments for the broader spectrum of AML and reduce their side effects. Current therapies, including chemotherapy and monoclonal antibodies, often come with substantial toxicities and limited efficacy in certain patient populations [2]. Notably, one subtype of AML has demonstrated success with targeted therapies like all-trans retinoic acid, yet similar advancements for other AML subtypes have been elusive [3]. This paper investigates AML pathophysiology, classification, and diagnosis while focusing on advancements in small molecule targeted therapies, analyzing their mechanisms of action, therapeutic efficacy, and the emergence of resistance. Through the review of current literature and clinical trial findings, the research aims to highlight advancements in small molecule therapies, such as IDH and FLT3 inhibitors, and their impact on patient outcomes. Understanding these therapies is key to

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improving treatment strategies and addressing unmet needs in AML management, ultimately enhancing patient survival and life quality.

2. Pathophysiology of AML

2.1. Genetic Mutations

AML pathogenesis is influenced by various genetic mutations. Based on the two-hit leukemogenesis model derived from animal studies, class I mutations arise in genes such as K/NRAS, c-KIT, FLT3, TP53 and STAT3, which are associated with the activating pro-proliferative pathways that promote cellular proliferation and survival [4]. For example, FLT3 (transmembrane tyrosine kinase receptor: RTK) is overexpressed on AML blasts, accounting for 1/3 of genetic mutation in AML patients. Upon ligand binding activation, it leads to cellular proliferation, apoptosis and differentiation inhibition. Mutation of FLT3 in AML will cause receptor constitutively activation without ligand signaling, leads to severe cellular proliferation [5]. TP53, a key tumor suppressor gene, is often mutated in AML, resulting in increased genomic instability, complex cytogenetic abnormalities, and chemoresistance [6]. In recent times, class III mutations have been identified, which involve genes such as DNMT3A, TET1, IDH1 and IDH2. These mutations affect epigenetic regulation, impacting cellular proliferation and differentiation. To illustrate, IDH genes encode for an NADP+-dependent enzyme which catalyzes the α-KG oxidative decarboxylation to generate NADPH, and its mutation in AML induces abnormal gene expression, increased DNA hypermethylation, cell proliferation and differentiation [7]. Understanding these mutations and their roles is critical to develop targeted therapies and improved outcomes in AML.

2.2. Chromosomal Rearrangements

In addition to genetic mutations, massive chromosomal rearrangements also play a key role in the pathogenesis of AML. Specific chromosomal translocation events, such as t(8;21) in core-binding factor-associated AML and t(15;17) in acute promyelocytic leukemia (APL), lead to the production of the chimeric proteins RUNX1-RUNX1T1 and PML-RARA. These chimeric proteins inhibit cell maturation and drive leukemic clonal expansion by blocking normal differentiation of myeloid precursor cells. Additionally, other chromosomal rearrangements further contribute to the pathology of AML by altering gene expression patterns and functions and directly interfering with cell signaling pathways. Complex interactions between chromosomal structural changes and gene mutations increase disease heterogeneity. For example, c-KIT mutations co-occur with t(8;21) or inv(16), and NPM1 mutations are frequently accompanied by FLT3-ITD mutations or alterations in the DNMT3A, IDH1/2 genes. The combined effect of these genetic abnormalities serves to accelerate the progression and deterioration of AML [4].

3. Classification and Diagnosis of AmL

The French-American-British (FAB) collaborative group made the first attempt to systematically classify AML into eight subtypes on the based morphological features and cytochemical staining reactions of leukemia cells in 1976. However, the FAB classification system did not adequately consider the role of molecular genetics and chromosomal abnormalities, and the limitations of the FAB system in clinical application gradually became apparent as the pathogenesis of AML was better understood. Therefore, in order to optimize the diagnostic criteria, the World Health Organization (WHO) launched a new classification system for AML in 2001, basing on the comprehensive evaluation of morphological, immunophenotypic, cytogenetic, and clinical features, and subdivided AML into six major disease entities. This classification not only reflects the molecular heterogeneity of AML, but also provides an important basis for prognostic assessment and individualized treatment [1].

The definitive diagnosis of AML typically commences with the analysis of peripheral blood, whereby the presence of a considerable number of aberrant leukocytes or a notable reduction in blood cell count frequently indicates the likelihood of AML. However, hematologic manifestations alone are not sufficient to confirm the diagnosis, and bone marrow aspiration is a critical step in the diagnosis.

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The application of morphological evaluation, cytogenetic analysis and molecular diagnosis to bone marrow samples can facilitate the identification of specific subtypes of leukaemia [8, 9]. Among them, multiparametric flow cytometry is an important diagnostic tool that can accurately differentiate AML from other hematologic disorders by detecting specific surface markers (e.g., CD13, CD33, and CD34) of leukemia cells. Furthermore, in situ hybridization fluorescence (FISH) techniques are commonly employed to identify specific chromosomal rearrangements and gene fusions, such as inv(16) and t(8;21), which are prevalent in AML. These chromosomal abnormalities frequently correlate with prognosis.

Although traditional diagnostic methods are highly accurate, methods such as bone marrow aspiration and tissue biopsy are highly invasive operations that often trigger significant discomfort and pain in patients [10]. Therefore, the development of less invasive testing methods has become a contemporary clinical need. Liquid biopsy, as an emerging non-invasive testing technique, has shown great potential for application in diagnosing and monitoring of AML in recent years. Liquid biopsy can dynamically reflect AML-related gene mutations and molecular alterations by analyzing exosomes in patients' blood or other body fluids, circulating tumor cells (CTCs), and circulating tumor DNA (ctDNA) [8, 10].

With the advancement of molecular diagnostic techniques, the liquid biopsies' detection sensitivity and specificity have been significantly improved, especially when combined with digital PCR (dPCR) and next-generation sequencing (NGS) technologies, liquid biopsies are able to capture AML-associated genetic variations more precisely. Studies have shown that liquid biopsy excels in detecting common AML mutations (e.g., NPM1 and FLT3-ITD) as well as identifying low-frequency clonal mutations, which is particularly clinically significant in the early identification of high-risk patients and monitoring of disease recurrence. Liquid biopsy not only reduces patient pain but also allows for more frequent monitoring than traditional bone marrow aspiration, and is particularly suitable for the detecting microscopic residual disease (MRD) during the course of the disease. Although liquid biopsy has brought a new way of thinking about AML diagnosis, its popularization in clinical application still faces many challenges. First, because of the highly heterogeneous nature of AML cells, some patients have low levels of circulating leukemia cells, which may affect the sensitivity of the test. Second, the standardization of different testing platforms has not been fully established, and the consistency of data across laboratories still needs further validation. Therefore, future studies should aim to improve the specificity and sensitivity of liquid biopsy technology, and promote the optimization and standardization of the testing process to ensure its wide application in AML diagnosis, prognostic assessment and efficacy monitoring [8, 10].

4. Therapeutic Strategies with Small Molecule Drugs

Although cytotoxic and antimetabolic chemotherapy remains the mainstay of treatment for AML, its extensive nonselective toxicity frequently leads to increased risk of mucositis, diarrhea, opportunistic infections, cardiotoxicity, and secondary neoplasms. Some monoclonal antibodies, such as Gemtuzumab Ozogamicin conjugated with anti-CD33 drug, have been linked to fatal hepatotoxicity despite limited efficacy in specific cytogenetic subtypes [2]. Despite advances in targeted therapies, only all-trans retinoic acid is currently efficacious in the subtype of APL by acting on the PML-RARA gene [3]. Targeted therapies for other AML subtypes still face significant challenges. In 2015, FDA approved the FLT3 inhibitor Midostaurin as a new drug for treating AML [11]. Subsequently, a series of new small molecule targeted drugs have shown therapeutic potential, as shown in Figure 1. And the mechanism of action, efficacy and clinical trial results of these drugs are described in detail below.

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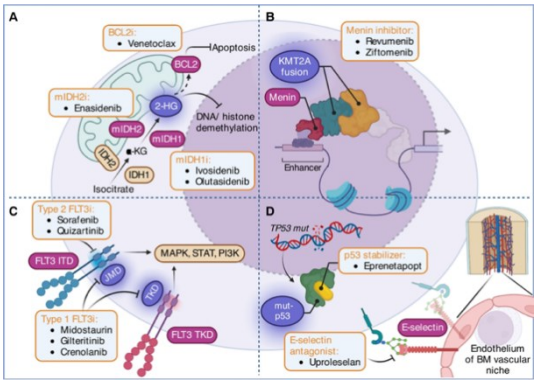

Figure 1. Small Molecules Targeting AML via Various Mechanisms (A. IDH inhibitors can antagonize secretion of 2-hydroxyglutarate, causing cell differentiation. BLC-2 inhibitor leads to the apoptosis of pro-apoptotic proteins; B. Menin inhibitor disrupts protein fusion KMT2A to lead to cell differentiation; C. Type I FLT3 inhibitors works by inhibiting both TKD and ITD mutation, and type 2 only inhibits ITD mutation; D. Enrenetapopt metabolite stabilizes mutant p53 and recover their DNA binding activity. E-selection antagonist helps restore cytotoxic medications sensitivity [12].

4.1. IDH Mutation Targeted Therapy

IDH gene mutations are particularly common in AML, with IDH1 and IDH2 mutations accounting for 8-14% and 9-19% of the patient population, respectively. These mutations hinder cell differentiation and promote leukemia by acquiring neoenzyme activity, leading to 2-hydroxyglutarate (2-HG) production. IDH1 and IDH2 is located in the cytoplasm and mitochondria respectively, and mutations in both inhibit the demethylation of key enzymes (e.g., TET2, KDM4C), leading to histones and DNA hypermethylation, and blocking the normal pathway of cell differentiation [13,14]. Enasidenib is the first FDA-approved mIDH2 inhibitor specifically designed for treating relapsed/refractory (R/R) AML with IDH2 mutations, which prevents 2-HG production by binding to and stabilizing the open conformation of mIDH2, lifting the blockage of differentiation and allowing normal blood cells to mature. In a phase 1/2 trial including 345 patients, a 100 mg daily dose of enasidenib resulted in an overall response rate (ORR) of 38.8% with a 5.6 months median duration of response. The median overall survival (OS) was 8.8 months and complete remission (CR) rate was 19.6%. Common grade 3-4 adverse events included IDH differentiation syndrome (6.4%), thrombocytopenia (6.7%), and indirect hyperbilirubinemia (10.4%). In an independent cohort of newly diagnosed AML patients, the ORR was 30.8% with a median survival of 11.3 months, but this cohort was not accounted within the FDA approval [15]. In contrast, an mIDH1 inhibitor: Ivosidenib blocks 2-HG production and restores cell differentiation by competitively inhibiting the active site of mIDH1. It was approved for R/R mIDH1 AML in 2018 July, with a 30.4% CR/CRh, an 41.6% overall response rate, and a 8.8 months median OS in clinical trials. Common adverse events included IDH differentiation syndrome (3.9%) and QT interval prolongation (7.8%). In 2019, ivosidenib was approved as the first-line treatment, with an elevated median OS of 12.6 months, CR/CRh rate of 42.4%, and significant improvements in blood counts and quality of life [15]. In addition, Olutasidenib is a novel mIDH1 oral inhibitor for treating R/R AML. In a pivotal study consisting of 153 patients treated with Olutasidenib, it achieved a 35% CR/CRh rate, an overall 48% response rate, 25.9 months of median duration of CR/CRh, and an overall 11.6 months survival. Thirty-four percent of transfusion-dependent patients achieved transfusion independence. Common grade 3-4 adverse events contained febrile neutropenia and anemia (20% each), demonstrating a manageable safety profile and durable efficacy in clinical use [16].

4.2. BCL-2 Inhibitor: Venetoclax

BCL-2 belonging to the B-cell lymphoma-2 family, is an anti-apoptotic factor localized in the mitochondrial outer membrane, which mainly regulates apoptotic pathway's permeability. BCL-2 gene mutations lead to the overexpression of its protein, which hinders pro-apoptotic signaling, and then leads

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to the dysregulated apoptosis and the promotion of the survival and accumulation of tumor cells, especially in hematological malignant tumors such as AML, where it plays a key role. Playing a key role in hematologic malignancies such as AML. Overexpressed BCL-2 protein inhibits its pro-apoptotic function by binding to pro-apoptotic proteins: BIM, thereby enhancing cellular resistance to apoptotic signaling [17]. Venetoclax is an FDA-approved, highly selective inhibitor of BCL-2. Its mechanism of action mimics the structural domain of BH3, displacing pro-apoptotic BIM from BCL-2: anti-apoptotic proteins, which activates BAK and BAX proteins, initiating increased permeability of the mitochondrial outer membrane, leading to the cytochrome c release, triggering downstream apoptotic signaling pathways, and ultimately contributing to the apoptotic death of malignant cells. Venetoclax was initially used for the lymphoid malignancies treatment, and monotherapy in AML showed modest activity but failed to achieve CR. However, when Venetoclax was combined with a demethylating agent, such as decitabine or azacitidine, efficacy was significantly enhanced. In a pivotal study of 145 elderly AML patients who were not suitable for intensive chemotherapy, the combination therapy resulted in 73% CR with incomplete hematologic recovery (CRi), with a 65% CR/CRi, particularly in patients with low-risk cytogenetics. A phase III (VIALE-A) study further demonstrated that the combination therapy resulted in a median OS of 14.7 months in contrast to 9.7 months for azacitidine alone, setting a new care standard for this specific patient population [16].

4.3. FLT3 Mutations Targeting Inhibitors

FLT3 is a RTK consisting of two tyrosine kinase structural domains (TKD1 and TKD2) and juxtamembrane structural domain (JMD), mainly expressed in lymphoid and myeloid progenitor cells [18, 19]. About 30% of AML patients carry FLT3 mutations, usually TKD1 internal tandem duplication (ITD) and JMD, which lead to sustained FLT3 activation and promote cell proliferation and survival [20, 21]. In addition, mutations in TKD codon 835 can lock FLT3 in an active state [22]. FLT3 inhibitors are divided into 2 generations. The first generation (e.g., sorafenib, midostaurin) lacks specificity and produces broad off-target effects, whereas the second generation (e.g., quisatinib, giltinanib) is more selective and targets only FLT3 [23]. Inhibitors can also be categorized as type I and type II: type I (midostaurin, giltinanib) antagonizes TKD and ITD mutations, and type II (sorafenib, quisatinib) specifically targets ITD mutations [24]. As of July 2023, only quisatinib is FDA-approved for FLT3-mutated AML, and other inhibitors still in clinical trials or for other diseases.

Among Type I FLT3 inhibitors, midostaurin reduced platelet counts in monotherapy but did not show CR. In the RATIFY trial, the median OS of patients with FLT3 mutations was significantly improved to 74.7 months compared with 25.6 months in the placebo group, resulting in FDA approval. However, some subgroup analyses have demonstrated limited efficacy and that midostaurin exhibits a higher risk of toxicity and infection when combined with hypomethylating agents (HMAs). In patients undertaking allogeneic hematopoietic cell transplantation (HCT), midostaurin is well tolerated, with a 26 months median survival in this patient population, and has therefore become the standard of care for patients with FLT3-mutant AML on intensive chemotherapy [12]. Gilitinib has an overall 50% response rate in R/R FLT3 mutant AML. The ADMIRAL trial showed an improved complete remission (CRc) rate of 54% (vs. 22%) and a median 9.3 months OS in comparison to 5.6 months in the chemotherapy arm when compared to salvage chemotherapy. Although the CRc rate was elevated to 58% in combination with azacitidine, the difference in OS was negligible. Gilteritinib in combination with Venetoclax had a CRc rate of 75%, but greatly triggered myelosuppression. Crenolanib is used in adult patients ($\geq$18 years of age) with newly diagnosed FLT3-mutant AML, combining with intensive chemotherapy (cytarabine and anthracyclines), and them by consolidation therapy and/or allogeneic transplantation. In a 44-patients study with a median 57 years, the complete remission (CR) was 77%, overall response rate was 86%, and 9% an incomplete remission (CRi). 90% of patients younger than 60 years old achieved a response, with a median event-free survival of 44.7 months, and when relpased, no new FLT3-mutant clones were identified. Seveere adverse reactions included febrile diarrhoea and neutropenia [25].

Among Type II FLT3 inhibitors, sorafenib showed a 10% complete response rate in a 55 R/R AML patients phase I trial. While sorafenib together with induction therapy improved relapse-free survival

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(RFS), it did not have a significant impact on OS. The trial also found increased toxicity, particularly in the non-FLT3 mutant group. Studies of sorafenib in the post-allogeneic (HCT setting have shown an improvement in RFS with a trend toward improved OS, and no excess toxicity was observed, making it recommended for treating high-risk FLT3-ITD patients [12]. Although quixatinib shows promise as a monotherapy for R/R AML, it has a non-targeting effect on c-Kit, which results in significant myelosuppression. In a phase II trial of 333 patients, FLT3-ITD patients had 50% complete response rate while non-FLT3-ITD patients had 30%. Although the phase III QuANTUM-R trial showed that quisatinib prolonged OS, the FDA has not yet approved it as monotherapy. Quisatinib, when combined with the "7+3" induction combination therapy, had an OS of 32 months, significantly better than the 15 months in the placebo group, despite an increased incidence of neutropenia, and is currently seeking FDA approval for use in recently diagnosed FLT3-ITD AML patients [12].

4.4. TP53 Mutated Targeting

Eprenetapopt is a prodrug identified by chemical screening to inhibit tumour growth in mutant TP53 cells. Its main mechanism is to bind to mutant p53, restoring its wild-type conformation and DNA-binding ability, which in turn activates tumour suppressor functions and p53 target genes, causing cell apoptosis and cycle arrest. In addition, Eprenetapopt exerts p53-independent effects by depleting glutathione (GSH), inducing ferroptosis and increasing reactive oxygen species (ROS). Its inhibition of thioredoxin reductase 1 (TrxR1) disrupts redox homeostasis, enhances ROS production and decreases deoxyribonucleotide (dNTP) levels, thus leading to cell apoptosis and cycle arrest [26]. In a phase I trial, 15 haematological malignancies patients and 7 prostate cancer patients were treated with Eprenetapopt. Although the eprenetapopt was well tolerated, no significant clinical response was observed. Subsequently, another phase I-II trial combining Eprenetapopt with azacitidine in 55 newly diagnosed patients with AML or myelodysplastic syndromes (MDS) and a TP53 mutation demonstrated an 80% overall response rate (ORR), an OS of 15 months and a median 8 months duration of response. Similar studies found 33% and 62% overall response rates in patients with AML and MDS, respectively. Also, a phase III trial contrasting the combination with azacitidine alone did not reach the primary endpoint of complete response rate; while a phase II study exhibited a 14.5 months median relapse-free survival in patients with TP53 mutations [12].

4.5. Menin Antagonists and E-selectin Inhibitors

By interacting with chromatin regulators and transcription factors, particularly KMT2A, menin regulates gene expression. This interaction is preserved in KMT2A fused proteins and is important for HOX gene promoter binding. KMT2Ar leukaemia exhibits overexpression of the HOX gene and MEIS1, whereas NPM1 mutations (NPM1c) lead to similar gene expression profiles and promote leukaemic transformation.Menin inhibitors such as revumenib and ziftomenib are able to disrupt the interaction of menin with KMT2A, inhibit the leukaemia-causing transcriptional program and induce apoptosis, while protecting normal haematopoiesis [27]. In the AUGMENT-101 trial, revumenib was shown to have an (53% ORR in patients with R/R AML) with KMT2Ar or NPM1mt mutations, of whom 18 patients achieved a median 9-month complete remission (CR). Grade 3 QT prolongation was the only dose-limiting toxicity. Ziftomenib, at the recommended dose of 600 mg in the KOMET-001 trial, had a 35% CR rate in patients which had NPM1mt AML. Both drugs are undergoing further studies to assess their safety and efficacy [27]. E-selectin, as a cell adhesion molecule, is overexpressed in AML that enhances the resistance of leukaemia cells to chemotherapy. The small molecule Uproleselan inhibits E-selectin and promotes the entry of leukaemia cells into the bloodstream, hence increasing their sensitivity to cytotoxic chemotherapy. In addition, E-selectin inhibition can affect tumour metastasis and reduce tumour cell resistance [12, 28]. The therapeutic efficacy of Uproleselan combining with mitoxantrone, etoposide, and cytarabine was evaluated in 91 newly diagnosed R/R AML patients in a phase 1/2 trial. Recommended 10mg/kg dose in phase II showed to be well tolerated, with only 2% of patients developing grade 3/4 mucositis. Overall remission rates were 72% in newly diagnosed patients and 41% in R/R patients, with 69% of evaluable patients achieving negative measurable residual disease. 8.8

months and 12.6 months median OS was detected in R/R patients newly diagnosed patients separately. Highly expressed of E-selectin ligands is associated with improved prognosis, necessitating further phase III trials [29].

5. Conclusion

This paper reviews the pathophysiology, classification and diagnosis of AML and focuses on recent advances in small molecule targeted therapies. Studies have indicated that IDH, FLT3 and BCL-2 antagonists have made significant progress in treating patients with specific mutant AML, and some drugs such as enasidenib and midostaurin have been approved by the FDA, raising the standard of care. In addition, novel inhibitors targeting TP53, menin and e-selectin are in clinical trials and show promise. However, AML is a highly heterogeneous disease whose incidence grows significantly with age, and the prognosis for elderly patients is particularly poor, with a mortality rate that remains as high as 70% within one year of diagnosis. Although targeted therapies have brought improvements for some patients, limitations remain. The molecular complexity of AML makes it difficult to completely eliminate leukemia stem cells with a single targeted therapy, and the risk of relapse remains high. In addition, there is limited therapeutic enhancement for older patients, and the resistance and safety of targeted therapies still need to be further evaluated. The high cost of targeted drugs and the toxic side effects of some therapies also limit their wide application. Future studies should pay more attention to the heterogeneity and molecular mechanisms of AML to optimize the combination strategy of targeted therapies. In addition, the development of low-toxicity therapies and novel biomarkers for elderly patients may advance the development of individualized treatment for AML.

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