ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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Hypomethylating Agents and Venetoclax in Acute Myeloid Leukemia

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H&O What are the outcomes associated with hypomethylating agents in acute myeloid leukemia (AML)?

CD Decitabine and azacytidine, the hypomethylating agents typically used in this setting, are associated with composite remission rates between 25% and 30%, and a median overall survival of approximately 10 months or less. For decades, single-agent hypomethylating agents have been the standard of care for older patients who are not candidates for intensive chemotherapy.

H&O What are the outcomes of single-agent venetoclax in AML?

CD Single-agent venetoclax was evaluated in the setting of relapsed AML. Venetoclax in this setting was not particularly effective, with an overall response rate of less than 25% and very short-lived responses. There was, however, a signal that outcome was improved among patients with isocitrate dehydrogenase mutations.

H&O How might venetoclax work with hypomethylating agents?

CD Venetoclax is a BCL-2 inhibitor. BCL-2 is overexpressed in many different types of cancers, particularly leukemias. Overexpression of BCL-2 turns off the machinery that leads to normal cell death (ie, it is utilized by cancer cells to avoid apoptosis). Venetoclax effectively synergizes with various therapies, including hypomethylating agents, to inhibit this pathway and allow sensitive cells with high BCL-2 expression to then undergo normal cell death.

H&O What did early clinical studies of venetoclax and hypomethylating agents in AML show?

CD The earliest clinical trials of the combination had dramatic results. Blast reductions within the first month of treatment were reported in nearly all patients. Remissions were reported in most patients, with most occurring even within the first cycle. These data raised much excitement throughout the community. From the beginning, the phase 1 studies of these combinations were showing positive results. The composite remission rates were more than double those expected with a hypomethylating agent alone. Responses occurred more quickly, and appeared to be more durable.

H&O Could you please discuss your study of azacytidine and venetoclax in previously untreated AML?

CD The phase 3 VIALE-A trial aimed to confirm whether the combination of azacytidine and venetoclax was as impressive as the initial clinical trials suggested.

The trial randomly assigned more than 400 patients from around the world to treatment with azacytidine alone or azacytidine with venetoclax. The patients were ineligible for standard induction therapy because of coexisting conditions or because they were ages 75 years or older. The goal was to show that the combination not only improved remission rates, but also that patients were living longer and doing better. The VIALE-A trial met this goal. Treatment with azacytidine plus venetoclax led to a composite remission rate of approximately 66%, which is more than double that expected and what was seen with azacytidine alone. The responses occurred quickly and lasted for over a year. The combination also improved survival, which was the primary endpoint of the trial. At a median follow-up of 20.5 months, the median overall survival was 14.7 months with azacitidine plus venetoclax vs 9.6 months with azacitidine plus placebo (hazard ratio for death, 0.66; 95% CI, 0.52-0.85; *P*<.001). The study therefore did confirm that the combination of azacytidine plus venetoclax can be considered a new standard of care in AML.

H&O Were the adverse events as expected with each agent?

CD They were. Infections of any grade were reported in 85% of patients treated with venetoclax plus azacitidine vs 67% of those who received azacitidine alone. Any-grade nausea occurred in 44% vs 35%, respectively. Among adverse events of grade 3 or higher, thrombocytopenia was reported in 45% vs 38%, neutropenia in 42% vs 28%, and febrile neutropenia in 42% vs 19%.

There are 2 main adverse events associated with azacytidine and venetoclax. There is a risk of tumor lysis, which can be addressed with mitigation procedures as outlined in guidelines. A patient's white cell count should be below 25,000/mm^3 when therapy begins. Daily laboratory work is needed throughout the first week, as the dose of venetoclax is ramped up, to check that the treatment is well-tolerated. Adherence to these management guidelines will practically eliminate the risk for tumor lysis, as cases typically manifest as abnormal chemical laboratory values that can be easily managed in real time.

The other main adverse event is cytopenias, in particular, neutropenia and neutropenic fever. The combination of azacytidine and venetoclax effectively clears leukemia from the bone marrow. During the first or second cycles, the bone marrow can become ablated, meaning the leukemia is cleared but the healthy bone marrow and blood cell count has not fully recovered. In this scenario, it is important to stop treatment with venetoclax for 1 or 2 weeks to allow the blood cell counts and bone marrow to recover before the next cycle is started. Clinicians must monitor for cytopenias, but these events can be effectively managed.

H&O Are there particular types of patients who are better candidates for venetoclax and a hypomethylating agent?

CD The combination of azacytidine and venetoclax is currently approved for patients who were ineligible for intensive chemotherapy. The trial enrolled patients ages 75 years or older, or who had underlying medical comorbidities or a poor performance status suggesting they would not tolerate intensive chemotherapy well. Clinicians in the leukemia community are now trying to determine whether the combination might be suitable for other patient populations.

H&O Is decitabine also used with venetoclax?

CD It should be noted that decitabine in combination with venetoclax is also an approved regimen. Data from the initial phase 1/2 study suggested that decitabine is as effective as azacitidine in combination with venetoclax. I have no particular preference in terms of which "hypomethylating-agent backbone" should be used in combination with venetoclax.

Disclosure

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Suggested Readings

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