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Contemporary Management of Acute Myeloid Leukemia
A Review

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IMPORTANCE Acute myeloid leukemia (AML) is a clonal hematopoietic cancer that disrupts normal hematopoiesis, ultimately leading to bone marrow failure and death. The annual incidence rate of AML is 4.1 per 100 000 people in the US and is higher in patients older than 65 years. Acute myeloid leukemia includes numerous subgroups with heterogeneous molecular profiles, treatment response, and prognosis. This review discusses the evidence supporting frontline therapies in AML, the major principles that guide therapy, and progress with molecularly targeted therapy.

OBSERVATIONS Acute myeloid leukemia is a genetically complex, dynamic disease. The most commonly altered genes include *FLT3*, *NPM1*, *DNMT3A*, *IDH1*, *IDH2*, *TET2*, *RUNX1*, *NRAS*, and *TP53*. The incidence of these alterations varies by patient age, history of antecedent hematologic cancer, and previous exposure to chemotherapy and/or radiotherapy for any cancer. Since 2010, molecular data have been incorporated into AML prognostication, gradually leading to incorporation of targeted therapies into the initial treatment approach of induction chemotherapy and subsequent management. The first molecularly targeted inhibitor, midostaurin, was approved to treat patients with AML with *FLT3* variants in 2017. Since then, the understanding of the molecular pathogenesis of AML has expanded, allowing the identification of additional potential targets for drug therapy, treatment incorporation of molecularly targeted therapies (midostaurin, gilteritinib, and quizartinib targeting *FLT3* variants; ivosidenib and olutasidenib targeting *IDH1* variants, and enasidenib targeting *IDH2*), and identification of rational combination regimens. The approval of hypomethylating agents combined with venetoclax has revolutionized the therapy of AML in older adults, extending survival over monotherapy. Additionally, patients are now referred for hematopoietic cell transplant on a more rational basis.

CONCLUSIONS AND RELEVANCE In the era of genomic medicine, AML treatment is customized to the patient's comorbidities and AML genomic profile.

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Acute myeloid leukemia (AML) is a clonal stem cell cancer characterized by proliferation of immature myeloid precursor cells and maturation arrest leading to bone marrow failure, consequent risks of infection and bleeding, and reduced overall survival (OS), with a 5-year survival rate of 31.7% (95% CI, 31.0%-32.3%).[1,2] The annual incidence rate of AML is 4.1 per 100 000; it is more common in men (5.0 per 100 000 vs 3.4 per 100 000 for women), in non-Hispanic White individuals compared with non-Hispanic Black individuals (3.6 per 100 000), Hispanic individuals (3.4 per 100 000), and non-Hispanic Asian and Pacific Islander individuals (3.2 per 100 000), and among older adults.[1] The median age at diagnosis is 69 years, and the annual incidence rate increases to 17.3 per 100 000 in people aged 70 years and older.[1] Additional predisposing factors include previous receipt of chemotherapy[3] or radiotherapy[4] for unrelated cancers; antecedent hematologic neoplasms, such as myelodysplastic syndromes[5] or myeloproliferative neoplasms[6]; environmental exposures to toxins, such as organic solvents[7]; and germline predisposition syndromes, such as those associated with *GATA2* or *DDX41* variants.[8,9]

Acute myeloid leukemia has a heterogeneous cytogenomic profile, treatment susceptibility, and prognosis. Advancements in next-generation sequencing technologies and increased recognition of the molecular underpinnings of AML have led to the incorporation of molecular data in AML prognostication and treatment recommendations.[10] The AML genome appears to harbor an average of 13 altered genes, of which an average of 5 are recurrently altered, including *FLT3*, *NPM1c*, *DNMT3A*, *IDH1*, *IDH2*, *TET2*, *RUNX1*, *TP53*, and *NRAS*.[11] Capitalizing on these advances in the understanding of AML biologic traits, since 2017, a number of AML treatments (**Table**) have gained regulatory approval in both molecularly defined subgroups (*FLT3* [midostaurin, quizartinib and gilteritinib], *IDH1* [ivosidenib and olutasidenib], and *IDH2* [enasidenib]) and agnostic subgroups (glasdegib, CPX-351, oral azacitidine, and combination hypomethylating agent [HMA] with venetoclax).[2] This has led to the incorporation of molecularly targeted agents into standard induction chemotherapy and additional therapies for patients with relapsed disease (**Figure 1**). Moreover, while previously older adults

Table. Commonly Used Treatments for AML

Drug	Indication	Mechanism of action	Typical dose	Efficacy data from registrational trials	Adverse effects of special interest
Gemtuzumab ozogamicin	CBF-AML	CD-33–directed antibody drug conjugate	3 mg/m^2 on days 1, 4, and 7 in combination with daunorubicin and cytarabine for first induction only; for consolidation, 3 mg/m^2 on day 1 in combination with cytarabine	No significant difference in CR rates between gemtuzumab ozogamicin with vs without gemtuzumab ozogamicin arms (82% vs 83%; P = .80); significant benefit of gemtuzumab ozogamicin observed (79% vs 51%; P < .001)	Grade ≥3 hemorrhages, 22.9%; veno-occlusive disease, 4.6%
Midostaurin	Newly diagnosed *FLT3*-altered AML, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation	Multikinase, type 1 *FLT3* inhibitor that targets both *FLT3*-ITD and -TKD variants	50 mg orally twice daily with food on days 8-21, with induction and consolidation	In 717 patients with *FLT3*-altered AML, CR rates were similar between midostaurin plus chemotherapy and PBO plus chemotherapy arms (59% vs 54%; P = .15); median OS, 74.6 mo in the midostaurin arm vs 25.6 mo in the PBO arm (P = .009)	Anemia, 93%; rash or desquamation, 14%
Quizartinib	Newly diagnosed *FLT3*-ITD-altered AML, in combination with chemotherapy in induction and consolidation, and as maintenance monotherapy following consolidation chemotherapy	Second-generation, type 2 FLT3 inhibitor that targets only *FLT3*-ITD variants	35.4 mg orally once daily on days 8-21 during induction and 35.4 mg orally once daily on days 6-19 during consolidation and continuously during maintenance therapy in those not proceeding to HCT	In 539 patients with newly diagnosed *FLT3*-ITD-altered AML, CR rates were similar between quizartinib plus chemotherapy and PBO plus chemotherapy arms (54.9% vs 55.4%); median OS, 31.9 mo for quizartinib plus chemotherapy vs 15.1 mo with PBO plus chemotherapy (P = .03)	Neutropenia, 20%; QT prolongation, 14%
CPX-351	Newly diagnosed therapy-related AML or AML with myelodysplasia-related changes	Dual drug liposomal encapsulation of cytarabine and daunorubicin that delivers a synergistic 5:1 drug ratio into leukemic blasts	Liposomal daunorubicin, 44 mg/m^2 and cytarabine, 100 mg/m^2 on days 1, 3, and 5 during induction vs liposomal daunorubicin, 29 mg/m^2 and cytarabine, 65 mg/m^2 on days 1 and 3 during consolidation	In 309 patients, CPX-351 demonstrated higher CR rate (37.3% vs 25.6%; P = .04) and improved OS (9.56 vs 5.95 mo; P = .003) vs the standard 7 + 3 regimen	Longer time to neutrophil (35 d) and platelet (36.5 d) recovery; bleeding event, 74.5%
Oral azacitidine	For continued treatment of patients with AML who achieved first CR or CRi following intensive induction chemotherapy and are unable to complete intensive curative therapy	Oral HMA administered in extended dosing schedules for sustained therapeutic activity	300 mg orally once daily on days 1-14 of each 28-d cycle	In 472 patients in first remission, azacitidine had a longer median OS vs PBO (24.7 vs 14.8 mo; P < .001)	Nausea, 65%; vomiting, 60%; diarrhea, 50%; neutropenia, 44%
Venetoclax with azacitidine	Newly diagnosed AML in patients aged ≥75 y or who are ineligible for IC	HMA in combination with bcl-2 inhibitor	Azacitidine, 75 mg/m^2, intravenously or subcutaneously once daily on days 1-7 of each 28-d cycle with venetoclax (dose adjusted for antifungal) daily for 28 d	In 431 patients, venetoclax with azacitidine had higher CR rates (36.7% vs 17.9%; P < .001) and improved median OS (14.7 vs 9.6 mo; P < .001) vs PBO with azacitidine	Neutropenia, 42%; febrile neutropenia, 42%; nausea, 44%; constipation, 43%; diarrhea, 41%; tumor lysis syndrome, 1%
Ivosidenib with azacitidine	Newly diagnosed *IDH1*-altered AML in patients aged ≥75 y or who are ineligible for IC	HMA in combination with IDH1 inhibitor	Azacitidine, 75 mg/m^2, intravenously or subcutaneously once daily on days 1-7 of each 28-d cycle with ivosidenib, 500 mg, once daily for 28 d	In 146 patients, ivosidenib with azacitidine had a CR rate of 38% vs 11% with PBO plus ivosidenib with azacitidine; median OS, 24 mo with ivosidenib plus azacitidine vs 7.9 mo with PBO plus azacitidine	Bleeding events, 41%; differentiation syndrome, 14%
Enasidenib	R/R *IDH2*-altered AML	IDH2 inhibitor	100 mg once daily	In 239 patients, CR rate, 20.2%; median DOR, 5.8 mo with enasidenib	Hyperbilirubinemia, 8%; differentiation syndrome, 7%

(continued)

Table. Commonly Used Treatments for AML (continued)

Drug	Indication	Mechanism of action	Typical dose	Efficacy data from registrational trials	Adverse effects of special interest
Ivosidenib	R/R *IDH1*- altered AML	IDH1 inhibitor	500 mg once daily	In 258 patients, CR rate, 21.6%; median DOR, 9.3 mo with ivosidenib	QT prolongation, 7.8%; differentiation syndrome, 3.9%
Olutasidenib	R/R *IDH1 R132*- altered AML	*IDH1* inhibitor	150 mg orally twice daily	In 153 *IDH1* inhibitor–naive patients, CR rate, 32%; median DOR, 28.1 mo with olutasidenib	Nausea, 38%; differentiation syndrome, 14%; liver enzyme level increase, 12%
Gilteritinib	R/R *FLT3*-altered AML	Type 1 FLT3 inhibitor that targets both *FLT3*-ITD and -TKD variants	120 mg orally once daily	In 371 patients, gilteritinib CR rate, 21.1%; median OS, of 9.3 mo vs salvage chemotherapy (CR, 10.5%; median OS, 5.6 mo)	Febrile neutropenia, 45.9%; anemia, 40.7%; thrombocytopenia, 22.8%; QT prolongation, 4.9%

Abbreviations: AML, acute myeloid leukemia; CBF, core-binding factor; CD, cluster differentiation; CR, complete remission; CRi, complete remission with incomplete blood count recovery; DOR, duration of response; HCT, hematopoietic cellular therapy; HMA, hypomethylating agent; IC, intensive chemotherapy; ITD, internal tandem duplication; OS, overall survival; PBO, placebo; R/R, relapsed/refractory; TKD, tyrosine kinase domain.

with AML who were unable to tolerate intensive chemotherapy were treated with HMA monotherapy, if at all,[12] the approval of the HMA plus venetoclax combination has led to an incremental survival benefit and likely more older adults with AML receiving therapy.[13] This review addresses the evidence guiding the diagnosis and treatment of adults with nonacute promyelocytic AML both in the frontline and relapsed settings.

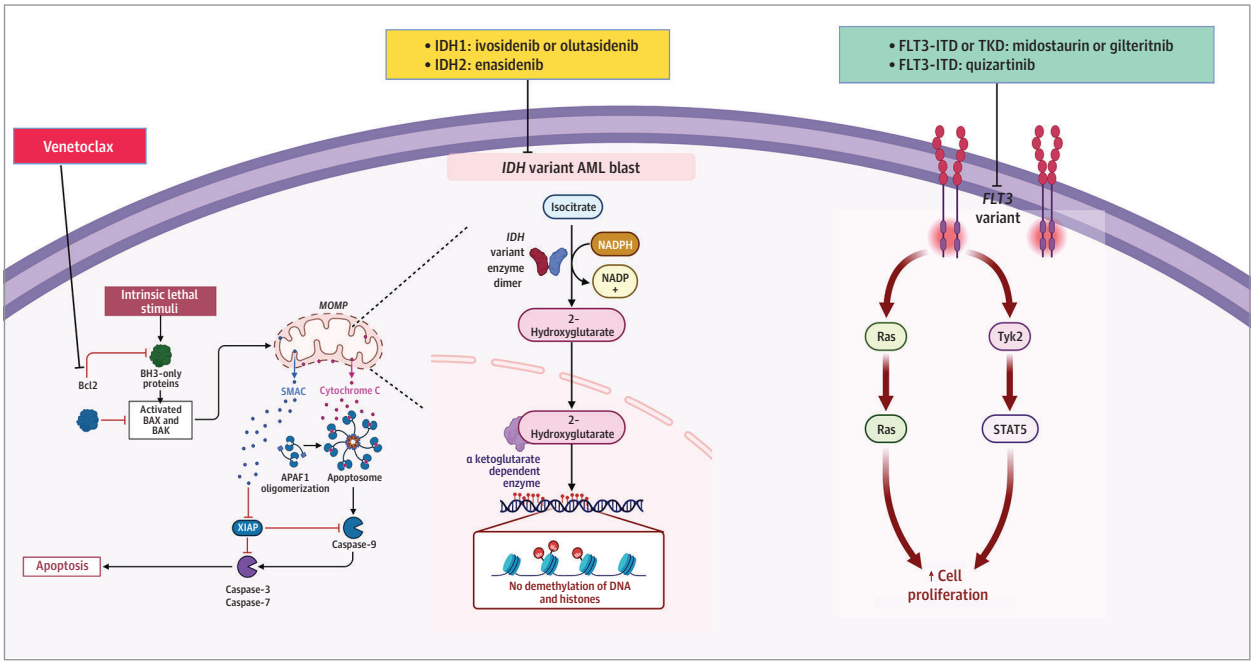
AML Diagnosis and Prognostication

A 2-pronged approach is used in the initial evaluation of patients with AML: assessing disease-specific factors that can estimate treatment response and inform the risk of relapse (eg, prior chemotherapy or radiotherapy exposure, antecedent hematologic neoplasms and cytogenomic abnormalities) and patient-specific factors that influence an individual's ability to tolerate chemotherapy (eg, age, comorbidities, and performance status).[14] Several scoring systems assess a patient's ability to tolerate therapy, incorporating factors such as age, nutritional status, preexisting organ damage, and physical function.[15] Instruments measuring frailty have also correlated worse scores with impaired OS, irrespective of age.[16,17] While there is no consensus on which scoring system best estimates an individual's ability to tolerate intensive therapy, age alone is clearly inadequate to appropriately determine up-front AML treatment.

In addition to a detailed medical history and physical examination, a bone marrow aspirate and core biopsy should be obtained to establish an AML diagnosis; the aspirate must be sent for cytogenetic analyses (karyotype and fluorescence in situ hybridization for AML-related chromosomal abnormalities) and next-generation sequencing testing for variants. In select circumstances, such as when a biopsy is technically difficult or burdensome and a patient has high levels of circulating blasts, the diagnosis can be made from peripheral blood samples. As certain variants (*FLT3*-internal tandem duplication [ITD] or *FLT3*-tyrosine kinase domain [TKD]) or specific cytogenetic abnormalities (t[8;21] or inv [16]) can immediately affect the choice of induction therapy, their assessment should be expedited.[18] Central nervous system evaluation should be performed in patients with neurologic symptoms or known extramedullary leukemia.

Newly diagnosed AML is risk-stratified using the European LeukemiaNet (ELN 2022) genetic risk classification system into favorable (younger: complete remission [CR], 86% and 3-year OS rate, 75%; >60 years: CR, 81% and 3-year OS rate, 45%), intermediate (younger: CR, 59% and 3-year OS rate, 45%; >60 years: CR, 50% and 3-year OS rate, 18%), and adverse risk groups (younger: CR, 49% and 3-year OS rate, 28%; >60 years: CR, 32% and 3-year OS rate, 4%) based on relapse likelihood and survival.[19] This ELN 2022 classification influences the choice of postremission therapy. Hematopoietic cell transplant (HCT) is the preferred strategy for the adverse risk group (including gene variants such as *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, or *ZRSR2*) and is considered on a case-by-case basis in the intermediate risk group (*FLT3*-ITD is intermediate risk regardless of allelic ratio or co-occurring *NPM1c*). The favorable risk group comprises core-binding factor (CBF) AML (t[8;21]: RUNX1-RUNX1T1 and inv[16]: CBFB-MYH11),[20] altered *NPM1c* without *FLT3*-ITD,[21] and in-frame variants affecting *CEBPA*.[22,23] Patients with AML containing these variants receive postremission chemotherapy (**Figure 2**).[24,25]

Figure 1. Mechanism of Action of Commonly Used Drugs in Acute Myeloid Leukemia (AML)



Bak, Bcl-2 antagonist killer 1; Bax, Bcl-2-associated X protein; Bcl2, B cell lymphoma 2; IDH, isocitrate dehydrogenase; ITD, internal tandem duplication; MOMP, mitochondrial outer membrane permeabilization; NADP+, nicotinamide adenine dinucleotide phosphate; NADPH, nicotinamide adenine dinucleotide phosphate; Raf, rapidly accelerated fibrosarcoma; Ras, rat sarcoma; SMAC, second mitochondrial-derived activator of caspases; STAT5, signal transducer and activator of transcription; and TKD, tyrosine kinase domain; Tyk2, tyrosine kinase 2.

Management Approach in Treatment-Naive Patients Able to Receive Intensive Induction Chemotherapy

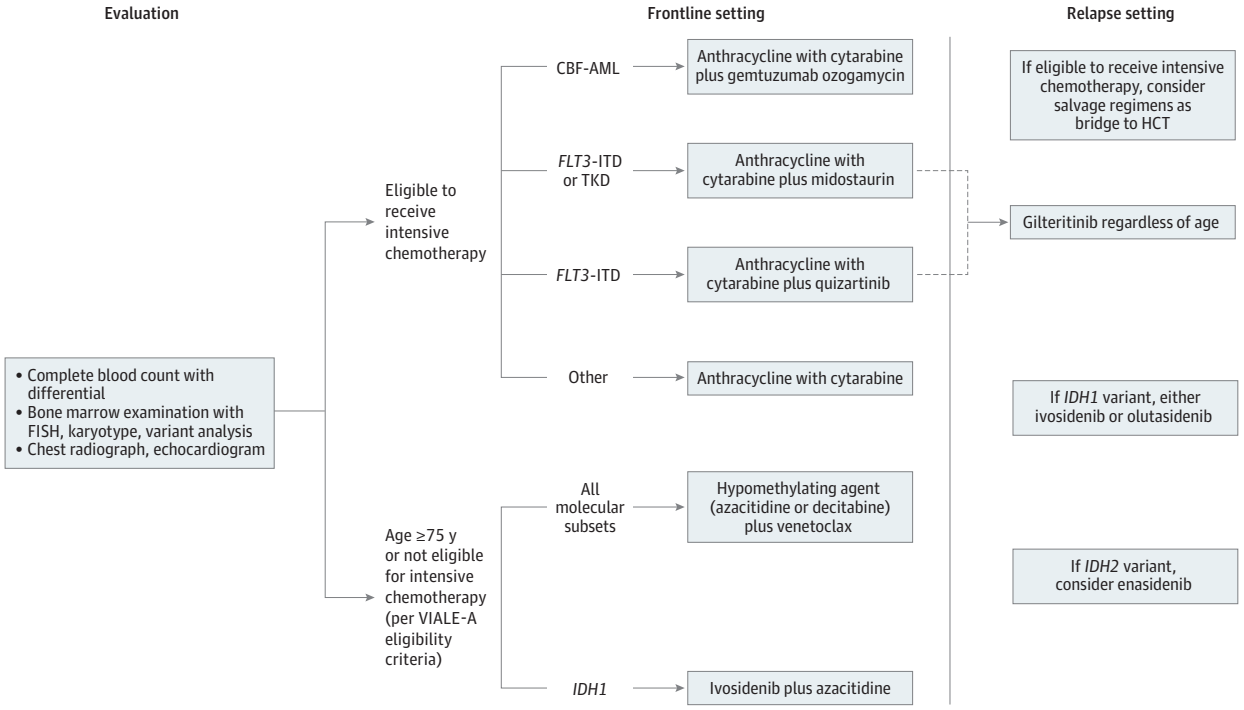
The goal of AML therapy is to induce remission and consolidate that remission with chemotherapy and/or HCT. Younger adults (variably defined as <55-65 years) or appropriately selected older adults with a good performance status, a paucity of comorbidities, and good-risk AML are candidates for intensive chemotherapy, the backbone of which consists of cytarabine and an anthracycline (daunorubicin or idarubicin) with the addition of gemtuzumab ozogamicin in CBF-AML, midostaurin in *FLT3* (ITD or TKD)-altered AML, or quizartinib in *FLT3*-ITD-altered AML.[26]

Core-binding factor leukemias are particularly sensitive to conventional induction and postremission chemotherapy (including intensified cytarabine), with no substantial differences in relapse-free survival or OS when cytarabine-based postremission strategies are compared with postremission HCT.[20] Patients with CBF-AML had improved relapse-free survival with 3 or 4 cycles of high-dose cytarabine compared with 1 or 2 cycles (7.1 vs 1.4 years; $P = .02$).[27] Gemtuzumab ozogamicin, a humanized anti-CD33 monoclonal antibody conjugated with the cytotoxic agent calicheamicin, can be added to standard induction therapy with daunorubicin and cytarabine for patients with newly diagnosed CBF-AML. In the UK Medical Research Council AML15 trial, patients with CBF-AML had a survival benefit with the addition of gemtuzumab ozogamicin to chemotherapy (hazard ratio [HR], 0.32; 95% CI, 0.18-0.59; $P = .001$) compared with those not receiving gemtuzumab ozogamicin.[28] These findings were supported in a meta-analysis of 5 randomized clinical trials (5-year OS: 76.3% with gemtuzumab ozogamicin vs 55.2% without gemtuzumab ozogamicin; HR, 0.47; 95% CI, 0.31-0.73; $P < .001$).[29]

Assessment of measurable residual disease can potentially identify the need for additional therapy. One trial prospectively evaluated the importance of measurable residual disease by quantitative reverse transcriptase polymerase chain reaction in estimating the cumulative incidence of relapse in patients with CBF-AML. At the end of induction, a greater than 3-log reduction of *RUNX1-RUNX1T1* transcripts in the bone marrow significantly decreased relapse risk by 67% compared with a reduction of less than 3 log, while less than 10 copies of *CBFB-MYH11* in the peripheral blood was associated with a 68% reduction in relapse risk, compared with having 10 or more copies. After treatment, having more than 500 copies of *RUNX1-RUNX1T1* in bone marrow (relapse estimate: 100% vs 7% [<500 copies]; $P < .001$) and more than 10 copies of *CBFB-MYH11* with placebo (estimate of relapse: 97% vs 7% [<10 copies]; $P < .001$) were associated with relapse.[30] Based on these data, serial monitoring of molecular transcripts at diagnosis, remission, treatment completion, and prespecified time points during surveillance of CBF-AML is recommended to identify patients with impending relapse to consider additional therapy.

Variants of *NPM1*c-AML occurs in 20% to 30% of patients.[31] The prognosis of *NPM1*c AML is context dependent, driven by the presence of co-occurring *FLT3*-ITD variants.[24] Compared with co-occurring *FLT3*-ITD variants, *NPM1*c-altered/*FLT3*-ITD wild-type AML is associated with numerically higher CR rates (74% vs 63% in *NPM1*c altered/*FLT3*-ITD altered) and superior OS ($P = .001$) in patients treated with conventional chemotherapy.[32] Measurable residual disease in *NPM1*c-altered AML should be serially monitored, as the persistence of *NPM1* transcripts at the end of induction and at treatment completion is associated with

Figure 2. Treatment Algorithm of Younger and Older Adults



AML indicates acute myeloid leukemia; CBF, core-binding factor; FISH, fluorescence in situ hybridization, HCT, hematopoietic cell therapy, IDH, isocitrate dehydrogenase; ITD, internal tandem duplication; TKD, tyrosine kinase domain; VIALE-A, venetoclax in combination with azacitidine.

increased relapse risk (HR, 4.80; 95% CI, 2.95-7.80; $P < .001$) and death (HR, 4.38; 95% CI, 2.57-7.47; $P < .001$) compared with the absence of *NPM1* transcripts.[33] The ELN 2022 guidelines recommend monitoring *NPM1* transcripts at diagnosis, at treatment completion, and 3 months for 2 years during surveillance.[24]

Traditionally, *FLT3*-ITD variants were categorized as intermediate to adverse risk based on the allelic ratio (higher being worse).[19] With the introduction of FLT3 inhibitors into therapy, *FLT3*-ITD variant is now considered intermediate risk regardless of the allelic ratio.[24] The prognosis of *FLT3*-TKD alteration is variable.[34] Midostaurin, a small molecule, multikinase FLT3 inhibitor, is approved to treat newly diagnosed *FLT3*-altered AML (ITD or TKD) combined with chemotherapy based on results from the RATIFY trial,[35] which evaluated the addition of midostaurin or placebo to induction and consolidation therapy, followed by 1 year of maintenance in patients with *FLT3*-altered AML aged 18 to 59 years. While there was no significant difference in CR rates in patients randomized to the midostaurin vs placebo arms (58.9% vs 53.5%; $P = .15$), midostaurin decreased the risk of death by 22% (HR, 0.78; 1-sided $P = .009$).[36]

Recently quizartinib, a selective FLT3-ITD inhibitor, was approved to treat patients with newly diagnosed *FLT3*-ITD-altered AML based on the results of the QUANTUM-First study,[37] in which 539 patients with *FLT3*-ITD–altered AML were randomized to receive quizartinib (n = 268) or placebo (n = 271) combined with standard induction and postremission chemotherapy. Patients receiving quizartinib had an OS advantage compared with patients in the placebo arm (HR, 0.78; 95% CI, 0.62-0.98; $P = .03$).[38] Quizartinib prescribing information carries a boxed warning for QTc prolongation, torsades de pointes, and cardiac arrest. Therefore, QTc monitoring and correction of electrolyte disturbances is recommended.[39] Whether quizartinib or midostaurin should be the preferred treatment in *FLT3*-ITD-altered AML is not known, as the drugs have not been compared directly.

For patients who are able to tolerate intensive chemotherapy but with ELN 2022 adverse risk genetics, the optimal treatment approach remains undefined.[24] With induction chemotherapy, CR rates are 48% in *TP53* variants, 42% in *KMT2A* rearrangements, and approximately 50% with monosomal karyotypes.[2] Whether these outcomes are better than other treatment approaches is not clear. Assessment in clinical trials is preferred, particularly for patients with *KMT2A* rearrangements who could receive targeted therapies, such as menin inhibitors.

A liposomal encapsulation of cytarabine and daunorubicin in a fixed 5:1 ratio, CPX-351 is approved to treat newly diagnosed therapy-related AML or AML with myelodysplasia-related changes in adults based on a randomized phase 3 clinical trial in patients with newly diagnosed high-risk/secondary AML (N = 309). Compared with a standard cytarabine- and daunorubicin-based chemotherapy regimen, CPX-351 led to a modest survival benefit (9.56 vs 5.95 months; HR, 0.69; 95% CI, 0.52-0.90; $P = .003$), including those with prior HMA exposure for antecedent myelodysplastic syndromes. The median time to neutrophil and platelet count recovery was prolonged with CPX-351 (neutrophils: 35.0 days; platelets: 36.5 days; with a 7 + 3 treatment regimen, both neutrophil and platelet count recovery was in 29 days), and use has been limited.[40]

In 2020, oral azacitidine (CC-486) was approved for continued treatment of AML in patients who achieved CR or CR with

incomplete blood count recovery (CRi) following induction chemotherapy.[41] QUAZAR, a randomized, placebo-controlled phase 3 trial, evaluated the role of oral azacitidine (300 mg daily in a 2 weeks on/2 weeks off schedule) or placebo in adults aged 55 years or older with AML with CR or CRi who were unable to complete standard intensive induction and postremission therapy. Patients randomized to receive oral azacitidine had an improved OS (HR, 0.69 vs placebo; 95% CI, 0.55-0.86; $P < .001$).[42] Most importantly, oral azacitidine is not a pharmacologic equivalent of subcutaneous or intravenous azacitidine and the formulations are not interchangeable.[43,44]

Management Approach in Treatment-Naive Patients Unable to Receive Intensive Induction Chemotherapy

Acute myeloid leukemia is more common in older adults, who also are more likely to have concomitant comorbidities and poor performance status.[45] Among patients aged 70 years or older or younger patients with poor performance status and/or major comorbidities, intensive chemotherapy is associated with a high risk of early mortality and truncated survival.[46] Likely as a consequence, 50% of older adults with AML between 2001 and 2013 did not receive any active therapy, including 42% with AML diagnosed in the last decade.[47] The 2020 approval of venetoclax (an orally available Bcl2 inhibitor) in combination with HMAs for newly diagnosed AML in older adults (aged ≥75 years or unable to receive intensive chemotherapy) has expanded the AML treatment landscape for this population.[48]

VIALE-A, a randomized, double-blind, placebo-controlled phase 3 study, investigated the efficacy and safety of venetoclax in combination with azacitidine compared with placebo plus azacitidine in patients with newly diagnosed AML who were older (age ≥75 years) or unlikely to tolerate intensive chemotherapy.[13] The composite CR rate (CRc: CR plus CRi) in the venetoclax plus azacitidine arm (64.7%) was significantly higher than in the placebo plus azacitidine arm (22.8%) ($P < .001$). At a median follow-up of 20.5 months, venetoclax plus azacitidine decreased the risk of death by 33.8% (HR, 0.662; $P < .001$), with a median survival duration of 14.7 vs 9.6 months for patients receiving placebo plus azacitidine.[13]

Focusing on patients with discrete variants, in those with an *FLT3* variant (ITD or TKD) treated with venetoclax plus azacitidine, the CRc rate was 67% and the median OS was 12.5 months (placebo plus azacitidine: CRc, 36%; median OS, 8.6 months).[49] Among patients with *IDH* variants or *IDH2* variants treated with venetoclax plus azacitidine, the CRc was 79% and the median OS was 24.5 months (placebo plus azacitidine: CRc, 11%; median OS, 6.2 months).[50]

In the subgroup analysis of patients with adverse cytogenetics, outcomes with venetoclax plus azacitidine were influenced by the presence or absence of *TP53* variation. Although the subgroup analysis was not powered to detect differences, venetoclax plus azacitidine treatment was associated with numerically higher response rates and OS (CRc, 70%; OS, 23.4 months) compared with placebo plus azacitidine (CRc, 23%; OS, 11.3 months) in those with adverse cytogenetics and *TP53* wild type. However, among patients with adverse cytogenetics and *TP53* variants (a surrogate marker for multihit *TP53*[51]), survival appeared similar between the arms (venetoclax plus azacitidine, 5.2 months; placebo plus azacitidine, 4.9 months).[52] Taken together, venetoclax plus azacitidine appears to be an effective therapy across the molecular subgroups in older adults with AML and those unable to tolerate intensive chemotherapy and should be continued ad infinitum, as long as a patient is deriving benefit. Venetoclax-based regimens can also be used when measurable residual disease clearance is suboptimal.[53] Whether the combination truly represents nonintensive therapy, whether outcomes differ from intensive induction chemotherapy in the same or in a younger population,[54] and the role of triplet therapy in patients with *FLT3*-altered AML (HMA plus venetoclax plus FLT3 inhibitor) is still being investigated.[55,56] Use of checkpoint inhibitors combined with standard chemotherapy is an area of active investigation.

In 2020, ivosidenib was approved to treat patients with relapsed or refractory (R/R) *IDH1*-altered AML, and in an extended approval in 2022, ivosidenib in combination with azacitidine was approved for newly diagnosed *IDH1*-altered AML in adults aged 75 years or older or who are unable to receive intensive induction chemotherapy. AGILE, a placebo-controlled, randomized phase 3 trial, enrolled 146 patients with newly diagnosed *IDH1*-altered AML to receive ivosidenib plus azacitidine or placebo plus azacitidine, with the primary end point of event-free survival. At a median follow-up of 12.4 months, the event-free survival was significantly longer for those randomized to ivosidenib plus azacitidine compared with the placebo plus azacitidine group (HR, 0.33; 95% CI, 0.16-0.69; $P = .002$). Differentiation syndrome, an ivosidenib-specific adverse event, occurred in 14% of patients receiving ivosidenib plus azacitidine vs 9% with placebo plus azacitidine.[57] Whether older adults with *IDH1* variants or those unlikely to tolerate intensive chemotherapy should receive initial ivosidenib plus azacitidine or venetoclax plus azacitidine is being investigated.[58]

Management of Relapsed AML

Despite the major headway in unraveling the byzantine molecular pathogenesis of AML and the identification of rational therapies, relapse is more common, with a 5-year OS of 10% in patients whose AML returns.[59] Currently, there is no consensus on a uniform reinduction strategy in patients who can tolerate intensive chemotherapy and who do not have actionable variants, and the choice of treatment is often based on the CR duration with the prior therapy. If the first remission duration is greater than 1 year, it is reasonable to reinduce with the same initial regimen. However, the likelihood of treatment response decreases with each relapse. Commonly used intensive chemotherapy regimens in the R/R setting include the mitoxantrone, etoposide, and cytarabine combination; fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin combination; or high-dose cytarabine (3 g/m^2). In patients not able to receive intensive chemotherapy, other regimens (eg, hypomethylating agents combined with venetoclax in those previously treated with cytotoxic chemotherapy) may be used.[60] The efficacy of these regimens is underwhelming, with CR rates ranging from 30% to 65% and a median duration of response typically less than 12 months.[26] The only cure for R/R AML is HCT, which may not require treatment before the transplantation-conditioning regimen. In the phase 3 ASAP trial, pre-HCT sequential conditioning with high-dose cytarabine or melphalan followed by reduced-

intensity conditioning in emergent HCT was noninferior to remission-induction chemotherapy prior to HCT (1-year leukemia-free survival: sequential conditioning, 71.5% vs remission-induction chemotherapy, 69.9%; *P* = .80).[61] Clinical trial options must be considered when available.

Patients with discrete, targetable variants have other therapeutic options. Enasidenib, an orally available, small-molecule IDH2 inhibitor, is approved to treat patients with R/R *IDH2*-altered AML. Its approval was based on the phase 1-2 AG-221-C-001 study, for which the primary end point was overall response rate (CR, CRi, CR with incomplete platelet recovery, partial remission, or morphologic leukemia-free state).[62] Enasidenib demonstrated an overall response rate of 40.3% and a CR or CR with partial hematologic recovery rate of 23% lasting a median of 5.8 months. Additionally, 34% of the patients became transfusion independent (red blood cells or platelets) during any 56-day postbaseline period. Enasidenib-specific adverse events included indirect hyperbilirubinemia (12%) and differentiation syndrome (7%). In the phase 3 study comparing enasidenib with conventional care in a similar patient population, however, enasidenib did not demonstrate a survival benefit (6.5 vs 6.2 months; *P* = .23), indicating that while it is a treatment option, it may not necessarily be a preferred treatment option.[63]

In the past 5 years, 2 IDH1 inhibitors, (ivosidenib and olutasidenib) have been approved to treat R/R *IDH1*-altered AML.[64] Ivosidenib and olutasidenib are both allosteric type II IDH1 inhibitors, but differ in their chemical structure and binding properties.[65,66] In the phase 1b trial that led to the approval of ivosidenib in R/R *IDH1*-altered AML, patients treated with ivosidenib had an overall response rate of 41.6%, including a CR or CR with partial hematologic recovery rate of 30.6%, and a median duration of response of 8.2 months among responders.[67] In the pivotal trial that led to the approval of olutasidenib in a similar population, the overall response rate was 48%, including a CR or CR with partial hematologic recovery rate of 35% and a median duration of response of 25.9 months among responders.[68] Ivosidenib and olutasidenib differ slightly in their adverse event profile, with ivosidenib carrying a boxed warning for QTc interval prolongation and olutasidenib for hepatotoxicity.[64] Given the lack of head-to-head comparison between ivosidenib and olutasidenib, the choice of IDH1 inhibitor in R/R *IDH1*-altered AML depends on likely patient tolerability, comorbidities, and prior exposure to other therapies.

Gilteritinib, a highly selective, oral FLT3 inhibitor active against ITD and TKD variants, is approved in the US to treat R/R *FLT3*-altered AML based on results of the ADMIRAL study.[69] Gilteritinib was compared with salvage chemotherapy (mitoxantrone, etoposide, and cytarabine combination; fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin combination; or low-dose cytarabine or azacitidine) in 371 patients with R/R *FLT3*-altered AML.[70] The CR or CR with partial hematologic recovery rates were significantly higher in patients treated with gilteritinib compared with patients treated with salvage chemotherapy (34% vs 15.3%; risk difference, 18.6%; 95% CI, 9.8%-27.4%). At a median follow-up of 17.8 months, gilteritinib demonstrated a significant improvement in OS compared with salvage chemotherapy (9.3 vs 5.6 months; HR, 0.64; 95% CI, 0.49-0.83; *P* < .001).[71] The gilteritinib labeling includes a boxed warning for differentiation syndrome and warnings for posterior reversible encephalopathy syndrome and QTc prolongation.[69]

Conclusions

Over the past decade, therapy for patients with AML has increasingly become tailored to both the disease molecular profile and patient- and disease-specific characteristics. Novel orally administered targeted agents pose coverage challenges and may necessitate paritylike legislative approaches to ensure patients can receive standard-of-care therapies regardless of administrative route. Drug development in AML is proceeding at a vigorous pace with continued exploitation of disease biologic factors, such as with the ongoing investigation of menin inhibitors against *KMT2A* and *NPM1c* variants.[72] Nevertheless, relapse, treatment refractoriness (common with *TP53* multihit status), and emergence of novel resistance variants remain major impediments to successful therapy.[73,74] Patients should be considered for clinical trials in up-front, relapsed, or refractory settings when available, given the persistent poor outcomes of this population. The approval of HMA plus venetoclax in older adults and those unlikely to tolerate intensive chemotherapy has spurred the evaluation of triplet therapies with an add-on third agent (either approved or investigational) to the HMA plus venetoclax backbone. Additional core questions, such as the optimal duration of venetoclax therapy, time-limited treatment, or appropriate sequencing of HMA plus venetoclax and molecularly targeted therapies, are under active investigation.[75-77] The concept of measurable residual disease assessment in AML is gaining traction and will likely serve as a marker to guide therapy duration and need for additional treatment interventions. Given the important prognostic information imparted by the cytogenomic makeup of AML, biomarker-focused clinical research using advanced approaches, such as basket, umbrella, and adaptive study designs, will accelerate drug development timelines. To quote Mark Twain, "the secret of getting ahead is getting started,"[78] and therapeutic development intended to improve the survival outcomes in patients with AML is well on its way.

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