Alternatives to Intensive Treatment in Patients With AML

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Abstract: A significant proportion of patients with acute myeloid leukemia (AML) are unable to tolerate standard induction chemotherapy regimens. This is particularly true for patients who are of advanced age, have a poor performance status, and/or have significant medical comorbidities. Recent advances in understanding the genetic and molecular properties of AML have led to a spate of new treatment options for patients considered ineligible for standard chemotherapy. Here, we discuss these new treatment options, provide an overview of the completed and ongoing trials of the new agents, and highlight promising future directions in the treatment of AML in patients ineligible for intensive induction chemotherapy.

Background

Acute myeloid leukemia (AML) is a common leukemia that affects primarily older adults, with more than half of new diagnoses made among those older than 65 years of age.1 Standard induction treatment for AML frequently involves intensive cytarabine-based chemotherapy regimens. Treatment-related morbidity and mortality are likely to occur in many patients with these regimens, however, so they may be deemed ineligible for intensive chemotherapy (IC). For decades following the introduction of cytarabine- and anthracycline-based induction chemotherapy in the 1970s, no new treatments were approved for patients with AML. However, recent therapeutic advances show promise for improving survival among patients ineligible for IC. Herein, we present an overview of the treatments for patients with AML ineligible for IC, including both those with US Food and Drug Administration (FDA) approval in AML (Table 1) and those currently under investigation in AML (Table 2). We also review each drug’s mechanism (Figure) and discuss the potential benefits and limitations of the treatments.

Determining Ineligibility for Intensive Chemotherapy

Older patients with AML, especially those aged 75 years and older, are more likely to experience treatment-related morbidity and mortality, have lower rates of complete remission (CR), and have relapsed
generally offered best supportive care (BSC), therapy based on low-dose cytarabine (LDAC), or hospice care. Although LDAC improves survival relative to BSC or hospice care, 1-year survival rates with LDAC remain at approximately 20% to 30%. Because of recent advances in the treatment of patients ineligible for IC, LDAC has largely been replaced as the standard of care, but interest continues in the possibility of alternative cytarabine formulations and combination therapies of LDAC with other agents.

In 2017, the FDA approved a liposomal cytarabine/daunorubicin formulation (CPX-351) for the treatment of therapy-related AML and AML with myelodysplasia-related changes. Approval was based on a phase 3 trial that randomly assigned 309 patients ages 60 to 75 years with newly diagnosed high-risk AML to receive either intensive induction chemotherapy or up to 2 cycles of CPX-351. Overall survival (OS) was significantly longer in the patients who were treated with CPX-351 (OS, 9.56 vs 5.95 months; \( P = .003 \)), and its safety profile was similar

### Table 1. Therapies With FDA-Approved Indications in the Treatment of AML

<table>
<thead>
<tr>
<th>Novel Therapies for AML</th>
<th>FDA-Approved Indication in AML</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypomethylating agents</td>
<td>Treatment of AML in combination with venetoclax for adults 75+ or with comorbidities that preclude IC</td>
</tr>
<tr>
<td>Azacitidine</td>
<td>Treatment of AML in combination with venetoclax for adults 75+ or with comorbidities that preclude IC</td>
</tr>
<tr>
<td>Decitabine</td>
<td>Treatment of AML in combination with venetoclax for adults 75+ or with comorbidities that preclude IC</td>
</tr>
<tr>
<td>CC-486</td>
<td>Maintenance therapy in patients who have AML with CR/CRi after induction chemotherapy and who cannot complete intensive curative therapy</td>
</tr>
<tr>
<td>BCL-2 inhibitors</td>
<td>In combination with AZA, DEC, or LDAC for adults 75+ or with comorbidities that preclude IC</td>
</tr>
<tr>
<td>Venetoclax</td>
<td>Treatment of patients age 75+ who have AML with a susceptible IDH1 mutation or with comorbidities that preclude IC, and treatment of R/R AML</td>
</tr>
<tr>
<td>IDH1/2 inhibitors</td>
<td>Treatment of adults who have R/R AML with a susceptible IDH2 mutation</td>
</tr>
<tr>
<td>Ivosidenib (IDH1)</td>
<td>In combination with IC, for treatment of adults who have AML with a FLT3 mutation</td>
</tr>
<tr>
<td>Enasidenib (IDH2)</td>
<td>Treatment of adults who have R/R AML with a FLT3 mutation</td>
</tr>
<tr>
<td>FLT3 inhibitors</td>
<td>Treatment of AML in combination with LDAC for adults 75+ or with comorbidities that preclude IC</td>
</tr>
<tr>
<td>Hedgehog pathway inhibitors</td>
<td>Treatment of newly diagnosed and refractory CD33+ AML</td>
</tr>
<tr>
<td>Glagolix</td>
<td>Treatment of AML in combination with LDAC for adults 75+ or with comorbidities that preclude IC</td>
</tr>
<tr>
<td>Antibody-drug conjugates</td>
<td>Treatment of newly diagnosed and refractory CD33+ AML</td>
</tr>
</tbody>
</table>

AML, acute myeloid leukemia; AZA, azacitidine; BCL-2, B-cell lymphoma 2; DEC, decitabine; CR, complete response; CRi, complete response with incomplete hematologic recovery; FDA, US Food and Drug Administration; FLT3, FMS-like tyrosine kinase 3; IC, intensive chemotherapy; IDH, isocitrate dehydrogenase; LDAC, low-dose cytarabine; R/R, relapsed or refractory.

or refractory (R/R) disease. In particular, the combination of advanced age and poor performance status (ie, an Eastern Cooperative Oncology Group performance status of at least 3) is associated with a high likelihood of death within 30 days of the start of IC. Additionally, the presence of a comorbidity such as ischemic heart disease, chronic kidney disease, or cerebral vascular disease is a significant pretreatment risk factor. To determine their eligibility for IC, prognostic models incorporating cytogenetic information, age, and clinical indicators attempt to risk-stratify patients according to their likelihood of experiencing treatment-related morbidity and mortality, but no prognostic scoring system has become standard. Thus, studies of therapies for patients ineligible for IC often differ in eligibility criteria.

### Cytarabine-Based Therapies

Until recently, few AML treatment options were available for patients ineligible for IC. These patients were generally offered best supportive care (BSC), therapy based on low-dose cytarabine (LDAC), or hospice care. Although LDAC improves survival relative to BSC or hospice care, 1-year survival rates with LDAC remain at approximately 20% to 30%. Because of recent advances in the treatment of patients ineligible for IC, LDAC has largely been replaced as the standard of care, but interest continues in the possibility of alternative cytarabine formulations and combination therapies of LDAC with other agents.
to that of conventional induction chemotherapy. A phase 2 trial of CPX-351 in patients unfit for IC randomly assigned them to receive CPX-351 at 50 U/m2, 75 U/m2, or 100 U/m2 and found the median OS to be 4.3 months among those receiving 50 U/m2, vs 8.6 months among those receiving 75 U/m2 and 6.2 months among those receiving 100 U/m2 (P=0.04). The most common nonhematologic grade 3/4 adverse events were febrile neutropenia (34%) and pneumonia (23%).

Hypomethylating Agents

Many cancers exhibit abnormal DNA methylation patterns affecting gene expression, which can promote the growth and survival of leukemic cells. DNA hypomethylating agents (HMAs) such as decitabine (DEC) and azacitidine (AZA) decrease DNA methylation and may sensitize cells to chemotherapy and immunotherapy. Clinical trials have found a survival advantage with HMA treatment relative to both LDAC and BSC. A phase 3 study (NCT01074047) compared the efficacy and safety of AZA administered subcutaneously (SC) at 75 mg/m2/d for 7 days per 28-day cycle for at least 6 cycles with the efficacy and safety of conventional care regimens in 488 patients aged 65 years and older with newly diagnosed AML; results indicated that the median OS was increased with AZA relative to OS with conventional care regimens (10.4 vs 6.5 months; P=0.1009). In another phase 3 trial (NCT00260832), which compared DEC at 20 mg/m2 per day for 5 consecutive days every 4 weeks vs BSC or cytarabine-based treatments in 485 patients with newly diagnosed AML aged 65 years and older, no significant differences in median OS were found, but improvements in CR plus CR with incomplete hematologic recovery (CRi) were observed with DEC (17.8 % vs 7.8% with other treatment options; P=.001).

Azacitidine vs Decitabine

AZA and DEC have been shown to have somewhat different effects in vivo. Whereas DEC metabolites are incorporated only into DNA, AZA metabolites are incorporated into DNA and RNA. This may account for some of the differences in the effects of these 2 agents. Population-based studies have found no substantial differences in survival between AZA and DEC. However, in a phase 3 trial (NCT00260832), which compared DEC at 20 mg/m2 per day for 5 consecutive days every 4 weeks vs BSC or cytarabine-based treatments in 485 patients with newly diagnosed AML aged 65 years and older, no significant differences in median OS were found, but improvements in CR plus CR with incomplete hematologic recovery (CRi) were observed with DEC (17.8 % vs 7.8% with other treatment options; P=.001).

Table 2. Therapies Under Investigation Without FDA Approval for Use in AML

<table>
<thead>
<tr>
<th>Therapies Under Investigation in AML</th>
<th>Mechanisms</th>
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<tbody>
<tr>
<td>Cladribine</td>
<td>Antimetabolite</td>
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<tr>
<td>Hypomethylating agents</td>
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<tr>
<td>Guadecitabine</td>
<td>Second-generation hypomethylating agent</td>
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<tr>
<td>CC-486</td>
<td>Oral azacitidine</td>
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<tr>
<td>Specific inhibitors</td>
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<tr>
<td>Quizartinib</td>
<td>FLT3 inhibitor</td>
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<tr>
<td>Iadademstat</td>
<td>LSD-1 inhibitor</td>
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<tr>
<td>Bemcentinib</td>
<td>AXL inhibitor</td>
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<tr>
<td>CR-5339</td>
<td>VCP/p97 inhibitor</td>
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<tr>
<td>Sorafenib</td>
<td>Multikinase inhibitor</td>
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<tr>
<td>Immunotherapies</td>
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<tr>
<td>Nivolumab</td>
<td>Anti–PD-1 monoclonal antibody</td>
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<tr>
<td>Pembrolizumab</td>
<td>Anti–PD-1 monoclonal antibody</td>
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<tr>
<td>Atezolizumab</td>
<td>Anti–PD-L1 monoclonal antibody</td>
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<tr>
<td>Durvalumab</td>
<td>Anti–PD-L1 monoclonal antibody</td>
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<tr>
<td>Sabatolimab</td>
<td>Anti–TIM3 monoclonal antibody</td>
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<tr>
<td>Magrolimab</td>
<td>Anti–CD47 monoclonal antibody</td>
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<tr>
<td>Vibecotamab</td>
<td>Anti–CD123 and anti-CD3 bispecific antibody</td>
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<tr>
<td>IMGN2</td>
<td>Anti–CD123 antibody-drug conjugate</td>
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<tr>
<td>Flotetuzumab</td>
<td>CD3×CD123 dual-affinity retargeting antibody</td>
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AML, acute myeloid leukemia; FDA, US Food and Drug Administration; PD-1, programmed death 1; PD-L1, programmed death ligand 1.
in survival or transfusion independence between patients with AML treated with AZA and those treated with DEC.\(^\text{13}\) However, a meta-analysis of 14 studies of HMA therapy in patients with myelodysplastic syndromes (MDS) and AML found a significantly greater risk for high-grade neutropenia in patients treated with DEC, but no difference in risk for febrile neutropenia or anemia.\(^\text{14}\) DEC and AZA were directly compared in patients with AML ineligible for IC in the phase 3 ASTRAL-1 trial (NCT02348489), in which patients were randomly assigned to receive AZA (n=171) or DEC (n=167) at standard doses and schedules. This trial found no significant difference in CR rates (17.5% in the AZA group vs 19.2% in the DEC group) or in the 1- and 2-year OS rates (39% and 15% in the AZA group vs 32% and 14% in the DEC group, respectively).\(^\text{15}\) Although, as noted above, a meta-analysis showed a greater risk for high-grade neutropenia in patients treated with DEC than in those treated with AZA, the ASTRAL-1 trial conversely found that serious adverse events (AEs) leading to death occurred more frequently in the AZA arm (38% with AZA vs 26% with DEC; \(P=.02\)), leaving it unclear if a safety advantage is associated with either DEC or AZA.\(^\text{15}\)

**Oral Hypomethylating Agents**

The QUAZAR AML-001 maintenance trial is a phase 3 trial (NCT01757535) comparing CC-486, an oral formulation of AZA, with placebo in patients with AML who achieved CR/CRI following induction therapy (and in some cases, limited consolidation therapy) but were not candidates for hematopoietic stem cell transplant. At a median follow-up of 41.2 months, OS in patients given CC-486 at 300 mg/d on days 1 to 14 of a 28-day treatment cycle was significantly improved relative to OS in the placebo group (24.7 vs 14.8 months; \(P=.0009\)).\(^\text{16}\) The FDA therefore approved CC-486 in September 2020 for maintenance therapy in patients with AML and in CR/CRI after IC who cannot complete curative therapy.\(^\text{17}\) The FDA also approved an oral combination of DEC and cedazuridine (Inqovi, Astex/Taiho/Otsuka), a cytidine deaminase inhibitor that overcomes metabolism in the liver and other organs, for the treatment of certain patients with MDS or chronic myelomonocytic leukemia (CMML). Approval was based on the results of 2 crossover trials (NCT0210347 and NCT03306264) that showed similar safety, efficacy, and pharmacokinetic profiles for the combination oral regimen and intravenous (IV) DEC.\(^\text{18}\) Although trial results are not available for oral AZA or DEC in treatment-naive patients with AML who are ineligible for IC, the promising trial results in other patient groups offer the possibility that these patients may eventually have access to an all-oral regimen.

**Venetoclax**

Members of the BCL-2 family of proteins promote the survival of cancers cells by sequestering pro-apoptotic proteins such as BIM.\(^\text{19}\) BCL-2 overexpression has been observed in AML,\(^\text{20}\) making it a therapeutic target. Venetoclax (VEN; Venclexta, AbbVie) is a selective small-molecule inhibitor of BCL-2. On the basis of trial findings reviewed below, VEN in combination with LDAC or HMA therapy received accelerated FDA approval in November 2018 and full FDA approval in October 2020 for the treatment of newly diagnosed AML in patients ineligible for IC.

**Hypomethylating Agents/Venetoclax**

A phase 1b trial (NCT02203773) evaluated either AZA at 75 mg/m\(^2\) on days 1 to 7 or DEC at 20 mg/m\(^2\) on days 1 to 5 in combination with VEN (400, 800, or 1200 mg daily) for a median of 5 cycles in treatment-naive patients ineligible for IC. The trial overall found rates of CR and CRI of 67% and 73%, respectively, in the AZA/VEN 400-mg cohort.\(^\text{21}\) The most common grade 3/4 AEs were febrile neutropenia (43%), leukopenia (31%), anemia (25%), and thrombocytopenia (24%).\(^\text{21}\) A phase 2 trial (NCT03403193) of 168 patients with AML ineligible for IC evaluated DEC at 20 mg/m\(^2\) IV for 10 days with VEN at 400 mg/d for induction, followed by DEC for 5 days with VEN at 400 mg/d.\(^\text{22}\) The trial found an overall response rate (ORR) of 74% (89% in newly diagnosed AML), with a median OS of 18.1 months in newly diagnosed AML, 7.8 and 6.0 months in untreated and treated secondary AML, respectively, and 7.8 months in R/R AML.\(^\text{22}\) However, the DEC/VEN regimen was less effective in patients with \(TP53\) mutations. CR rates were lower in patients with mutated \(TP53\) than in those with wild-type \(TP53\) (35% vs 57%; \(P=.026\)), and median OS was shorter (5.2 vs 19.4 months; \(P<.001\)).\(^\text{23}\)

The phase 3 VIALE-A trial (NCT02993523) enrolled 431 patients with a median age of 76 years and previously untreated AML who were ineligible for IC. The trial compared treatment with AZA at 75 mg/m\(^2\) given SC or IV on days 1 to 7 per 28-day cycle with or without VEN at 400 mg/d. At a median follow-up of 20.5 months, the median OS was significantly longer in the AZA/VEN group, at 14.7 vs 9.6 months, and the CR rate was 36.7% in the AZA/VEN group vs 17.9% in the AZA-alone group (\(P<.001\)); however, these benefits were accompanied by higher rates of thrombocytopenia and febrile neutropenia.\(^\text{23}\) Subgroup analyses of patients with mutated \(FLT3\) and mutated \(IDH1/2\) showed significantly higher CR/CRI rates and longer median OS in patients treated with AZA/VEN than in those treated with AZA alone. Among the patients with mutated \(FLT3\),
the CR/CRi rate was 65% and median OS was 13.3 months with AZA/VEN, whereas the CR/CRi rate was 18% and median OS was 8.6 months with AZA alone. These improvements were driven primarily by patients with \( \text{FLT3} \) tyrosine kinase domain mutations. Among patients with \( \text{IDH1/2} \) mutations, the CR/CRi rate was 72% and median OS was 24.5 months with AZA/VEN vs a CR/CRi rate of 7% and median OS of 6.2 months with AZA alone.25,26

**Low-Dose Cytarabine/Venetoclax**
Recent research has investigated combining LDAC with other treatments, notably with VEN. In the phase 3 VIALE-C trial (NCT03069352), 221 patients with AML who were ineligible for IC were randomly assigned to receive LDAC SC at 20 mg/m^2/d for days 1 to 10 per 28-day cycle with or without VEN started at 100 mg on day 1, increased over 4 days to a target dose of 600 mg/d, and continued from day 4 to day 28. Patients who received LDAC/VEN demonstrated improvements in rates of CR (27% vs 7%; \( P < .001 \)) and CR/CRi (48% vs 13%; \( P < .001 \)), with significant improvements in median OS (8.4 vs 4.1 months; \( P = .04 \)), relative to patients who received LDAC alone.27 LDAC/VEN was well tolerated; the most frequent AEs were febrile neutropenia (32% with LDAC/VEN vs 29% with LDAC alone), neutropenia (46% with LDAC/VEN vs 16% with LDAC alone), thrombocytopenia (45% with LDAC/VEN vs 37% with LDAC alone), and anemia (25% with LDAC/VEN vs 22% with LDAC alone).27 Trials of LDAC/VEN and trials of HMAS/VEN reported prolonged myelosuppression requiring cycle interruptions for count recovery.25,27

Analysis of patient-reported outcomes from the VIALE-A trial of AZA with VEN and the VIALE-C trial of LDAC with VEN showed delays in time to deterioration with the addition of VEN to either regimen.28
However, the majority of patients treated with AZA/VEN in the VIALE-A trial required VEN dosing modifications or delays in cycles to manage cytopenias. Examination of the exposure-efficacy and the exposure-safety relationships supports the use of VEN at 400 mg/d in combination with an HMA, and at 600 mg/d in combination with LDAC. Although no head-to-head trials have compared LDAC/VEN vs HMA/VEN, it appears that the HMA/VEN combination likely offers better efficacy. However, recent trials have shown promising results in regard to the possibility of adding cladribine (Mavenclad, EMD Serono), a purine nucleoside approved for the treatment of hairy cell leukemia, to LDAC and alternating this combination with a traditional HMA (DEC or AZA).

**IDH1 and IDH2 Inhibitors**

Mutations in the isocitrate dehydrogenase genes (IDH1 and IDH2) occur in approximately 20% of patients with AML, with IDH2 mutations seen more commonly. These mutations contribute to impaired hematopoietic differentiation, making them potential therapeutic targets in AML. Enasidenib (Idhifa, Celgene), a small-molecule inhibitor of mutant IDH2, was approved by the FDA in 2017 for adults with R/R IDH2-mutated AML on the basis of phase 1/2 trials demonstrating its safety and efficacy at 100 mg/d in this group, with a CR rate of 19% for a median duration of 8.2 months and a CRi rate of 4% for a median duration of 9.6 months. In the phase 3 IDHENTIFY study (NCT02577406), enasidenib led to no improvement in OS compared with conventional care regimens in patients with R/R AML. A phase 1/2 trial of enasidenib in patients with newly diagnosed IDH2-mutated AML ineligible for IC showed good safety and tolerability at 100 mg/d; the most common grade 3/4 AEs were cytopenias and IDH1-mediated differentiation syndrome. In a phase 2 trial (NCT02677922) comparing enasidenib at 100 mg/d plus AZA at 75 mg/m² on days 1 to 7 of every 28-day cycle vs AZA alone in patients with newly diagnosed IDH2-mutated AML ineligible for IC, enasidenib/AZA produced higher response rates than AZA alone (ORR, 68% vs 42%; P=0.0155; CR rate, 50% vs 12%; P=0.0002), suggesting a role for enasidenib in the treatment of IDH2-mutated AML.

A phase 1 trial (NCT02074839) investigating the safety and activity of ivosidenib (Tibsovo, Agios), a small-molecule inhibitor of mutant IDH1, found that at a dose of 500 mg/d, the frequency of grade 3 or higher treatment-related AEs (most commonly differentiation syndrome and febrile neutropenia) was minimized. Among patients with newly diagnosed IDH1-mutated AML ineligible for IC, an ORR of 54.5% and a median OS of 12.6 months (with a median follow-up of 23.5 months) was observed. Ivosidenib was approved for patients with IDH1-mutated R/R AML in 2018, and in 2019 the FDA extended the approval to include patients with newly diagnosed IDH1-mutated AML ineligible for IC. Also promising were results from a phase 1b/2 trial (NCT02677922) of combination ivosidenib at 500 mg/d and AZA at 75 mg/m² in patients with IDH1-mutated AML ineligible for IC, with an ORR of 78% and a CR rate of 61%. The ongoing phase 3 AGILE trial (NCT03173248) is comparing the combination of ivosidenib at 500 mg taken continuously and AZA at 75 mg/m² for 7 days in 28-day cycles vs AZA alone in patients with IDH1-mutated AML ineligible for IC. A phase 2 trial of the combination of ivosidenib/VEN/AZA is also underway.

Because no trials have directly compared HMA plus an IDH inhibitor vs HMA/VEN, it remains unclear which agents should be used in the initial treatment of patients with IDH-mutated AML who are ineligible for IC. Clinical trials will be needed to determine the correct sequencing of these therapies. However, given the significant risk for myelosuppression associated with VEN, IDH inhibitors may be a better choice for patients with IDH-mutated AML who present with significant cytopenias.

**FLT3 Inhibitors**

Mutations in the FMS-like tyrosine kinase 3 (FLT3) gene are seen in approximately 30% of patients with AML. Among patients with FLT3 mutations, internal tandem duplication (ITD) is more common, but point mutations in the tyrosine kinase domain are also seen. ITD FLT3-mutated AML in particular has been associated with a poor prognosis, and interest has grown in FLT3 as a potential therapeutic target in AML.

A phase 2 trial (NCT01093573) of the combination of the multikinase inhibitor midostaurin (Rydapt, Novartis) and AZA in patients with AML ineligible for IC found that multiple cycles of AZA at 75 mg/m² per day for days 1 to 7 of a 28-day cycle plus midostaurin at 75 mg orally twice daily on days 8 to 21 were poorly tolerated, causing hematologic, gastrointestinal, and infectious toxicities, but that intermittent dosing of midostaurin may be beneficial.

Another multikinase inhibitor, sorafenib (Nexavar, Bayer), which is FDA-approved for use in some solid tumors, has also been investigated in AML. An analysis of 27 patients aged 61 to 86 years with newly diagnosed FLT3-mutated AML treated with sorafenib/AZA under 2 different trial protocols (NCT02196857 and NCT01254890) found a CR rate of 26%, a CRi rate of 44%, and a median OS of 8.3 months, with no early deaths reported.
Hedgehog Pathway Inhibitors

AML blasts overexpress components of the Hedgehog signaling pathway, which induces expression of pro-survival genes and is associated with chemoresistance and worse patient survival.53 Glasdegib (Daurismo, Pfizer) is an oral antagonist of Smoothened (SMO), a Hedgehog pathway activator. The phase 2 BRIGHT-AML trial (NCT01546038) compared glasdegib/LDAC vs LDAC alone. A total of 115 patients aged 75 years and older with newly diagnosed AML or with comorbidities precluding treatment with IC were randomly assigned to receive LDAC with or without glasdegib at 100 mg/d.54 At a median follow-up of 20 months, the median OS was 8.3 months in the glasdegib/LDAC combination arm and 4.3 months in the LDAC-alone arm (P<.004). CR rates were also significantly higher in the glasdegib arm (17% vs 2.3%, respectively; P<.05; with a median duration of 9.9 vs 6.5 months, respectively. Glasdegib had an acceptable safety profile, with pneumonia (16.7%) and fatigue (14.3%) among the most common grade 3/4 AEs.56 These results were confirmed in a follow-up study with an additional 20 months of observation,57 after which the FDA approved glasdegib for the treatment of newly diagnosed AML in patients aged 75 years and older or with comorbidities that preclude treatment with IC.58

A phase 1b trial (NCT02367456) evaluated the safety of a combination of glasdegib and AZA in patients with MDS, AML, or CMML ineligible for IC. Among 30 patients with AML who received glasdegib at 100 mg/d and AZA at 75 mg/m² per day on days 1 to 7 of a 28-day cycle, the most common serious AEs were febrile neutropenia (20%) and pyrexia (13%); 20% of the patients achieved a CR, and the probability of 6-month survival was 70%, although the median OS was not evaluable.59 The combination of glasdegib and an HMA is being further evaluated in the ongoing phase 2 GLAD-AML study (NCT03798678), designed to investigate the efficacy of glasdegib at 100 mg/d in combination with either 5 or 10 days of treatment with DEC.60

Additional Small-Molecule Inhibitors Under Investigation

The search for other specific targets in patients with AML ineligible for IC is ongoing. Other therapies currently in phase 1 and 2 trials include idadastemast, an inhibitor of LSD1 (a regulator of stem cell differentiation)61; bemcentinib, an inhibitor of AXL (a surface membrane protein kinase receptor that contributes to the growth of AML cells)62; CB5339, an inhibitor of VCP/p97 (an enzyme vital for cancer cell growth)63; and CFI-400945, an inhibitor of PLK4 (a regulator of centriole duplication).64

Antibody-Drug Complexes and Immunotherapy

Gemtuzumab

Gemtuzumab ozogamicin (GO; Mylotarg, Pfizer) is a conjugate comprising an anti-CD33 monoclonal antibody and a chemotherapeutic agent. CD33 is expressed on leukemic blasts in more than 80% of patients with AML but is not present on normal hematopoietic pluripotent stem cells, offering the possibility of antitumor effects with reduced systemic toxicity.65 GO was initially approved by the FDA in 2000 for patients with R/R AML and patients with AML ineligible for IC; however, it was withdrawn from the market in 2010 after a phase 3 trial demonstrated higher rates of fatal toxicity (most notably, from veno-occlusive liver disease) with GO than with
standard therapy. In 2017, GO was restudied in a phase 3 trial (NCT00091234) that used a different administration schedule. This trial compared GO monotherapy with BSC as first-line therapy in 237 adults with AML ineligible for IC.67 Median OS was significantly longer in the patients who received GO at 6 mg/m² on day 1 and at 3 mg/m² on day 3 than in those who received BSC (4.9 months with GO vs 3.6 months with BSC; P = .005).67 On the basis of these results, GO was reapproved by the FDA in 2017 as monotherapy for patients with CD33-positive AML ineligible for IC.66

**PD-1 and PD-L1 Inhibitors**

A promising area of immunotherapy is investigating the activation of an antitumor immune response through the inhibition of immune control checkpoints. Two potential targets that serve as negative control checkpoints in AML are programmed death 1 (PD-1) and its cognate ligand, programmed death ligand 1 (PD-L1). PD-1 overexpression has been observed in AML and is thought to cause T-cell dysfunction and impaired antitumor immune responses.68 Two PD-1 inhibitors, nivolumab (Opdivo, Bristol Myers Squibb) and pembrolizumab (Keytruda, Merck), and two anti–PD-L1 monoclonal antibodies (atezolizumab [Tecentriq, Genentech] and durvalumab [Imfinzi, AstraZeneca]), have shown promise in AML. Nivolumab is FDA-approved for the treatment of a variety of cancers, including melanoma and small cell lung cancers. A phase 2 trial (NCT02397720) of nivolumab at 3 mg/kg on days 1 and 14 every 4 to 6 weeks in combination with AZA at 75 mg/m² on days 1 to 7 in 70 patients with R/R AML found an ORR of 33%, with 22% achieving CR/CRi69; nivolumab has not yet been studied in patients with newly diagnosed AML who are ineligible for standard chemotherapy. A phase 2 trial (NCT04284787) is currently underway to evaluate the utility of adding pembrolizumab to a combination of AZA and VEN in patients with newly diagnosed AML ineligible for IC.70

A phase 2 trial (NCT02775903) randomly assigned 129 patients with AML ineligible for IC to receive either AZA alone at 75 mg/m² on days 1 to 7 or AZA in combination with durvalumab at 1500 mg on day 1 of each 28-day cycle. The trial found no significant difference in the ORRs and no new safety signals with the combination of AZA and durvalumab.71 A phase 1b trial of atezolizumab in combination with AZA in treatment-naïve patients with higher-risk MDS was terminated early owing to high rates of treatment-related early death.72

**Other Immunotherapies**

T-cell immunoglobulin and mucin domain 3 (TIM3) is another negative regulatory immune checkpoint, and anti-TIM3 antibodies such as sabatolimab (MGB453) have been shown to improve eradication of AML leukemic stem cells in preclinical models.73 A phase 1b trial (NCT03066648) of sabatolimab in combination with an HMA in 48 patients with newly diagnosed AML ineligible for IC found the combination to be well tolerated. Patients received sabatolimab IV at a dose of 240 or 400 mg every 2 weeks or at 800 mg every 4 weeks in combination with DEC (20 mg/m² IV on days 1-5) or AZA (75 mg/m² IV/SC on days 1-7) per 28-day cycle; the maximum tolerated dose was not reached.74 The most common AEs were cytopenias. Trial participants had an ORR of 41.2% and an estimated 12-month progression-free survival (PFS) rate of 44%.74 The phase 2 STIMULUS-AML1 trial (NCT04150029), planned to further evaluate the safety and efficacy of sabatolimab in combination with AZA and VEN in patients with AML ineligible for IC, is underway.75

Another antibody being assessed in AML is magrolimab, which blocks CD47, a macrophage immune checkpoint. In a phase 1b trial, treatment-naïve patients with AML unfit for IC were treated with a dose-escalation regimen of magrolimab IV weekly at 1 to 30 mg/kg, followed by 30 mg/kg IV every 2 weeks for cycles 3 and beyond, in combination with AZA at 75 mg/m² on days 1 to 7 of a 28-day cycle. The most common AEs were anemia (31%) and neutropenia (19%), and no grade 4 or 5 AEs were observed. Overall, 44% of patients achieved CR (an additional 12% achieved CRi), and the median OS was 18.9 months. Results were also encouraging in patients with TP53 mutations, in whom the CR rate, CRi rate, and median OS were 48%, 19%, and 12.9 months, respectively.76 Trials of magrolimab in combination with AZA and VEN are currently underway.77

Several additional immunotherapies are currently under study for R/R AML. Although these trials are in relatively early stages, it is possible that similar immunotherapies may have utility in treating patients with newly diagnosed AML who are ineligible for IC. CD123 is overexpressed in AML, making it a potential therapeutic target. Vibecotamab is a bispecific antibody that targets CD123 and CD3 to stimulate the T-cell–mediated destruction of CD123+ cells; it is being studied in a phase 1 trial (NCT02730312) in patients with R/R AML, among other cancers.78 IMGN263, a CD123-targeted antibody-drug conjugate that has been shown to have a synergistic antileukemic effect with AZA and VEN in preclinical models,79 is currently in phase 1/2 trials (NCT03386513) in patients with R/R AML.80 Another bispecific antibody, the CD3×CD123 dual-affinity retargeting antibody flotetuzumab, is also in phase 1/2 trials (NCT02152956) in patients with R/R AML, with a maximum tolerated dose of 500 ng/kg per day, and early...
results have demonstrated an ORR of 30% and median OS of 10.2 months.\textsuperscript{81} AMG 330, a bispecific T-cell engager molecule that binds CD3+ T cells and CD33+ AML blasts, is in phase 1 trials (NCT02520427) in patients with R/R AML.\textsuperscript{82}

Conclusions

Significant progress has been made in the development of therapeutic regimens for patients with AML who are unfit for IC; however, challenges remain. Although the performance status of a small subset of patients improves as a result of these nonintensive regimens, so that they can proceed to more intensive treatment, including hematopoietic cell transplant,\textsuperscript{83} the therapies reviewed here should be viewed primarily as life-prolonging, not curative.

One challenge encountered in comparing treatments for medically unfit adults with AML across trials is the lack of standardization regarding who is deemed ineligible for standard IC. For example, some trials include patients of all ages who are ineligible for IC because of poor performance status or comorbidities, whereas other trials include only patients 65 years of age and older. Furthermore, trials may differ in the endpoints they examine, with recent evidence suggesting that measurable residual disease is an independent prognostic indicator in patients treated with HMAs and may thus be a useful endpoint.\textsuperscript{84}

HMA therapy quickly became a mainstay of treatment in adults with AML who are ineligible for IC. The promising results reported from trials of HMA/VEN combinations suggest that this ambulatory regimen should be considered the first-line treatment in this setting. In patients with specific actionable mutations (eg, IDH1, IDH2, FLT3), targeted inhibitors may also be an attractive option. Several of the therapies presented here have been shown in preclinical models and early-stage clinical trials to have synergistic antileukemic effects while maintaining good patient tolerability, and investigations of combinations of drugs, in particular HMAs, VEN, and other therapies, are ongoing. Given the broad activity of HMA/VEN combinations across distinct mutational profiles, an emerging challenge is selection of the optimal first-line therapy in patients with actionable mutations. This challenge highlights the need to develop molecularly informed, personalized treatment plans for patients from diagnosis to relapse.

References


help ensure that the best new models and data computation algorithms become available in the coming years.

**H&O** What is next for these technologies?

**AP** Deployment of these technologies is starting. In the European Union, a machine learning–assisted digital pathology tool received the “CE” designation for breast cancer and prostate cancer, indicating that it met certain health, safety, and environmental protection requirements. (These tools are known as the Paigz Prostate Clinical [CE-IVD] and Paigz Breast Clinical [CE-IVD] devices). As models continue to improve, it may be possible to reliably extract “hidden” molecular information from samples in a rapid, efficient way. The goal is to decrease the time and cost that is required to obtain accurate, personalized information to guide the treatment of patients. Machine learning–based digital models have the potential to be transformative in the development of these new domains.

(Continued from page 535)


71. Zeidan AM, Cavaghan J, Voso MT, et al. Efficacy and safety of azacitidine (AZA) in combination with the anti-PD-1 durvalumab (durvala) in the front-line treatment of older patients (pts) with acute myeloid leukemia (AML) who are unfit for intensive chemotherapy (IC) and pts with higher-risk myelodysplastic syndromes (HR-MDS): results from a large, international, randomized phase 2 study [ASH abstract 829]. *Blood*. 2020;134(1)(suppl).


78. Ravandi F. Complete responses in relapsed/refractory acute myeloid leukemia (aml) patients on a weekly dosing schedule of vibecotamab (XmAb14045), a CD123 x CD3 T cell-engaging bispecific antibody: initial results of a phase 1 study [ASH abstract 460]. *Blood*. 2020;136(1)(suppl).


**Disclosure**

Dr Pearson is a member of the advisory board of Prelude Therapeutics.

**Suggested Readings**


