clinical reviews

The Cup Runneth Over: Treatment Strategies for Newly Diagnosed Acute Myeloid Leukemia

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abstract

Since 2017, the number of agents for acute myeloid leukemia (AML) has rapidly expanded. Given the increased therapeutic options, better identification of high-risk subsets of AML and more refined approaches to patient fitness assessment, the decisions surrounding selection of intensive chemotherapy versus lower-intensity treatment have grown increasingly more nuanced. In this review, we present available data for both standard and investigational approaches in the initial treatment of AML using an intensive chemotherapy backbone or a lower-intensity approach. We summarize management strategies in newly diagnosed secondary AML, considerations around allogeneic stem-cell transplantation, and the role of maintenance therapy. Finally, we highlight important areas of future investigation and novel agents that may hold promise in combination with standard therapies.

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INTRODUCTION

Acute myeloid leukemia (AML), characterized by the clonal expansion of myeloid blasts in the blood and bone marrow, is the most common form of leukemia in adults with approximately 20,000 new cases diagnosed annually in the United States.[1] Since 2017, the armamentarium for AML has expanded to include new frontline strategies for older or unfit patients, mutation-targeted agents for specific disease subsets, and maintenance agents. Here, we summarize the current evidence informing treatment decisions in the frontline therapy of AML. We review factors influencing the selection of intensive versus lower-intensity regimens, novel combination approaches, and pressing management questions in need of prospective data.

FACTORS IN THE ASSESSMENT OF INTENSIVE VERSUS LOWER-INTENSITY TREATMENT

The median age of diagnosis for patients with AML in the United States is 68 years.[2] Patients older than age 60 years suffer worse survival because of higher treatment-related mortality and inherent resistance of disease to intensive chemotherapy (IC).[3-5] Owing to these considerations and the recent development of lower-intensity treatment regimens with considerable efficacy, initial assessment of a patient with AML requires careful determination of their candidacy for IC.

Several patient-related factors play into this determination. An analysis of 1,127 patients with AML on Southwestern Oncology Group protocols and 2,238 patients treated on MD Anderson protocols identified age and performance status as the most significant predictors of treatment-related mortality; however, age may primarily serve as a surrogate of patient-specific comorbidities and disease-specific factors.[6] In an analysis of 998 patients with AML or myelodysplastic syndrome (MDS) treated with IC, patients with an Eastern Cooperative Oncology Group performance status of 0-1 (n = 629) had an 8-week mortality of 23% and 1-year overall survival (OS) of 35%, compared with 72% and 7%, respectively, in those with an Eastern Cooperative Oncology Group of 3-4 (n = 120).[7] Physicians routinely gauge patient fitness on the basis of intuition, a subjective process prone to bias. Consensus-based criteria have been developed to help add objectivity to the identification of patients at risk of significant toxicity from IC including the Ferrara criteria.[8] Subsequent analysis of patients treated with IC found a median OS of 4.8 months in patients with criteria defining unfitness for IC compared to a median OS of 36.8 months in patients meeting no unfitness criteria.[9] Geriatric assessment (GA) is a valuable tool in predicting outcomes as well. A GA composed of cognitive testing, psychological function, physical function, and comorbid conditions in patients older than 60 years (n = 74) ultimately treated with IC identified impaired cognition and physical function as risk factors for poorer OS.[10] A separate prospective study of GA in patients older than 60 years treated with IC (n = 105) also confirmed the negative impact of impairment in a GA domain on OS.[11] These data highlight that age alone should not guide decision making around the use of IC in frontline management of AML.

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Even in patients who are considered candidates for IC, disease-specific factors should be taken into consideration as well. Higher-risk disease as defined by cytogenetics and molecular mutations may not benefit from IC.[12] Given the advancements of effective lower-intensity regimens in AML, it is becoming increasingly complex to identify the patients most likely to benefit from IC.[13] The Acute Leukemia French Association 1,200 investigators investigated outcomes of patients 60 years or older with newly diagnosed AML treated with IC by integrating the European Leukemia Net (ELN) 2017 risk classification with mutation status in seven genes. On the basis of this, patients were stratified into those whose predicted outcome was favorable (2-year OS 66.1%), intermediate (2-year OS 39%), and adverse (2-year OS 2.8%), reflecting marked chemoresistance in the latter subset.[14] A single-center prospective study integrating GA along with genetic markers in the selection of therapy for adults 60 years or older with AML (n = 28) demonstrated feasibility of this approach with a 30-day mortality of 4% and 1-year OS of 66%.[15] Finally, a propensity-matched analysis of patients receiving IC compared with hypomethylating agent (HMA) with venetoclax (VEN) suggested benefit of HMA-VEN over IC in certain high-risk populations such as those with *RUNX1* mutations.[16] Treatment approaches in high-risk subsets of AML such as secondary AML (sAML) and *TP53*-mutated AML that have poor outcomes with IC are discussed later in this review. Given the importance of genetic and cytogenetic markers in identifying patients who are most likely to benefit from IC, obtaining this information before initiating therapy should be considered and can be safely done.[17] In summary, treatment recommendations in newly diagnosed AML should go beyond age and patient-related factors but also need to incorporate disease-related factors that may predict for those patients most likely to benefit from IC.

INTENSIVE CHEMOTHERAPY APPROACHES

IC is considered the treatment of choice in young and/or fit patients. For decades, the 7 + 3 (7 days of continuous cytarabine combined with 3 days of an anthracycline) induction regimen followed by high-dose cytarabine (HIDAC) consolidation was considered the standard-of-care intensive approach. In recent years, alternative IC backbones have emerged, leading to numerous options without a clear consensus on the favored regimen among them.[18] Given the variation in IC regimens used across institutions, we will focus instead on the addition of novel agents to an IC backbone (Table 1).

Midostaurin and *FLT3*-Mutated AML

Patients with *FLT3*-mutated AML are candidates for midostaurin, an oral multitargeted kinase inhibitor, in combination with IC. The phase III RATIFY trial randomly assigned patients with *FLT3* internal tandem duplication or a point mutation in the tyrosine kinase domain of the protein to 7 + 3 induction, followed by consolidation and maintenance with or without midostaurin. Patients in the midostaurin arm enjoyed a significantly longer median OS of 75 months compared with 26 months in the control arm. Notably, 57% of patients on trial underwent allogeneic hematopoietic cellular transplantation (allo-HCT); 28.1% of patients in the midostaurin group underwent allo-HCT in first complete remission (CR1), and 22.7% of patients in the placebo group underwent allo-HCT in CR1.When data were censored at the time of allo-HCT, the 4-year OS in the midostaurin group was 64% compared with 56% in the control group ($P = .08$).[19]

Although the inclusion of midostaurin to IC in *FLT3*-mutated AML is the current standard of care, investigation of second-generation FLT3 inhibitors in the frontline setting is ongoing.[20] The phase III QuANTUM-First trial (NCT02668653) investigating quizartinib combined with IC versus IC alone in patients with *FLT3*-internal tandem duplication–mutated AML demonstrated superior median OS in the quizartinib arm (31.9 months *v* 15.1 months) and similar rates of CR/CR with incomplete hematologic recovery (CRi) (71.6% *v* 64.7%).[21] Phase III trials comparing IC with gilteritinib and IC with crenolanib against IC with midostaurin are also underway (NCT03836209 and NCT03258931).

Gemtuzumab Ozogamicin

Intensive regimens have been combined with gemtuzumab ozogamicin (GO). GO is an antibody-drug conjugate targeting CD33, a transmembrane receptor expressed in most cases of AML. Although initial data on the addition of GO to standard chemotherapy demonstrated increased mortality and led to the drug being withdrawn from market, more recent studies using a lower and fractionated dose have demonstrated benefit in specific disease subsets. The benefit of GO combined with IC appears to be most well defined in core-binding factor (CBF) AML, which is characterized by the presence of either t(8;21)(q22;q22) or inv(16)(p13q22)/t(16;16) and is classified as favorable risk.[12,22,23] A meta-analysis of five randomized trials reported significantly longer 5-year OS in favorable risk AML treated on GO arms compared with non-GO containing arms (76% *v* 55%), with the primary driver of improved survival being reduced rates of relapse.[24] Another approach being investigated in CBF AML is the addition of dasatinib, a multikinase inhibitor targeting receptor tyrosine kinase, to standard IC. Early-phase studies have demonstrated high CR rates and durable OS with this approach.[25,26]

GO has also been prospectively investigated in *NPM1*-mutated AML. The AMLSG 09-09 study randomly assigned patients age 18 years or older with newly diagnosed NPM1-mutated AML to receive IC with or without GO with the primary end point of event-free survival (EFS). There was no significant difference in EFS with a 2-year EFS of 52.6% in the standard arm and 58.1% in the GO arm. Two-year cumulative incidence of relapse in patients

TABLE 1. Select Novel Approaches in Frontline Treatment of AML

Reference	Study	Treatment	Response Rate	OS
IC approaches				
FLT3-mutated AML				
Stone et al[19]	Phase III study in ND *FLT3*m AML	Midostaurin plus IC *v* Placebo plus IC	Midostaurin plus IC CR rate: 58.9% Placebo plus IC CR rate: 53.5%	Midostaurin plus IC mOS: 74.7 months[a] Placebo plus IC mOS: 25.6 months
Erba et al[21]	Phase III study in ND *FLT3*-ITDm AML	Quizaritinib plus IC *v* Placebo plus IC	Quizartinib plus IC CR/CRi rate: 71.6% Placebo plus IC CR/CRi rate: 64.9%	Quizartinib plus IC mOS: 31.9 months[a] Placebo plus IC mOS: 15.1 months
CBF AML				
Paschka et al[25]	Phase Ib/IIa study in ND CBF-AML	Dasatinib plus IC	CR/CRi rate: 94%	4-year OS: 74.7%
Marcucci et al[26]	Phase II study in ND CBF-AML	Dasatinib plus IC	CR rate: 90%	3-year OS: 77%
NPM1-mutated AML				
Schlenk et al[27]	Phase III study in ND *NPM1*m AML	GO plus IC *v* IC	GO plus IC CR/CRi rate: 85.3% IC CR/CRi rate: 88.5%	GO plus IC 2-year OS: 92% IC 2-year OS: 93%
VEN-containing regimens				
Wang et al[29]	Phase II study in ND de novo AML	VEN plus 3 + 7	cCR rate: 91%	1-year OS: 97%
Kadia et al[30]	Phase II study in ND AML, mixed phenotype acute leukemia, and high-risk MDS	VEN plus CLIA	cCR rate: 94%	1-year OS: 85%
DiNardo et al[31]	Phase II study of ND and R/R AML	VEN plus FLAG-IDA	ND cCR rate: 90% R/R cCR rate: 61%	ND 1-year OS: 94% R/R 1-year OS: 68%
IDH1 or *IDH2*-mutated AML				
Stein et al[33]	Phase I study in ND *IDH1*m or *IDH2*m AML	*IDH1*m:Ivo plus IC *IDH2*m:Ena plus IC	Ivo CR rate: 55% Ena CR rate: 47%	Ivo 1-year OS: 78% Ena 1-year OS: 76%
Lower-intensity treatment approaches				
IDH1 inhibitor-including therapies				
Roboz et al[42]	Phase I study in ND *IDH1*m AML ineligible for IC	Ivo monotherapy	CR plus CRh rate: 42.4%	mOS: 12.6 months
Montesinos et al[43]	Phase III study in ND *IDH1*m AML ineligible for IC	Ivo plus Aza *v* Aza	Ivo plus Aza CR rate: 47%[a] Aza CR rate: 15%	Ivo + Aza mOS: 24.0 months[a] Aza mOS: 7.9 months

(continued on following page)

TABLE 1. Select Novel Approaches in Frontline Treatment of AML (continued)

Reference	Study	Treatment	Response Rate	OS
Lachowiez et al[95]	Phase Ib/II trial in *IDH1*m AML or MDS (ND or R/R)	DL1: Ivo plus VEN 400 mg once daily DL2: Ivo plus VEN 800 mg once daily DL3: Ivo plus VEN 400 mg once daily plus Aza	Overall cCR rate: 84% DL1 = 67% DL2 = 100% DL3 = 85%	Overall 1-year OS: 68% DL1 = 50% DL2 = 67% DL3 = 78%
IDH2 inhibitor-including therapies				
Pollyea et al[44]	Phase I/II trial in ND *IDH2*m AML ineligible for IC	Ena monotherapy	CR/CRi rate: 21%	mOS = 11.3 months
DiNardo et al[46]	Phase II trial in ND *IDH2*m AML ineligible for IC	Ena plus Aza *v* Aza	Ena plus Aza CR rate: 54%[a] Aza CR rate: 12%	Ena plus Aza mOS: 22.0 months Aza mOS: 22.3 months
Venugopal et al[45]	Phase II trial in ND or R/R *IDH2*-mutated AML	Enasidenib plus Aza with or without VEN	Overall CRc rate: 69% ND CRc rate: 100% R/R CRc rate: 58%	ND 1-year OS: 83% 1R 1-year OS: 75% ≥ 2R 1-year OS: 10%
FLT3 inhibitor-including therapies				
Maiti et al[96]	Phase II trial in ND or R/R *FLT3*m-mutated AML	VEN plus decitabine plus FLT3 inhibitor (gilteritinib, sorafenib, or midostaurin)	Overall CRc rate: 76% ND CRc rate 92% R/R CRc rate: 62%	ND 2-year OS: 80% R/R 2-year OS: 29%
Short et al[97]	Phase I/II trial in ND or R/R *FLT3*m-mutated AML not eligible for IC	VEN plus Aza plus gilteritinib	ND CR/CRi rate: 82% R/R CR/CRi rate: 27%	ND mOS: NR R/R mOS: 10.8 months
Yilmaz et al[98]	Phase II trial in ND or R/R *FLT3*m-mutated AML	VEN plus decitabine plus quizartinib	ND CRc rate: 100% R/R CRc rate: 69%	ND mOS: NR R/R mOS: 7.1 months

Abbreviations: AML, acute myeloid leukemia; Aza, azacitidine; CBF, core-binding factor; cCR, composite complete remission; CLIA, cladribine, high-dose cytarabine, idarubicin; CR, complete remission; CRh, complete remission with partial hematologic recovery; CRi, complete remission with incomplete hematologic recovery; DL1, dose level 1; DL2, dose level 2; DL2, dose level 3; Ena, enasidenib; FLAG-IDA, fludarabine, cytarabine, granulocyte colony-stimulating factor; GO, gemtuzumab ozogamicin; IC, intensive chemotherapy; IDH, isocitrate dehydrogenase; ITD, internal tandem duplication; Ivo, ivosidenib; MDS, myelodysplastic syndrome; mOS, median OS; ND, newly diagnosed; NR, not reached; OS, overall survival; R/R, relapsed/refractory; VEN, venetoclax.

[a]Statistically significant.

achieving a CR/CRi was lower in the GO arm. However, cumulative incidence of death at 2 years was similar in the two arms (8.3% GO arm, 7.1% standard arm), and the early death rate was 10.7% in the GO arm compared with 5.7% in the standard arm ($P = .05$).[27] Of note, the spleen tyrosine kinase inhibitor entospletinib has demonstrated favorable efficacy in early-phase trials combining it with IC for *NPM1*-mutated AML, and a randomized phase III trial is currently underway (NCT05020665).[28]

Venetoclax

Given the efficacy of VEN, an oral selective B-cell leukemia/lymphoma-2 inhibitor, as part of non-IC regimens for AML, there is much interest in exploring its role in combination with IC as well. Most recently, Wang et al[29] evaluated VEN combined with 7 + 3; CR rate was 91% with nearly all patients testing negative for measurable residual disease (MRD) at the end of induction. A propensity score–matched, cohort study of two such ongoing trials[30,31] found improved CR rates and EFS in patients treated with VEN-containing IC regimens as compared with IC alone but no significant difference in OS,[32] highlighting that these promising single-arm results must be evaluated prospectively against current standards of care.

IDH1- and *IDH2*-Mutated AML

Other agents being investigated in combination with IC include the isocitrate dehydrogenase (IDH)1 and IDH2 inhibitors, ivosidenib and enasidenib, respectively. A phase I study investigated ivosidenib with 7 + 3 for patients with newly diagnosed *IDH1*-mutated AML and enasidenib with 7 + 3 for patients with newly diagnosed *IDH2*-mutated AML. Among patients treated with IC plus ivosidenib, the CR rate was 55% with no dose-limiting toxicities while CR rate among patients treated with IC plus enasidenib was 47% with one dose-limiting toxicity observed. Median OS was not reached for the IDH1-mutated cohort and was 26 months for the IDH2-mutated cohort.[33] Although the combination of an IDH inhibitor with IC appears to be safe and efficacious, randomized, prospective analyses of these regimens are needed to identify the benefit of IDH inhibition in the frontline setting versus at the time of relapse or progression. The HOVON150AML study is a randomized trial currently seeking to answer this question (NCT03839771).

LOWER-INTENSITY REGIMENS IN AML

As discussed, IC may be associated with significant morbidity and mortality; thus, the development of efficacious lower-intensity regimens has been an active area of investigation.

Hypomethylating Agents With Venetoclax

HMAs are often used as a backbone for lower-intensity therapy. Azacitidine and decitabine monotherapy have demonstrated clinical benefit over low-dose cytarabine (LoDAC) in AML,[34-36] although survival with this approach is quite limited.[37] This has led to the exploration of combination therapy. VIALE-A, a randomized phase III trial comparing azacitidine with and without VEN in patients with newly diagnosed AML ineligible for IC, demonstrated that the combination led to significantly improved OS (14.7 *v* 9.6 months). Significantly improved median OS was also seen in sAML (16.4 *v* 10.6 months) and intermediate-risk AML (20.8 *v* 12.4 months).[38] A single-center propensity-matched cohort analysis sought to identify subgroups that may benefit from azacitidine-VEN in comparison with IC. Factors that favored azacitidine-VEN included age 65 years or older, high-risk disease by ELN 2017 criteria, and *RUNX1* mutations although ELN 2017 intermediate-risk disease had more favorable outcomes with IC.[16] Although this doublet has become the standard lower-intensity regimen for newly-diagnosed AML in patients who are not candidates for IC, its impact in other subsets is still being ascertained. HMA-VEN is being investigated in younger patients with adverse-risk AML, and a phase II study of HMA-VEN in patients age 18-59 years with ELN 2017 adverse-risk disease is ongoing. Interim analysis of 14 patients demonstrated a CR/CR with partial hematologic recovery rate of 64% compared with a historical CR/CR with partial hematologic recovery rate of 38%.[39] Use of HMA-VEN in other high-risk AML subsets such as sAML and *TP53*-mutated AML is discussed later in this review.

Targeted Therapy

Targeted therapies (with FDA-approved drugs available against mutated *FLT3*, *IDH1*, and *IDH2*) represent an opportunity for delivering treatment efficacy with tolerable toxicity in patients with AML ineligible for IC. The phase III LACEWING trial evaluated gilteritinib plus azacitidine versus azacitidine monotherapy in patients with *FLT3*-mutated AML ineligible for IC; the primary end point of median OS was not significantly different across arms (approximately 9 months) despite higher response rates in the gilteritinib-containing arm.[40] In contrast, pooled analyses of patients with newly diagnosed *FLT3*-mutated AML treated with HMA-VEN demonstrate a median OS of 12 months[41] Given these data, there is much interest in the investigation of FLT3 inhibitors combined with the HMA-VEN backbone (Table 1).

Ivosidenib monotherapy was evaluated as up-front treatment in patients with *IDH1*-mutated AML ineligible for IC; composite CR rate (CR + CRi) was 42.4% with a median OS of 12.6 months, results that supported its approval as first-line treatment in this population.[42] A phase III trial randomly assigned a similar population to azacitidine with and without ivosidenib; the combination arm showed significantly improved 12-month EFS (37% *v* 12%) and OS (24.0 *v* 7.9 months).[43] An early-phase trial of enasidenib monotherapy in patients with *IDH2*-mutated, newly diagnosed AML ineligible for IC demonstrated an overall response rate of 31% and a median OS of 11.3 months.[44]

Enasidenib combined with azacitidine is also under investigation in the frontline setting: a phase II trial demonstrated promising response rates, with a composite CR rate of 100% in the seven patients with newly-diagnosed AML.[45] A randomized phase II study of azacitidine with or without enasidenib demonstrated a significantly higher response rate in the combination arm (74% *v* 36%); however, median OS was similar in both arms (approximately 22 months).[46] Using these data in practice presents a challenge, as HMA-VEN has been shown to be especially beneficial in patients with *IDH1* or *IDH2* mutations.[47] A direct comparison of these targeted strategies with HMA-VEN would provide more clarity on the optimal sequence of these therapies. Trials are also incorporating targeted therapy into VEN-based regimens in newly diagnosed AML patients. Available data for these combination approaches are summarized in Table 1.

Low-Dose Cytarabine Combination Therapy

In unfit patients with newly diagnosed AML, other low intensity chemotherapy backbones can be considered. Although LoDAC as a single agent has shown limited antileukemia activity,[48] it has been used in combination with other agents with more favorable results. Although LoDAC with glasdegib and LoDAC with VEN have demonstrated improved OS compared with LoDAC alone,[49,50] the efficacy of azacitidine-VEN has established it as the standard of care lower-intensity regimen in the frontline setting.

Another lower-intensity regimen investigated in the frontline setting is the combination of adenosine nucleoside analogues with LoDAC alternating with decitabine. A combined analysis of two phase II trials of clofarabine or cladribine combined with LoDAC alternating with decitabine in patients with newly diagnosed AML age 60 years or older and unfit (n = 248) showed an overall response rate of 66%. With a median follow-up of 60 months, median OS was 12.5 months and survival among older adults compared favorably with historical controls when stratified by age. The 4- and 8-week mortality rates were 2% and 11%, respectively.[30,51,52] In addition, a phase II study investigating alternating cycles of LoDAC plus cladribine plus VEN with cycles of azacitidine plus VEN demonstrated a composite CR rate of 93% with median OS not reached at a median follow-up of 22 months.[53]

SECONDARY AML AND THERAPY-RELATED AML

Although the 2022 WHO and International Consensus Classification criteria do not have a specific diagnosis for sAML, we will define it as AML arising from an underlying hematologic condition (eg, MDS or myeloproliferative neoplasm).[22,23,54] Cases of AML that develop in patients with previous exposure to cytotoxic chemotherapy or radiotherapy will be defined as therapy-related AML (t-AML).[22,23,55] Because of the particularly poor OS in these subsets of AML and *TP53*-mutated AML, there is significant interest in the development of novel therapeutic strategies for such patients in the frontline setting.[56-59]

CPX-351, a liposomal encapsulation of cytarabine and daunorubicin, has been prospectively investigated in t-AML, AML arising from MDS or chronic myelomonocytic leukemia, and AML with MDS-related cytogenetic abnormalities. Lancet et al conducted a phase III trial of CPX-351 compared with 7 + 3 in this patient population (age 60-75 years) and demonstrated an improved CR rate (37% *v* 26%) and improved OS (9.5 *v* 5.9 months). Median time to count recovery after induction was longer in the CPX-351 arm with similar rates of neutropenic fever in both arms. Long-term follow-up demonstrated a 5-year OS rate of 18% in the CPX-351 group and 8% in the 7 + 3 group.[60] Thirty-five percent of patients had *TP53* mutations, and median OS among these patients was not significantly different in the CPX-351 and 7 + 3 arms (4.5 *v* 5.1 months).[61] Of note, both reinduction and consolidation therapy in the 7 + 3 group was 5 days of continuous cytarabine with 2 days of daunorubicin (5 + 2) as opposed to HIDAC.

Recent analyses comparing CPX-351 with other treatment strategies support clinical equipoise in this subtype of disease. A retrospective analysis comparing HIDAC and purine analogue–based regimens with CPX-351 in sAML, AML with MDS-related cytogenetics, and t-AML demonstrated similar OS in both cohorts.[62] A multicenter retrospective analysis recently compared outcomes of CPX-351 versus HMA-VEN in newly diagnosed AML; however, this was not restricted to the patient population investigated in the phase III CPX-351 trial. Median OS was higher in the CPX-351 group, but when controlling for rates of allo-HCT, survival was similar.[63] Another analysis demonstrated a similar median OS in patients treated with CPX-351 compared with HMA-VEN (13 *v* 11 months, $P = .22$).[64] Prospective analyses of CPX-351 versus HMA-VEN or HIDAC-based regimens are needed for these subsets of disease. Novel therapies in sAML have also had limited success. Similarly poor outcomes are noted in patients with *TP53*-mutated AML, which is significantly enriched among sAML/t-AML. An analysis of 291 patients with *TP53*-mutated AML found a median OS of < 10 months across all treatment approaches, including a median OS of 9.2 months for patients treated with 7 + 3 and 6.7 months for those treated with HMA-VEN.[56] Table 2 summarizes select outcomes data in sAML and *TP53*-mutated AML with novel treatment approaches.

TRANSPLANT CONSIDERATION/MAINTENANCE THERAPIES IN FIRST REMISSION

Minimizing time from AML diagnosis to allo-HCT should be the treating physician's goal, as time to allo-HCT affects survival,[65,66] and each consolidation cycle confers accumulating toxicity with no proven benefit in those destined for transplant.[67,68] Considering the weeks required for donor arrangements and rigorous patient evaluations, consultation with a transplant physician should occur at time of diagnosis which, in most circumstances, means while the patient is still hospitalized.

TABLE 2. Selected Treatment Approaches for MPN-Blast Phase and *TP53*-Mutated AML

Reference	Study	Treatment	Response Rate	Median Overall Survival
MPN blast phase				
VEN-containing regimens				
Gangat et al[99]	Retrospective analysis of 32 patients (frontline and R/R treatment)	HMA-VEN	CR/CRi rate: 44%	8 months
Masarova et al[100]	Retrospective analysis of 31 patients (frontline and R/R treatment)	VEN-including regimens	CR/CRi rate: 23%	4 months
King et al[101]	Retrospective analysis 27 patients with MPN-AP/BP (frontline and R/R treatment)	VEN-including regimens	ALR-C/CCR rate: 37%	MPN-BP: 6 months MPN-AP: 3.6 months
JAK inhibitor-including therapies				
Mascarenhas et al[102]	Phase II study of 25 patients with MPN-AP/BP	Ruxolitinib plus decitabine	ORR: 44%	9.5 months
IDH inhibitor-including therapies				
Patel et al[103]	Retrospective analysis of 8 patients with *IDH2*-mutated MPN-AP/BP (frontline and R/R treatment)	Enasidenib-including regimens	ORR: 37.5%	NR (median follow-up 9 months)
Chifotides et al[104]	Retrospective analysis of 12 patients with *IDH1*- or *IDH2*-mutated MPN-BP (frontline and R/R treatment)	IDH inhibitor-including regimens	CR rate: 25%	10 months
TP53-mutated AML				
Magro-containing regimens				
Daver et al[105]	Phase Ib/II study of 38 patients with newly diagnosed or R/R AML	Aza plus VEN plus magro	ND CR/CRi rate: 94% VEN-naive CR/CRi rate: 63% Prior VEN exposure CR/CRi rate: 27%	ND: NR VEN-naive: NR Prior VEN exposure: 3.1 months
Sallman et al[106]	Phase Ib study of patients with newly diagnosed AML including 34 patients with *TP53* mutation	Aza plus magro	ORR: 71%[a]	12.9 months[a]
Eprenetapopt (APR-246)-containing regimens				
Sallman et al[107]	Phase Ib/II study of 55 patients with *TP53*-mutated MDS, MDS/MPN, or AML with ≤ 30% blasts	Aza plus eprenetapopt	ORR: 71%	10.8 months
Cluzeau et al[108]	Phase II study of 52 patients with *TP53*-mutated MDS or AML	Aza plus eprenetapopt	ORR: 52%	12.1 months
Garcia-Manero et al[109]	Phase I study of 30 patients with *TP53*-mutated AML	Aza plus VEN plus eprenetapopt	CR/CRi rate: 53%	Not reported

Abbreviations: ALR-C, acute leukemia response—complete; AML, acute myeloid leukemia; AP, accelerated phase; Aza, azacitidine; BP, blast phase; CCR, complete cytogenetic response; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; HMA, hypomethylating agent; IDH, isocitrate dehydrogenase; Magro, magrolimab; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; NR, not reached; ORR, overall response rate; R/R, relapsed/refractory; VEN, venetoclax.

[a]Data from patients with *TP53*-mutation.

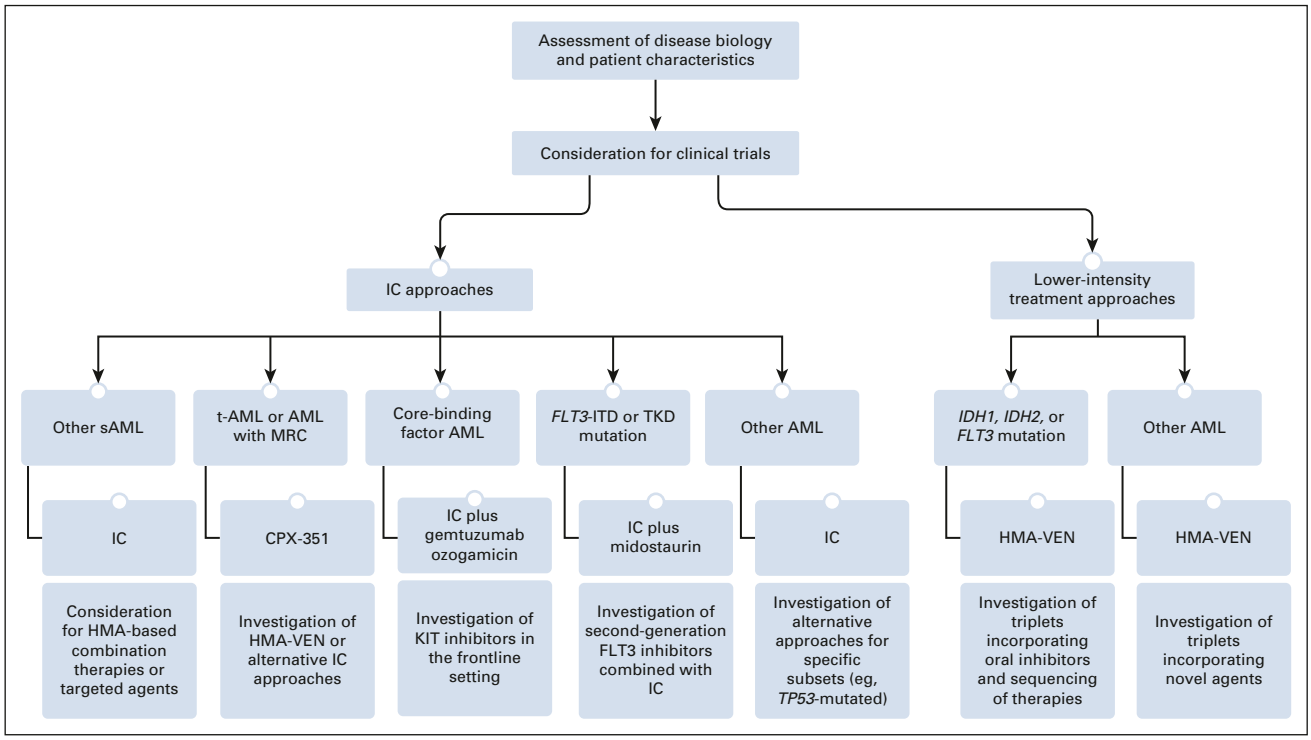

FIG 1. Our treatment approach to newly diagnosed AML and areas of investigation. HMA, hypomethylating agent; IC, intensive chemotherapy; ITD, internal tandem duplication; KIT, receptor tyrosine kinase; MRC, myelodysplasia-related changes; sAML, secondary acute myeloid leukemia; t-AML, therapy-related AML; TKD, tyrosine kinase domain; VEN, venetoclax.

In appropriate transplant candidates, allograft in first remission is widely recommended in all subtypes of AML except favorable risk disease without MRD at the end of induction.[69] Even so, there are notable exceptions: Favorable risk features appear to be less advantageous with increasing age, with older patients faring worse due in part to inherent chemoresistance[70-72]; and co-occurring mutations influence prognosis and refine existing prognostic schemes.[73] Molecular characteristics at diagnosis in patients 60 years or older with AML who undergo allo-HCT in CR1 are predictive of leukemia-free survival and persistence of MRD.[74] These data should, therefore, be integrated into the transplant decision.

The question of age and its relationship to transplant candidacy is frequently encountered given the median age of AML onset. Allo-HCT can be well tolerated in older adults including carefully selected septuagenarians,[75,76] with the GA used to assess physiological age[77,78]; biological age alone does not, therefore, represent a barrier to transplant referral. Reduced intensity conditioning enables harnessing the graft-versus-leukemia effect while minimizing the toxicity of allo-HCT, expanding the pool of candidates who may benefit from this therapy.[79,80] Although there are not randomized data in this regard, an analysis of adults age 60-75 years treated on National Clinical Trials Network protocols demonstrated higher transplant-related mortality in patients who underwent allo-HCT but also improved 5-year OS compared with those who received consolidation alone (29% *v* 14%).[81] Analysis of adults age 60-70 years treated on the National Cancer Research Institute AML16 trial who achieved a CR/CRi demonstrated similar results, with a significantly improved 5-year OS in patients who underwent allo-HCT compared with those treated with chemotherapy (37% *v* 20%, $P < .0001$).[82]

Finally, for those not candidates for allo-HCT, oral azacitidine represents the only approved maintenance strategy in AML, indicated for nontransplant candidates in remission after intensive induction chemotherapy with or without consolidation.[83] Oral azacitidine extended survival compared with placebo in favorable risk subgroups such as mutated *NPM1* and in patients at high risk of relapse on the basis of *FLT3* or MRD status.[84,85] Importantly, the majority of patients in this study received 0-1 cycles of consolidation so the added benefit of oral azacitidine after optimal consolidation is unknown. Maintenance FLT3 inhibition remains an unproven strategy as existing studies looking at the addition of a FLT3 inhibitor to frontline therapy did not include a second random assignmet at the time of maintenance.[19,86,87] Patients in remission after lower-intensity therapy including HMA with or without VEN or targeted inhibitors should continue therapy indefinitely on the basis of current available evidence.[88]

SUMMARY

Since 2017, the treatment landscape for AML has markedly changed. Our approach to newly diagnosed AML is summarized in Figure 1. In patients appropriate for IC, utilization of

disease-specific factors should determine the addition of additional therapies to the IC backbone (eg, GO for CBF-AML, midostaurin for *FLT3*-mutated AML). Questions of high clinical relevance include the identification of AML subsets likely to benefit from novel therapies added to IC and whether lower-intensity therapy is the appropriate choice for high-risk subsets unlikely to benefit from IC such as *TP53*-mutated AML. For patients appropriate for a lower-intensity regimen, our preferred approach is the use of HMA-VEN. Utilization of novel agents in combination with HMA-VEN, incorporation of MRD negativity into clinical management in patients on lower intensity therapy, and identification of patients appropriate for a trial of therapy discontinuation are pressing areas of investigation.[16,89,90] There is also much interest in the development of all-oral regimens for the treatment of newly diagnosed AML.[91] As treatment paradigms continue to evolve to include indefinite therapies for AML, ensuring quality-of-life preservation alongside treatment efficacy is vital.[92,93] Finally, a number of novel agents hold promise and are being investigated in combination with a variety of backbones. Some agents of note include the anti-CD47 antibody magrolimab, *TP53* reactivator eprenetapopt, MDM2 inhibitors, and immunotherapeutic agents.[94] In summary, treatment selection for newly diagnosed AML has become an increasingly nuanced decision; patient-specific factors and disease biology should be carefully considered and should inform novel combination approaches in the context of prospective trials.

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EQUAL CONTRIBUTION

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The Cup Runneth Over: Treatment Strategies for Newly Diagnosed Acute Myeloid Leukemia

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