



# Management of Chemotherapy-Ineligible Acute Myeloid Leukemia: Beyond Hypomethylating Agent Monotherapy



**Expert Interview With**  
Eytan M. Stein, MD

Stein, director of Drug Development in Leukemia at Memorial Sloan Kettering Cancer Center in New York, New York, provided insights and best practices for chemotherapy-ineligible patients, diagnosed with acute myeloid leukemia, practical considerations for venetoclax and hypomethylating agent therapy, and promising future therapeutic approaches.



To see the full video with Stein, scan the QR code.

## KEY TAKEAWAYS

- In patients with newly diagnosed acute myeloid leukemia (AML), treatment with venetoclax monotherapy or in combination with hypomethylating agents (HMAs) is associated with response rates of approximately 70% to 80%—this treatment approach provides a vast improvement in response rates over HMA alone.
- Small molecule inhibitors for the treatment of relapsed or refractory AML with specific genetic mutations have improved outcomes over traditional chemotherapy.
- Venetoclax plus an HMA is a novel standard of care for newly diagnosed elderly AML patients who are not candidates for intensive induction chemotherapy.
- There are 2 important considerations when selecting therapy: the patient's ability to tolerate the therapy (fitness) and the likelihood that the disease will respond to the treatment (based on cytogenetic and molecular profiles).
- Cytopenias from HMAs plus venetoclax can be mitigated with scheduling strategies.

**A**lthough the standard treatment for acute myeloid leukemia (AML) involves intensive induction chemotherapy, many diagnosed patients are ineligible because of advanced age and preexisting comorbidities.<sup>1</sup> Lower-intensity regimens, such as monotherapy with a hypomethylating agent (HMA) or low-dose cytarabine, were traditionally given to patients who were ineligible for chemotherapy; however, HMAs are associated with low rates of remission and

short overall survival.<sup>1</sup> In an interview with CancerNetwork®, Eytan M. Stein, MD, director of Drug Development in Leukemia at Memorial Sloan Kettering Cancer Center, New York, New York, discussed recent advances in standard of care for patients diagnosed with first-line chemotherapy-ineligible AML, data on combination therapy with venetoclax plus an HMA, predictive and prognostic factors of outcomes in AML, practical considerations for venetoclax and

HMA therapy, and promising future therapeutic approaches.

According to Stein, the majority of patients with a diagnosis of AML who are ineligible for chemotherapy traditionally received supportive care alone, which led to an overall survival of approximately 3 to 6 months. Use of HMAs such as 5-azacitadine and decitabine increased starting in 2009, but the low rates of remission (approximately 20%) and long time to response (4-6 cycles) are major limitations, according to Stein.

“The longer a patient is not in remission, the longer they have to get an infection, which might cause severe morbidity or mortality,” said Stein. “Or [they may] have a bleeding event from thrombocytopenia that could lead also to morbidity and mortality,” said Stein.

Stein noted that small molecule inhibitors, such as venetoclax, are being used as monotherapy or in combination with HMAs in chemotherapy-ineligible patients with promising efficacy: “The use of venetoclax in combination with HMAs ... has really revolutionized how we treat newly diagnosed patients who are ineligible to receive intensive induction chemotherapy.”

Single-agent therapies approved for relapsed or refractory AML, including gilteritinib (for patients with *FLT3* mutations), ivosidenib (for patients with *IDH1* mutations), and enasidenib (for patients with *IDH2* mutations), have also changed treatment for relapsed and refractory AML harboring specific genetic mutations, according to Stein. Although Stein noted that currently available immunotherapeutic approaches, such as checkpoint inhibitors, chimeric antigen receptor T cell therapy, and bispecific T cell-engaging antibodies, have been largely unsuccessful for AML, he said that the anti-CD47 monoclonal antibody magrolimab combined with azacitidine has shown promise in clinical trials of AML. “This drug reactivates macrophages,” said Stein. “It allows macrophages to recognize myeloid

“The longer a patient is not in remission, the longer they have to get an infection, which might cause severe morbidity or mortality.”

leukemia blasts and then phagocytose those myeloid leukemia blasts.”

Stein added that another promising approach lies in the development of new, bispecific, T cell-engaging antibodies that transport the myeloid blasts close to T cells, which eradicate the blasts. Flo-tetuzumab, a bispecific, antibody-based molecule that targets CD3ε and CD123 in a dual-affinity retargeting antibody format, led to complete remissions (with full or partial hematologic recovery) in 18% of patients with AML who had primary induction failure or relapse within 6 months and received the recommended phase 2 dose.<sup>2</sup>

Stein also pointed out the importance of selecting clinically relevant and expedient end points in clinical trials for AML. He noted that because many of the ongoing trials stratify patients by cytogenetic and molecular genetic subgroups, the number of patients available for analysis is small in a clinical trial with end points such as overall survival or event-free survival. “To wait for a time-to-event end point can take many, many years, and those are years too many for the patients who are actually suffering from these diseases,” he said.

Therefore, minimal residual disease (MRD) of less than 0.01% in the marrow has been accepted by the FDA as an outcome measure that supports evidence of efficacy for new drugs that have shown a durable complete response in relapsed or refractory AML.<sup>3</sup> “Specifically, the eradication of MRD might be able to serve as a surrogate for clinical benefit for patients who get therapies for their [AML],” said Stein.

### First-Line Therapy for Chemotherapy-Ineligible Patients

Stein noted that several drugs are approved for patients with a diagnosis of AML who are ineligible for chemotherapy. Glasdegib, a Hedgehog pathway inhibitor, combined with low-dose cytarabine was approved for treatment of newly diagnosed AML in patients aged 75 years and older or patients with comorbidities that make them ineligible for intensive induction chemotherapy.<sup>4</sup> This approval was based on findings from a multicenter, open-label, randomized, phase 2 study (NCT01546038) that showed an improvement in median overall survival with glasdegib plus low-dose cytarabine compared with low-dose cytarabine alone in patients diagnosed with AML (8.3 months vs 4.3 months; HR, 0.46;  $P = .0002$ ).<sup>5</sup> However, Stein said that he does not use glasdegib often, in part because of the adverse events (AEs) associated with the drug (glasdegib with low-dose cytarabine led to temporary and permanent discontinuation in 56.0% and 10.7% of patients, respectively, in the experimental arm of the phase 2 trial).<sup>5</sup>

According to Stein, venetoclax combined with an HMA has become the standard of care for frontline therapy of most elderly patients who are ineligible for intensive induction chemotherapy. The phase 3 VIALE-A trial (NCT02993523) showed that venetoclax-azacitidine therapy significantly improved overall survival over placebo-azacitidine (14.7 months vs 9.6 months; HR for death, 0.66; 95% CI, 0.52-0.85;  $P < .001$ ).<sup>1</sup> Additionally, composite complete

remission occurred in 66.4% of the venetoclax-azacitidine group (vs 28.3% of the placebo-azacitidine group;  $P < .001$ ) and occurred before the initiation of cycle 2 in 43.4% and 7.6% of the venetoclax and placebo groups, respectively.<sup>1</sup> The addition of venetoclax to azacitidine also led to higher rates of complete remission (with or without hematologic recovery) in patients with *IDH1* mutations (59% vs 9% with azacitidine-placebo), *IDH2* mutations (75% vs 7%, respectively), *FLT3* mutations (65% vs 18%, respectively), and *FLT3* internal tandem duplications (61% vs 23%, respectively) in analyses of pooled data from a phase 3 study (NCT02993523) and a prior phase 1b study (NCT02203773).<sup>6,7</sup> Furthermore, an analysis of participants in the VIALE-A trial showed that among patients who achieved composite complete remission and MRD less than  $10^{-3}$ , the estimated 12-month duration of response, overall survival, and event-free survival were 81.2%, 94.0%, and 83.2%, respectively.<sup>8</sup>

“For the vast majority of my patients, I am giving them a hypomethylating agent and venetoclax as their initial therapeutic approach,” said Stein. However, he noted that some patients who are extremely frail may not be able to tolerate venetoclax with an HMA because of the cytopenias associated with the regimen. In the VIALE-A trial, the most commonly

reported hematologic AEs of grade 3 or higher in the venetoclax and placebo groups included thrombocytopenia (45% and 38%, respectively), neutropenia (42% and 28%, respectively), febrile neutropenia (42% and 19%, respectively), anemia (26% and 20%, respectively), and leukopenia (21% and 12%, respectively).<sup>1</sup> “It’s not so easy to get that [older] patient back to where they were before they developed the neutropenic fever,” said Stein.

For these patients (particularly those with *IDH1* or *IDH2* mutations) who have comorbidities that may increase risk for cytopenias, Stein considers targeted IDH inhibitors. Ivosidenib, an *IDH1* inhibitor, is approved by the FDA for newly diagnosed AML harboring an *IDH1* mutation in patients who are aged 75 years or older or who have comorbidities that make them ineligible for intensive induction chemotherapy.<sup>9</sup> Whereas the *IDH2* inhibitor enasidenib is not approved by the FDA for AML, the National Comprehensive Cancer Network (NCCN) guidelines list it as an option for newly diagnosed patients harboring an *IDH2* mutation who are ineligible for intensive chemotherapy.<sup>10</sup>

“If they’re older than 88 years or they have some particular comorbidity that makes me nervous about cytopenias and they have an *IDH* mutation, I might give them a single-agent IDH inhibitor,” said Stein.

## Predictive and Prognostic Factors

Stein said that knowing the fitness of the patient for treatment and the ability of the patient’s disease to respond to therapy are the most important assessments when seeing a new patient diagnosed with AML. According to Stein, evaluating the patient’s fitness for treatment is relatively straightforward and involves assessing medical history and mobility in the office. However, he emphasized that telemedicine, which has been used increasingly during the COVID-19 pandemic, is not ideal for the initial assessment of a patient with AML. “I’m unable to get a good sense of a patient’s performance status when I’m looking at them on a video screen,” he said. “I think you really need to see that patient in the office before you can decide their level of fitness and their performance status.”

Stein added that predicting the ability of the disease to respond to treatment involves a careful evaluation of the molecular and cytogenetic profile, which can be prognostic and predictive. “They’re prognostic because, [with] certain cytogenetic and molecular genetic abnormalities, you don’t expect the patient to respond very well to anything... or to various therapies. Certain molecular genetic aberrations, [however], can be predictive of response to certain targeted agents.”

Stein added that sending the molecular and cytogenetic information on the bone marrow biopsy at the time of diagnosis and at the time of relapse is important to optimize therapy for the patient. Although identifying actionable mutations is useful, Stein said that getting a broad profile of the molecular genetics from commercial panels that perform mutational analyses of myeloid malignancies gives a general idea about the expected response to initial therapy.

## Practical Considerations for Therapy With Venetoclax and Hypomethylating Agents

Stein noted that according to the NCCN guidelines, HMAs with venetoclax have the



**“Maybe, in the future, we will be able to combine oral decitabine with oral venetoclax, which will make the lives of our patients much easier. You want to be sure before you start giving oral combinations that you’re not going to get some drug-drug interaction that’s going to limit the efficacy or increase the toxicity of either of the drugs.”**

highest category recommendation for newly diagnosed patients older than 60 years who are unfit for intensive chemotherapy. Stein noted that he generally uses azacitidine as his HMA of choice, because it was used in the VIALE-A trial.<sup>10</sup> However, he noted that decitabine, which involves 5 consecutive days of infusions, may be a more convenient option for treatment at facilities that are unable to provide infusions for the 7 consecutive days needed for azacitidine therapy. Stein added that an oral formulation of decitabine is available and could be a more convenient infusion-free option in the future, but he does not currently use it with venetoclax because of lack of data supporting efficacy and safety.

“Maybe, in the future, we will be able to combine oral decitabine with oral venetoclax, which will make the lives of our patients much easier,” said Stein. “You want to be sure before you start giving oral combinations that you’re not going to get some drug-drug interaction that’s going to limit the efficacy or increase the toxicity of either of the drugs.”

Because myelosuppression is a major concern with venetoclax plus HMAs, Stein said that giving the therapeutic cycles on a fixed 28-day schedule is generally not recommended, because it could lead to chronic neutropenia and adverse outcomes. Instead, he gives the first cycle of therapy without dose reductions or interruptions (unless the patient becomes

seriously ill) and performs a bone marrow biopsy on day 28. He does not start the second cycle until the blasts have cleared from the bone marrow and the blood counts have recovered. For patients who are in a complete remission or who have blood counts that take a long time to recover, Stein decreases the duration of venetoclax from 28 days to 21 days during cycle 2. “If they continue to have myelosuppression after cycle 2 of therapy, then I decrease it from 21 days to 14 days and even down to 7 days, sometimes,” he said. “I, generally speaking, do not change treatment regimens, especially if the treatment is working. I just try to modify doses, so I can continue giving the patient the [HMA] and venetoclax.”

### Promising Future Therapeutic Approaches

Stein said that there is “a wealth of riches” in terms of clinical studies and approaches for newly diagnosed patients with AML. Some of the promising approaches include combining venetoclax with fludarabine and cytarabine, IDH1 and IDH2 inhibitors with intensive induction chemotherapy in the first-line setting, magrolimab with HMAs, and venetoclax with gilteritinib. Some of the promising approaches include venetoclax in combination with other agents, such as fludarabine and cytarabine, gilteritinib, and IDH1 and IDH2 inhibitors plus intensive induction

chemotherapy in the first-line setting. Other combinations being explored are magrolimab with HMAs as well as entospletinib, an oral selective inhibitor of spleen tyrosine kinase, with chemotherapy in *NMP1*-mutant AML.

“There are a variety of different approaches that I think are going to end up being successful,” said Stein. “It’s important to enroll these patients in clinical trials so we can really understand what the best outcomes are.” ■

### REFERENCES

1. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. *N Engl J Med*. 2020;383(7):617-629. doi:10.1056/NEJMoa2012971
2. Uy GL, Aldoss I, Foster MC, et al. Flotetuzumab as salvage immunotherapy for refractory acute myeloid leukemia. *Blood*. 2021;137(6):751-762. doi:10.1182/blood.2020007732
3. Acute myeloid leukemia: developing drugs and biological products for treatment: guidance for industry. FDA. August 2020. Accessed July 25, 2021. <https://www.fda.gov/media/140821/download>
4. FDA approves glasdegib for AML in adults age 75 or older or who have comorbidities. FDA. Updated December 14, 2018. Accessed July 25, 2021. <https://www.fda.gov/drugs/fda-approves-glasdegib-aml-adults-age-75-or-older-or-who-have-comorbidities>
5. 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(2):379-389. doi:10.1038/s41375-018-0312-9
6. Pollyea DA, DiNardo CD, Arellano ML, et al. Results of venetoclax and azacitidine combination in chemotherapy ineligible untreated patients with acute myeloid leukemia with IDH1/2 mutations. *Blood*. 2020;136(suppl 1):5-7. doi:10.1182/blood-2020-134736
7. Konopleva M, Thirman M, Pratz KW, et al. Results of venetoclax and azacitidine combination in chemotherapy ineligible untreated patients with acute myeloid leukemia with FLT3 mutations. *Blood*. 2020;136(suppl 1):8-10. doi:10.1182/blood-2020-134100
8. Pratz K, Jonas BA, Pullarkat V, et al. Measurable residual disease response in acute myeloid leukemia treated with venetoclax and azacitidine. *J Clin Oncol*. 2021;39(suppl 15):7018. doi:10.1200/JCO.2021.39.15\_suppl.7018
9. FDA approves ivosidenib as first-line treatment for AML with IDH1 mutation. FDA. Updated May 3, 2019. Accessed July 26, 2021. <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-ivosidenib-first-line-treatment-aml-idh1-mutation>
10. National Comprehensive Care Network. Clinical Practice Guidelines in Oncology. Acute myeloid leukemia. V.3.2021. Updated March 2, 2021. Accessed July 25, 2021. [https://www.nccn.org/professionals/physician\\_gls/pdf/aml.pdf](https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf)

EDITOR'S NOTE: Interview quotes slightly modified for readability.