Updates in the Management of Newly Diagnosed Acute Myeloid Leukemia

Presented by Alice S. Mims, MD, MS

ABSTRACT

For patients with newly diagnosed acute myeloid leukemia (AML) who are candidates for intensive induction regimens, all therapies include anthracycline- and cytarabine-based backbones. Core-binding factor AML is typically treated with gemtuzumab ozogamicin and 7 + 3 chemotherapy. Patients with *FLT3*-mutated (ITD or TKD) disease should have midostaurin + 7 + 3 and consolidation, and those with secondary or therapy-related AML should be considered for CPX-351. For patients ineligible for intensive induction regimens, venetoclax has changed the game and should be used in combination with hypomethylating agents or cytarabine. Glasdegib is also approved in combination with low-dose cytarabine. Patients with *IDH1/2*-mutated disease can be treated with ivosidenib and enasidenib, respectively. Although enasidenib has yet to secure its spot in the up-front setting, data support its use in newly diagnosed AML. An ongoing question in the field concerns how to treat patients with *TP53*-mutated AML, because most patients do not respond well to currently available therapies and continue to have poor overall outcomes.

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Over the past 5 years, the treatment landscape for acute myeloid leukemia (AML) has changed remarkably, according to Alice S. Mims, MD, MS, Associate Professor, The Ohio State University Comprehensive Cancer Center–James Cancer Hospital and Solove Research Institute. At the NCCN 2021 Virtual Congress: Hematologic Malignancies she explained that 2017 brought the addition of targeted therapies with the *FLT3* inhibitor midostaurin, then the *IDH2* inhibitor ivosidenib, followed by liposomal daunorubicin and cytarabine (CPX-351), which is now approved for secondary or therapy-related AML. After further analysis in both the up-front and relapsed/refractory (R/R) settings, gemtuzumab ozogamicin (GO) came back onto the scene. In 2018, the field saw the approvals of ivosidenib for *IDH1*-mutated AML, gilteritinib for R/R *FLT3*-mutated AML, combination therapies with venetoclax and hypomethylating agents, venetoclax in combination with cytarabine, and glasdegib in combination with cytarabine.¹

“We hope the field continues to move forward toward personalizing cancer therapy for individual patients, which will hopefully lead to continued better outcomes,” said Dr. Mims.

The current potential treatment approaches are based on the knowledge of genomic data, secondary AML, therapy-related disease, or CD33 positivity. “These treatment approaches have really opened up the possibility for different therapeutics for patients, but it has also made things quite a bit more complicated,” Dr. Mims noted. “So, for a simpler way to think about all of these new therapeutic options in the up-front setting, I typically divide them into intensive and nonintensive regimens.”

Treating Candidates With Intensive Induction Regimens

For patients who are candidates for intensive induction regimens, all therapies include an anthracycline and cytarabine-based backbone. For core-binding factor AML, most leukemia physicians will add GO to 7 + 3 induction and consolidation, noted Dr. Mims. Patients with *FLT3*-ITD or *FLT3*-TKD mutations should have midostaurin added to their 7 + 3 induction and consolidation, and those with secondary or therapy-related AML should be considered for CPX-351.

“Although none of these treatments have come with any age restrictions per the FDA labels, it should be noted that the midostaurin study that led to approval included only patients between the ages of 18 and 60 years, and the CPX-351 study included only those aged 60 to 75 years. Thus, fewer data are available for patients outside of these age ranges,” she pointed out.

Reintroduction of GO

Accelerated approval by the FDA was initially granted for GO in May 2000 based on phase II trials in which the overall response rate (ORR) was 30% in first-line therapy for relapsed AML.² However, the drug was voluntarily withdrawn from the market in 2010 based on the SWOG phase III trial that compared standard induction chemotherapy (7 + 3) with or without GO in patients aged <60 years. Data from the study showed an increased early mortality rate (6% vs 1%) in the standard arm (ClinicalTrials.gov identifier: NCT00085709).

Multiple randomized phase III studies have examined the addition of GO to induction therapy. The ALFA-0710 study demonstrated improved relapse-free survival and overall survival (OS) in the GO arm, but patients had a higher hematologic toxicity—although with no increased risk of death from toxicity.³ The MRC AML16 study also showed improvement in relapse risk and OS, with no increase in early mortality.⁴ The AML-17 phase III study, which added GO to mitoxantrone/etoposide/cytarabine (MEC), showed similar OS rates, but with a higher induction and 60-day mortality.⁵

To provide a more comprehensive view of the data, a meta-analysis was then performed of 5 randomized controlled trials of >3,000 patients aged ≥ 15 years.⁶ Data from this study demonstrated a reduced risk of relapse and improved 5-year OS with GO. A substudy analysis showed that patients with favorable-risk cytogenetics experienced the best response, those with intermediate-risk cytogenetics experienced some benefit, but patients with adverse-risk cytogenetics experienced no benefit. Based on these findings, GO was introduced back into the market in 2017 for the up-front setting (either in combination with 7 + 3 and consolidation or as a single agent) and as a single agent in the R/R setting.⁷

“Most clinicians use GO in the setting of induction therapy with favorable-risk core-binding factor AML,” Dr. Mims said. “There is a potential risk of hepatotoxicity, so keep this in mind if planning for allogeneic transplant as part of the patient’s care, which is not typical for many patients with core-binding factor disease.”

FLT3 Inhibitors

Mutations in *FLT3* are present in approximately 30% of adults with newly diagnosed AML, and approximately 75% of these patients have an *FLT3*-ITD mutation. These mutations are associated with a poor prognosis, due to a high relapse rate. Approximately another 8% of patients with newly diagnosed AML have an *FLT3*-TKD mutation, although the effect of *TKD* mutations on prognosis is uncertain.

Both subtypes of *FLT3* mutations yield ongoing activation of *FLT3* signaling and its downstream signaling pathways, including MAPK/ERK, JAK/STAT5, and PI3K/AKT. This results in uncontrolled proliferation, inhibition of differentiation, and reduction of apoptosis in AML cells.

The RATIFY study was the pivotal trial that changed the current standard of care for patients with *FLT3*-ITD- and *FLT3*-TKD-mutated AML who are candidates for intensive induction therapy.⁸ After meeting its primary endpoint of OS compared with a placebo-controlled arm, the RATIFY trial led to the addition of midostaurin to induction chemotherapy and consolidation. “As many patients did not go on to receive maintenance therapy,

the FDA approval was just for midostaurin during induction and consolidation,” she said. “This was not meant to continue as a maintenance therapy, because there were not enough patients to understand the full benefits of maintenance.”

CPX-351 is approved for the treatment of adults with newly diagnosed therapy-related AML or AML with myelodysplastic syndrome-related changes. In the study that led to its FDA approval, CPX-351 showed superior OS in older patients with AML (age 60–75 years), with a median OS of 9.3 versus 5.9 months in the control arm.⁹

Patients Ineligible for Intensive Induction Regimens

According to Dr. Mims, venetoclax has changed the landscape of AML and has become the go-to agent for most physicians when used in combination with azacitidine or decitabine.

The VIALE-A study led to full FDA approval of venetoclax in combination with hypomethylating agents in patients aged ≥ 75 years and in younger patients ineligible for intensive induction.¹⁰ In this randomized phase III trial, the complete response rate was 36.7% in the venetoclax/azacitidine arm versus 17.9% in the placebo arm. The study met its primary endpoint of OS, with a median OS of 14.7 months in the venetoclax/azacitidine arm versus 9.6 months in the placebo arm, with a median follow-up of 20.5 months at the time of analysis (Table 1).

Dr. Mims pointed out the need for novel therapies beyond venetoclax to improve the outcome of patients with *TP53*-mutated AML, because these patients do not typically respond well to most therapies and continue to have poor outcomes (the ability to achieve remission with standard chemotherapy is $\sim 30\%$). Additionally, research has shown that the addition of venetoclax to standard treatment regimens did not improve outcomes in younger or older patients with this mutation.¹¹ “With new data emerging in favor of therapy with hypomethylating agents, there should be a discussion with these patients about the risks and benefits of treatment options,” advised Dr. Mims.

Venetoclax is also approved in combination with low-dose subcutaneous cytarabine in patients aged ≥ 75 years or in younger patients with comorbidities who cannot tolerate intensive induction chemotherapy, based on results from the VIALE-C study.¹² However, this combination is used less frequently than venetoclax and hypomethylating agents. Additionally, glasdegib is a Hedgehog inhibitor approved for use in combination with low-dose subcutaneous cytarabine in the same patient population based on the results from the BRIGHT AML 1003 study.¹³

According to Dr. Mims, all 3 of these regimens (venetoclax + hypomethylating agents, venetoclax + cytarabine, and glasdegib + cytarabine) are currently

Table 1. Response Rates and EFS

	Azacitidine + Venetoclax (n=286) % (95% CI)	Azacitidine + Placebo (n=145) % (95% CI)	P Value
CR + CRi	66.4 (60.6–71.9)	28.3 (21.1–36.3)	<.001
CR + CRi by start of cycle 2	43.4 (37.5–49.3)	7.6 (3.8–13.2)	<.001
CR rate	36.7 (31.1–42.6)	17.9 (12.1–25.2)	<.001
Transfusion independence ^a			
RBC	59.8 (53.9–65.5)	35.2 (27.4–43.5)	<.001
Platelets	68.5 (62.8–73.9)	49.7 (41.3–58.1)	<.001
CR + CRi rate in subgroups			
IDH1/2	75.4 (62.7–85.5)	10.7 (2.3–28.2)	<.001
FLT3	72.4 (52.8–87.3)	36.4 (17.2–59.3)	.021
NPM1	66.7 (46.0–83.5)	23.5 (6.8–49.9)	.012
TP53	55.3 (38.3–71.4)	0	<.001
EFS, mo (95% CI)	9.8 (8.4–11.8)	7.0 (5.6–9.5)	<.001
Median age: 76 y (range, 49–91 y)			

Abbreviations: CR, complete remission; CRi, complete remission with incomplete hematologic recovery; EFS, event-free survival.

^a≥56 days with no RBC or platelet transfusion between first and last day of treatment.

Data from DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. *N Engl J Med* 2020;383:617–629.

approved for all-comers, and they are not genomically specified.

IDH1 is mutated in approximately 6% to 10% of patients with AML, whereas *IDH2* is mutated in approximately 15% to 20% of patients. Ivosidenib is an *IDH1* inhibitor approved for use in both the newly diagnosed setting (for those aged ≥75 years or who have comorbidities that preclude the use of intensive induction chemotherapy) and in the R/R setting.¹⁴ Enasidenib is FDA-approved for use in R/R disease, but because data support its use in newly diagnosed *IDH2*-mutated AML, it is often used off-label in this setting as well (ClinicalTrials.gov identifier: NCT03013998).

“However, there is the question of whether *IDH* inhibitors are better choices for *IDH*-mutated disease than venetoclax/hypomethylating agents, as patients treated with venetoclax + hypomethylating agents can

have high complete remission rates,” noted Dr. Mims. “New data are also forthcoming with the addition of hypomethylating agents in combination with *IDH* inhibitors and *IDH* inhibitors in combination with venetoclax, so the standard of care may change rapidly for this specific genomic subgroup of patients.”

Dr. Mims outlined the current risk stratification of patients with AML, based on cytogenetic and molecular features in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for AML. Typically, patients with favorable-risk disease who achieve a complete remission with 7 + 3 therapy will go on to receive high-dose cytarabine consolidation as potentially curative-intent therapy. Those with poor- or adverse-risk disease are counseled to proceed to transplant in their first complete remission if they are candidates, because this offers

Table 2. Targetable Mutations Influencing Current Practice

Target	Incidence	Comments
NPM1	25%–30%	Favorable with absence of FLT3-ITD or FLT3-ITD ^{low}
FLT3-ITD/TKD	25%–30%	7+3 + midostaurin
Double CEBPA	10%	Favorable
c-KIT	6%	Presence changes favorable t(8;21) to intermediate risk
IDH2	10%–15%	Enasidenib for R/R AML
IDH1	7%–10%	Ivosidenib for newly diagnosed or R/R AML
TP53	10%–15%	Unfavorable

Abbreviations: AML, acute myeloid leukemia; R/R, relapsed/refractory.

Data from Refs.^{16,17}

the best chance of cure.¹⁵ Older intermediate-risk patients should also be offered transplant on first remission, if they are candidates. “But for younger intermediate-risk candidates, I will say it is more of a discussion,” she noted. “However, these risk categories were initially based on 7 + 3 induction therapy and outcomes, so they will continue to evolve as longer outcome data from the new therapeutics come to light.”

According to Dr. Mims, the guidelines will be updated as the field better incorporates measurable residual disease data into outcomes data, because depth of response may help lead to better predictability in regard to long-term outcomes. She also discussed the mutations that currently influence day-to-day practice for the treatment of AML (Table 2).^{16,17}

Future Directions

Regarding future directions for treatment of patients with newly diagnosed AML, the “current wave” is made up of

combination regimens: adding additional therapy to intensive induction backbones such as IDH inhibitors, newer-generation FLT3 inhibitors, venetoclax, menin inhibitors, and CD47 antibodies, to name a few.

The assessment of triplet therapies with hypomethylating agents and venetoclax backbones are also underway. “With the newer oral hypomethylating agent formulations, trials assessing all-oral regimens will hopefully have similar efficacy with better quality-of-life components,” Dr. Mims said. “Finally, we are currently working on understanding and improving outcomes as we learn more about measurable residual disease in AML.”

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References

- Carter JL, Hege K, Yang J, et al. Targeting multiple signaling pathways: the new approach to acute myeloid leukemia therapy. *Signal Transduct Target Ther* 2020;5:288.
- Bross PF, Beitz J, Chen G, et al. Approval summary: gemtuzumab ozogamicin in relapsed acute myeloid leukemia. *Clin Cancer Res* 2001;7:1490–1496.
- Castaigne S, Pautas C, Terre C, et al. Effect of gemtuzumab ozogamicin on survival of adult patients with de-novo acute myeloid leukaemia (ALFA-0701): a randomised, open-label, phase 3 study. *Lancet* 2012;379:1508–1516.
- Burnett AK, Russell NH, Hills RK, et al. A comparison of clofarabine with ara-C, each in combination with daunorubicin as induction treatment in older patients with acute myeloid leukaemia. *Leukemia* 2017;31:310–317.
- Amadori S, Suci S, Stasi R, et al. Sequential combination of gemtuzumab ozogamicin and standard chemotherapy in older patients with newly diagnosed acute myeloid leukemia: results of a randomized phase III trial by the EORTC and GIMEMA consortium (AML-17). *J Clin Oncol* 2013;31:4424–4430.
- Hills RK, Castaigne S, Appelbaum FR, et al. Addition of gemtuzumab ozogamicin to induction chemotherapy in adult patients with acute myeloid leukaemia: a meta-analysis of individual patient data from randomised controlled trials. *Lancet Oncol* 2014;15:986–996.
- US Food and Drug Administration. FDA approves gemtuzumab ozogamicin for CD33-positive AML. Accessed September 23, 2021. Available at <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-gemtuzumab-ozogamicin-cd33-positive-aml>
- Stone RM, Mandrekar SJ, Sanford BL, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. *N Engl J Med* 2017;377:454–464.
- Lancet JE, Uy GL, Cortes JE, et al. CPX-351 (cytarabine and daunorubicin) liposome for injection versus conventional cytarabine plus daunorubicin in older patients with newly diagnosed secondary acute myeloid leukemia. *J Clin Oncol* 2018;36:2684–2692.
- DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. *N Engl J Med* 2020;383:617–629.
- Venugopal S, Shoukier M, Konopleva M, et al. Outcomes in patients with newly diagnosed TP53-mutated acute myeloid leukemia with or without venetoclax-based therapy. *Cancer* 2021;127:3541–3551.
- Wei AH, Montesinos P, Ivanov V, et al. Venetoclax plus LDAC for newly diagnosed AML ineligible for intensive chemotherapy: a phase 3 randomized placebo-controlled trial. *Blood* 2020;135:2137–2145.
- Cortes JE, Heidel FH, Hellmann A, et al. Randomized comparison of low dose cytarabine with or without glasdegib in patients with newly diagnosed acute myeloid leukemia or high-risk myelodysplastic syndrome. *Leukemia* 2019;33:379–389.
- Roboz GJ, DiNardo CD, Stein EM, et al. Ivosidenib induces deep durable remissions in patients with newly diagnosed IDH1-mutant acute myeloid leukemia. *Blood* 2020;135:463–471.
- Tallman MS, Pollyea DA, Altman JK, et al. NCCN Clinical Practice Guidelines in Oncology: Acute Myeloid Leukemia. Version 3. 2021. Accessed October 6, 2021. To view the most recent version, visit NCCN.org
- Papaemmanuil E, Gerstung M, Bullinger L, et al. Genomic classification and prognosis in acute myeloid leukemia. *N Engl J Med* 2016;374:2209–2221.
- Eisfeld AK, Mrózek K, Kohlschmidt J, et al. The mutational oncoprint of recurrent cytogenetic abnormalities in adult patients with de novo acute myeloid leukemia. *Leukemia* 2017;31:2211–2218.