A personalized approach to acute myeloid leukemia therapy: current options

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Abstract: Therapeutic options for acute myeloid leukemia (AML) have remained unchanged for nearly the past 5 decades, with cytarabine and anthracyclines and use of hypomethylating agents for less intensive therapy. Implementation of large-scale genomic studies in the past decade has unraveled the genetic landscape and molecular etiology of AML. The approval of several novel drugs for targeted therapy, including midostaurin, enasidenib, ivosidenib, gemtuzumab–ozogamicin, and CPX351 by the US Food and Drug Administration has widened the treatment options for clinicians treating AML. This review focuses on some of these novel therapies and other promising agents under development, along with key clinical trial findings in AML.

Keywords: acute myeloid leukemia, personalized medicine, chemotherapy, molecular markers

Background

Acute myeloid leukemia (AML) is characterized by blocked myeloid-lineage differentiation and accumulation of myeloid blast cells in the bone-marrow that results in catastrophic bone-marrow failure. AML is a highly heterogeneous disease driven by different mutations that affect signaling pathways, transcription factors, and epigenetic regulators. The current treatment for AML starts with induction chemotherapy (7+3), followed by a few cycles of consolidation chemotherapy or an allogeneic hematopoietic stem-cell transplantation (allo-HSCT).

The disease's prognosis and outcomes in adults and the elderly, who account for the majority of AML patients, remains poor. The ever-growing advancement in genomic technologies allows us to have an unprecedented view of the spectrum and frequency of mutations, their clonal nature, and their evolution during progression of the disease and the epigenetic modulation of the disease. Incorporating "omics" data with ex vivo high-throughput drug screening has the potential to tailor therapy for patients. This review provides an overview on novel targeted therapies, approved drugs, and ongoing clinical trials with the aim of personalizing AML therapy (Figure 1).

A nucleoside analogue and an antibiotic

Cytarabine, a nucleoside analogue, and anthracyclines (daunorubicin, idarubicin, doxorubicin) derived from antibiotics have been an integral part of the chemotherapy regimen in treating AML for the past 5 decades. Cytarabine as a continuous infusion for 7 days with addition of anthracyclines as a short infusion in the first 3 days forms the basis of chemotherapy (7+3 regimen), drastically reducing the leukemia burden in
patients. This, followed by high-dose cytarabine therapy for consolidation or allo-HSCT, has remained the standard treatment for AML patients. We and others have evaluated the mechanisms of resistance to cytarabine and anthracyclines extensively, and have shown how leukemic cells evolve and adapt to become resistant to chemotherapy.\textsuperscript{8–14} In vitro and preclinical studies with novel agents in combination with standard chemotherapeutic drugs have shown to overcome drug resistance in AML.\textsuperscript{15–19} This could pave the way to the introduction of promising agents that would help to personalize therapy for AML patients.

**CPX351**

Cytarabine and daunorubicin have been the backbone of conventional chemotherapy in AML over the past four decades. CPX351, a novel nanoliposomal formulation of cytarabine and daunorubicin in a 5:1 molar ratio, leads to enhanced intracellular uptake of the drug and reduced clearance compared to the conventional 7+3 regimen.\textsuperscript{20–22} A multicenter phase III trial comparing CPX351 with standard induction and consolidation among elderly patients showed significantly improved overall survival (OS; 9.6 months vs 5.9 months, \(P=0.005\)) with CPX351 compared to the standard 7+3 arm (A group of patients receiving a specific treatment). Patients in the CPX351 arm showed a substantial increase in mean terminal half-life compared to the conventional 7+3 infusion (24.5 hours for CPX351 vs 3 hours for cytarabine), although the time to neutrophil and platelet recovery was longer. Also, more patients in the CPX351 arm were eligible for an allotransplant than the 7
+3 arm (34% versus 25%). CPX351 was approved by the FDA in 2017 for fit elderly patients with treatment-related AML (t-AML) and for de novo AML with myelodysplastic syndrome (MDS).

Hypomethylating agents
The hypomethylating agents azacitidine (Aza) and decitabine are analogues of cytosine with replacement of the fifth carbon atom by a nitrogen atom. For the past decade, they have been commonly used in AML patients who are not eligible for cytarabine-based intensive therapy. Aza has a short half-life. The new oral formulation of Aza, CC486 is in early-stage trials testing its efficacy. CC486 could possibly enhance antileukemic activity by increasing drug-exposure time. Extended-dosing studies with CC486 have shown it to be well tolerated, with a toxicity profile comparable to Aza. Patients who fail therapy with Aza respond well with extended dosing of CC486, indicating involvement of contrasting demethylation patterns due to prolonged exposure. Efficacy of CC486 as maintenance therapy post-HSCT (NCT01835587) and after induction/consolidation for AML/MDS patients is under investigation.

Guadecitabine is a next-generation decitabine that is resistant to deamination by cytidine deaminase, thereby increasing its half-life and leading to prolonged exposure during the S-phase and enhanced cell kill. Patients ineligible for intensive therapy who are treatment-naive responded well to guadecitabine in early-phase trials, with >50% of patients achieving composite complete remission (CR). A large multicenter phase III trial with guadecitabine or treatment of choice by the physician is under way for previously treated AML (NCT02920008).

Isocitrate dehydrogenase inhibitors
IDH catalyzes the oxidative decarboxylation of isocitrate to α-ketogluutarate while converting NAD(P)⁺ to NAD(P)H and maintaining cellular redox homeostasis. Mutations in IDH1 and IDH2 are seen in approximately 6%–10% and 9%–13% of patients with AML. Mutant IDH starts catalyzing the α-ketoglutarate (αKG) to the oncometabolite D₂-hydroxyglutarate (D₂HG). This in turn acts as a competitive antagonist for αKG and downregulates the family of αKG-dependent dioxygenases, in particular histone lysine demethylases and the Ten eleven translocation (TET) family of DNA hydroxylases, both in vitro and in vivo. There is a resultant elevation in histone methylation and 5-methylcytosine, leading to global hypermethylation with lack of global gene expression, causing maturation arrest. IDH2 mutations produce high amounts of D₂HG with increased cellular expression compared to IDH1-mutated cells. Studies have shown that IDH1-mutated cells depend on the wild-type (WT) IDH1 allele for enhanced D₂HG production.

Enasidenib (previously known as AG221) has been shown to selectively target the IDH2 mutation. In a recent study conducted on relapsed refractory AML (RR-AML) patients with IDH2 mutations treated with enasidenib monotherapy, the overall response rate was 40%, median response duration 5.8 months and median OS 9.3 months. Among the 34 patients who achieved CR with enasidenib, the median OS was 19.7 months. Inhibitors of IDH have been shown to produce synergy with Aza, as both drugs reduce DNA methylation and evade blockade in cell differentiation. Ivosidenib (AG120) was approved in 2018 for RR-AML with IDH1 mutation. Ivosidenib efficacy was tested in a multicenter trial with 179 RR-AML patients. The overall response rates was 41.6%, with 21.6% achieving CR. Treatment using enasidenib and ivosidenib induces differentiation syndrome, owing to the drugs’ mechanisms of action.

FLT3 inhibitors
Approximately a third of adult patients with AML carry mutations in the FMS like tyrosine kinase 3 (FLT3) receptor. FLT3 mutation leads to aberrant downstream proliferation signals independently of ligand activation. Internal tandem duplication (ITD) mutations in the FLT3 gene are seen in about 22% of AML patients, and is one of the driver mutations that presents with high leukemic burden and confers a poor prognosis (high incidence of relapse). The remaining 8% of mutations occur in the tyrosine-kinase domain (TKD), with unknown prognosis. The FLT3-WT vs FLT3-ITD allelic ratio is also an important prognostic factor. According to European LeukemiaNet guidelines, patients with an allelic ratio <0.5 or low ITD with an Nucleophosmin (NPM1) mutations are classified under “good prognosis”, while patients with high allelic ratio (>0.5 or high ITD) and NPM1-WT are grouped under the adverse-risk category.

Given the adverse clinical outcomes due to the FLT3-ITD mutation in AML patients, induction chemotherapy followed by HSCT is warranted, as it lowers the incidence of relapse and improves survival rates. The incidence of relapse is higher in patients with ITD mutations undergoing allo-HSCT with lower OS compared to FLT3-WT.
This has vastly driven attempts to target the FLT3 mutation with kinase inhibitors (KIs) and clinical trials for FLT3 targeted therapy in combination with induction chemotherapy or as maintenance therapy following HSCT.

Midostaurin (Mido), a multi-KI, has been shown to inhibit FLT3 ITD–receptor activity and showed synergistic effects with the standard chemotherapeutic drugs cytarabine and daunorubicin in preclinical studies.46 A phase II trial using Mido as monotherapy for RR-AML/MDS patients with FLT3 mutations showed reduction in peripheral blasts in 70% of patients.47 Subsequently, a phase III randomized trial (RATIFY) that spanned 10 years48 comparing Mido and placebo along with standard chemotherapy in AML patients <60 years of age harbouring FLT3 mutations (ITD, TKD) was conducted. Mido treatment resulted in significant improvements in OS (HR 0.78, P=0.009) and event-free survival (HR 0.78, P=0.002) at 4 years, despite an insignificant difference in the rate of CR. OS was also higher for patients in the Mido arm who underwent HSCT in first remission49 As a multi KI, Mido may also have inhibitory action on the FLT3-WT receptor, as shown by significant blast reduction in FLT3-WT receptor, based on which a phase III study on FLT3-WT AML patients with Mido has been initiated (NCT003512197).50 In April 2017, Mido in combination with conventional chemotherapy was approved for treatment in newly diagnosed AML patients with FLT3 mutations <60 years of age by the FDA.

Second-generation FLT3 tyrosine-kinase inhibitors

The first generation tyrosine KIs (TKIs) sorafenib, lestaurtinib, and Mido are broad spectrum multi-KIs. The next-generation TKIs quizartinib, crenolanib, and gilteritinib are more selective and potent oral drugs that are currently in clinical trials. These drugs have reduced toxicity compared to the first-generation TKIs.51 There are encouraging clinical data for these second-generation TKIs, as shown in Tables 1 and 2.52–57 Resistance to TKIs has been a major roadblock in AML therapy,

<table>
<thead>
<tr>
<th>Table 1 Select clinical studies on second-generation TKIs with induction therapy</th>
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<td><strong>Study</strong></td>
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<td>Crenolanib</td>
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<td>Quizartinib</td>
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**Abbreviations:** TKIs, tyrosine-kinase inhibitors; AML, acute myeloid leukemia; CR, complete remission.

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<th>Table 2 Select clinical studies on second-generation TKIs as monotherapy</th>
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<td><strong>Study</strong></td>
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**Abbreviations:** TKIs, tyrosine-kinase inhibitors; AML, acute myeloid leukemia; CR, complete remission.
making these TKIs less efficient as single agents. Resistance mechanisms are diverse, and one known mechanisms is acquisition of FLT3 point mutations in TKD during therapy that may mediate resistance. Elevated levels of FLT3 ligands in the bone-marrow microenvironment after induction therapy leads to activation of FLT3-WT receptors that are sensitive to ligands but resistant to FLT3 inhibitors. In addition, rewired signaling pathways and additional driver mutations in other genes also lead to TKI resistance. One strategy to overcome resistance is to employ combination therapy that targets different entities of the leukemic cell. FLT3 inhibitors in combination with the hypomethylating agent 5-Aza has been shown to alter methylation patterns in FLT3-mutated cells and overcome stromal protection.

**Gemtuzumab ozogamicin**

The CD33 antigen is a transmembrane receptor and myeloid-differentiation marker that is expressed in most AMLs. Its extracellular immunoglobulin-like V domain can be exploited using antibody–drug conjugate (anti-CD33-directed) therapy to target CD33-positive leukemic blasts. Gemtuzumab ozogamicin (GO) is an anti-CD33-directed antibody–drug conjugate comprised of a human mAb linked to calicheamicin. GO binds to the CD33 antigen present on the surface of leukemic blasts and myeloid-precursor cells and localizes into the cell. The complex breaks after localization and the released calicheamicin binds to DNA, resulting in DNA double-strand breaks and initiates apoptosis. GO was initially approved in 2000 as monotherapy (two doses of 9 mg/m², 14 days apart) for older patients (60 years) in first relapse with CD33-positive AML who were not eligible for chemotherapy. In 2010, during the phase III SWOG S0106 study the drug was withdrawn from the market, due to increased mortality when used in combination with induction and consolidation therapy (single dose of 6 mg/m² on day 4).

Subsequent trials (ALFA-0701 phase III study, AML-19 phase III study, MyloFrance 1 and 2 studies) were conducted with lower doses of GO (3 mg/m² on days 1, 4, and 7, and 6 mg/m² on day 1 and 3 mg/m² on day 4) in patients with de novo AML. After a long break, GO was reapproved by the FDA in 2017 for treating CD33-positive newly diagnosed or RR-AML, with a black-book warning for hepatotoxicity and veno-occlusivedisease. A subtype of AML known as core binding factor (CBF) AML responds well to GO. The biological significance of CBF-AML blast cells arises from matured committed leukemia-initiating cells with CD33 expression. Multi drug transporter 1 (MDR1) is known to extrude GO from leukemic cells and reduce its efficacy. CBF-AML inherently has reduced expression of MDR1, allowing cells to retain GO and enhance cytotoxicity.

**Targeting leukemic stem cells**

Leukemic stem cells (LSCs) are believed to be responsible for disease relapse in AML, as they escape conventional chemotherapy. Targeting LSCs in AML has been a paramount task because of the absence of a consistent surface marker that distinguishes HSCs from LSCs. Many studies have described multiple immunophenotypic differences that may distinguish LSCs from HSCs (CD25, CD44, CD96, CD93, and CD123), but a universal surface marker for LSCs is yet to be identified. CD123 has been the only marker under constant investigation to target LSCs compared to the other surface markers. SL401 is the first CD123 monoclonal antibody fused with a catalytic unit of a diphtheria toxin introduced to target LSCs. In a phase I trial conducted on 74 patients with RR-AML or de novo AML, CR was observed in two patients, four patients showed 50% blast reduction in bone marrow, while 14 showed reduction in blast percentage from baseline. Capillary-leak syndrome was one of the noted adverse events in this trial, but was manageable with early intervention. SL401 is now currently being investigated as remission-maintenance therapy for high-risk AML in CR1 or CR2 to improve relapse-free survival (phase II trial NCT02270463).

Flotetuzumab is a bispecific (CD123 × CD3) dual-affinity retargeting novel T cell–redirecting molecule. A phase I dose-escalation study in RR-AML/MDS related AML patients demonstrated an overall response of 43% (six of 14 patients), while two patients showed consistent disease with only 20–25% blast reduction. Consistent activation of CD4 and CD8 T cells was observed in the peripheral blood. Toxicity profiles mainly consisted of cytokine-release syndrome. The study continues with cohort expansion (24 RR-AML and 24 MDS-AML [NCT02152956]).

**Novel therapies**

**Mutant TP53 activation**

Tumour suppressor p53 (TP53) is one of the commonly mutated genes in malignancies. About 5–10% of de
novo AML and 30% of t-AML harbor TP53 mutations, conferring poor prognosis. The mutation leads to misfolded formation of the transcription factor and voiding its ability to bind DNA. The prodrug APR246 spontaneously gets converted to its active compound methylene quinuclidinone at physiological pH. This compound then stabilizes the mutant protein by covalently binding to cysteine residues, leading to refolding and restoration of p53 function.

Promising initial results were observed from phase IB/II trials using APR246 in combination with Aza conducted on MDS/AML patients with TP53 mutations (n=11). There was a 100% response rate by International Working Group criteria, and nine of eleven patients achieved CR.

BCL2 inhibitor
B-cell lymphoma 2 (BCL2), an antiapoptotic protein highly expressed in AML cells, confers resistance to conventional therapy by increasing mitochondrial fitness and prevents apoptosis. BCL2 is also highly upregulated in the LSC compartment, aiding quiescence and disease relapse. Venetoclax (Ven) is a BCL2 inhibitor that blocks its antiapoptotic activity, potentiates the effect of other partnered drugs, and enhances apoptosis. In a phase IB/II trial of Ven in combination with low-dose cytarabine in elderly AML patients unfit for intensive therapy, 62% of patients achieved CR, with median OS of 11.4 months. Further promising results were observed combining Ven with Aza in elderly AML patients unfit for therapy, with CR 61% and median OS 17.5 months in early-phase trials. Phase III randomized trials are ongoing comparing the combination of Aza and Ven versus Aza monotherapy (NCT02993523).

Immune checkpoint inhibitors
Allogenic transplant remains the superior therapy for AML, mainly due to the graft vs. leukemia effect produced by the donor cells. AML cells express high levels of Programmed death ligand 1 (PDL-1), an inhibitory molecule that suppresses the cytotoxic activity of T cells, leading to immune exhaustion, and increases the chances of relapse. Immune modulation could effectively work in the AML context, rewiring the immune system. Early-phase trials with nivolumab (PD1 inhibitor) and Aza in RR-AML patients have demonstrated CR of 22% and median OS of 15 months in responders. Phase II trials combining nivolumab with conventional 7+3 in newly diagnosed AML showed CR and CR with an incomplete hematologic recovery rate of 72%, and nine patients were eligible for transplant. Studies evaluating the efficacy of pembrolizumab (PD1 inhibitor) with other agents are ongoing NCT02996474, NCT02845297. A list of other novel agents in early- and late-phase trials is presented in Table 3.

Standard chemotherapy to personalizing therapy: a reality?
Over the past few decades of treatment and trials, it has become clear that “one size does not fit all” in terms of treating AML. The best and first example would be acute promyelocytic leukemia. Until 1987, this was treated solely with intensive chemotherapy. It was only after 1992 that the combination of all-trans retinoic acid and arsenic trioxide to induce apoptosis and differentiation created a benchmark in the treatment of acute promyelocytic leukemia. Years later, the genomic landscape of AML helped us to understand that somatic mutations carry prognostic importance no less than recurrent cytogenetic abnormalities. Only after the discovery of somatic mutations did personalizing therapy for treating AML came into the limelight.

Though there are studies to substantiate the need and importance of novel therapies targeting different drivers of mutation, there is a setback when this is translated with genomic information alone. Even though genomic testing has been employed in a number of clinical trials on AML patients, it has been hardly used to stratify, due to extended turnaround times, which often delay the treatment. On the other hand, drug-sensitivity testing/ex-vivo high-throughput drug screening can be performed, as it is not time-consuming and a large variety of drugs can be screened within a short time.

Clinical trials like the BEAT AML study aimed to integrate genomic profiling and drug-sensitivity testing in a large cohort of elderly AML patients, which seems promising for making personalization of the treatment regimen for each individual with the disease a reality. We believe that the combination of molecular profiling and ex-vivo drug screening would significantly improve the survival of patients with newly diagnosed and RR-AML (Table 4). Further clinical trials are recommended to substantiate the data obtained from both genomic profiling and ex-vivo high-throughput drug screening in patients. However, newer paradigms incorporating
### Table 3 Novel agents in clinical trials

<table>
<thead>
<tr>
<th>Category of drug target</th>
<th>Drug target</th>
<th>Drug</th>
<th>Trial phase</th>
<th>Remarks</th>
<th>Single agent/combination</th>
<th>Status</th>
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<td>Cell surface receptors</td>
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<td>SL401</td>
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<td>FLT3</td>
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**Table 3** (Continued).

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<td>Combination with low-dose cytarabine (LDAC)</td>
<td>Recruiting</td>
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<td>II</td>
<td>Nonremission AML</td>
<td>Combination with azacitidine</td>
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<td>Category of drug target</td>
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<td>Drug</td>
<td>Trial phase</td>
<td>Remarks</td>
<td>Single agent/combination</td>
<td>Status</td>
<td>Reference</td>
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<td>DOT1L</td>
<td>Pinometostat</td>
<td>I/II</td>
<td>Newly diagnosed AML and MLL gene rearrangement</td>
<td>With standard chemotherapy</td>
<td>Recruiting</td>
<td>NCT03724084</td>
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<td>VII</td>
<td>Relapsed, refractory, or newly diagnosed AML with 11q23 rearrangement</td>
<td>Combination with azacitidine</td>
<td>Not yet recruiting</td>
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<td>IDH1/2</td>
<td>AG221</td>
<td>III</td>
<td>Late stage AML harboring an isocitrate dehydrogenase 2 mutation (IDHENTIFY)</td>
<td>AG221 versus conventional-care regimens (CCRs)</td>
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<td>Bromodomain</td>
<td>CPI0610</td>
<td>VII</td>
<td>Previously treated acute leukemia, MDS, myelodysplastic/myeloproliferative neoplasms, and myelofibrosis</td>
<td>With and without ruxolitinib</td>
<td>Recruiting</td>
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<td>FT1101</td>
<td>I</td>
<td>AML/MDS or non-Hodgkin lymphoma (NHL)</td>
<td>Monotherapy</td>
<td>Recruiting</td>
<td>NCT02543879</td>
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<td>CDK</td>
<td>Alvocidib</td>
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<td>Relapsed/refractory AML with Noxa BH3 priming ≥40% by mitochondrial profiling in bone marrow</td>
<td>Combination with induction therapy</td>
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<td>Palbociclib</td>
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<td>MLL-rearranged acute leukemias AMLSG 23-14/Palbo-AL</td>
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novel agents as monotherapy or in combination with standard care still pose a daunting task.

**Acknowledgments**

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**Disclosure**

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**References**


**Table 4** Ex vivo drug screening–based clinical trials

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<th>High-Throughput Drug-Sensitivity Assay and Genomics-Guided Treatment of Patients with Relapsed or Refractory Acute Leukemia BEAT AML Core Study</th>
<th>Remarks</th>
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<td>Recruiting</td>
<td>NCT02927106</td>
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60 years old with newly diagnosed FLT3-mutated acute myeloid leukemia (AML).

Altman JK, Foran JM, Pratz KW, Trone D, Cortes JE, Tallman MS.


