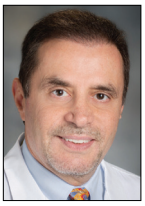
ADVANCES IN LLM

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

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Lessons and Limitations of the PARADIGM Trial in Acute Myeloid Leukemia



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H&O The combination of a hypomethylating agent (HMA) and venetoclax (Venclexta, AbbVie) is approved as frontline therapy for older, unfit patients with acute myeloid leukemia (AML). What are the most relevant studies to look at the use of HMA/venetoclax for younger, fit patients with AML?

HK Multiple studies have looked at whether lower-intensity therapy could replace intensive chemotherapy for people with AML who are younger and fit. A meta-analysis that included more than 3800 patients with newly diagnosed AML from 15 retrospective cohort studies compared the use of HMA/venetoclax vs intensive chemotherapy, defined as 3 days of an anthracycline plus 7 days of cytarabine (3 + 7).[1] The meta-analysis suggested that overall survival (OS) was better with the HMA/venetoclax regimen than with intensive chemotherapy, especially in patients with the *NPM1* mutation. Results of the 2 regimens were similar for complete response (CR), CR or CR with incomplete blood cell count recovery, overall response rate, and 30-day mortality.

Following that publication, we saw the results of a randomized phase 2 study from China that compared lower-intensity therapy vs intensive chemotherapy as induction in untreated young, fit patients with AML.[2] Patients aged 18 to 59 years who were eligible for intensive chemotherapy were randomized in a 1:1 ratio to receive decitabine plus venetoclax or intensive chemotherapy with idarubicin plus cytarabine. All patients received intensive chemotherapy and allogeneic transplant after induction, so the randomization applied only to the induction phase. The researchers reported that results of the 2 strategies were similar, with a 1-year OS rate of approximately 63%.

H&O Could you describe the design and results of the PARADIGM trial?

HK The open-label phase 2 PARADIGM trial was designed to compare lower-intensity therapy with intensive chemotherapy in fit adults with newly diagnosed AML. A total of 172 patients with a median age of 64 years were randomized in a 1:1 ratio to the HMA azacitidine plus venetoclax or to conventional chemotherapy, which consisted of either 3 + 7 or liposomal daunorubicin plus cytarabine (CPX351; Vyxeos, Jazz Pharmaceuticals).[3] Patients were excluded if they were younger than 60 years and had core binding factor fusions, *FLT3* mutations, or *NPM1* mutations, all of which would affect the choice of treatment unless the patient was older. For example, patients who have *FLT3* mutations should receive an FLT3 inhibitor if they are eligible.

The researchers found that the overall response rate was significantly higher with azacitidine/venetoclax than with intensive chemotherapy (88% vs 62%). The rate of combined CR, hematologic CR, and CR with incomplete blood cell count recovery also was higher with azacitidine/venetoclax than with intensive chemotherapy (81% vs 55%). In addition, more people in the azacitidine/venetoclax group were able to proceed to transplant (61% vs

40%), and the 1-year event-free survival (EFS) rate was significantly better in that group than in the intensive chemotherapy group (53% vs 39%).

> The unfortunate consequence of PARADIGM is that oncologists in community practices all around the world will think that HMA/venetoclax is a good standard of care for all patients.

H&O What would you say are the lessons and limitations of the PARADIGM trial?

HK One of the things I like about this study is that it enrolled patients of all ages. I would also like to congratulate the investigators for designing, conducting, and completing a randomized trial without pharmaceutical company support. No drug company stands to benefit when physicians choose azacitidine/venetoclax over 3 + 7 or CPX351; these are all inexpensive agents approved by the US Food and Drug Administration (FDA). The key to completing this study was choosing EFS as the endpoint, which was wise because using OS would have produced a null result.

I also found the study valuable for showing that at 3 years, the OS rate was less than 50% and the EFS rate was in the range of 20% to 30% in both arms. These are not good results. Oncologists are entrenched in their belief that 3 + 7 is a good standard of care for younger, fit patients and that HMA/venetoclax is a good standard of care for older, unfit patients, when they are both in fact bad standards of care. This study disabuses us of the notion that either approach is excellent.

The study also had several limitations. First, I would like to draw attention to the fact that 40% of the patients in the 3 + 7 group were taken off that treatment after just one course of therapy, and in most cases they were switched to azacitidine/venetoclax. This is contrary to the way in which 3 + 7 is typically practiced. The standard of care in community practice for patients who do not respond to 3 + 7 is to receive a second induction or consolidation therapy with 2 + 5. I think that this decision made azacitidine/venetoclax seem better than it really is because it was mostly comparing a single course of intensive chemotherapy with 4 courses of HMA/venetoclax.

Another limitation of the study is that 3 + 7 is no longer considered the gold standard of care. In this era, it makes more sense to compare azacitidine/venetoclax with a better regimen, such as cladribine plus low-dose cytarabine and venetoclax (CLADILLAC). This regimen is an example of a triple-nucleoside regimen plus venetoclax. In the younger patients who are fit for intensive chemotherapy, we can now start conducting studies with better regimens: cladribine, idarubicin, and cytarabine (CLIA) plus venetoclax (CLIA-VEN) or fludarabine, cytarabine, filgrastim, and idarubicin plus venetoclax (FLAG-IDA-VEN). Younger patients are also candidates for CLADILLAC. Older patients are eligible for triplet regimens with an HMA plus venetoclax.

H&O What are your concerns related to the interpretation of PARADIGM?

HK The unfortunate consequence of PARADIGM is that oncologists in community practices all around the world will think that HMA/venetoclax is a good standard of care for all patients, regardless of their age, cytogenetics, and mutations. These are patients who might benefit much more from an intensive chemotherapy regimen.

In our phase 2 data from MD Anderson on CLIA-VEN in younger patients, the bone marrow CR rate was 94% and the 5-year survival rate was 70%.[4] As for older patients, our phase 2 data on 190 patients show that alternating the CLADILLAC regimen with azacitidine/venetoclax produced a bone marrow CR rate of 94% and a 3-year OS rate of 60%.[5] These results are in contrast to a 3-year OS rate of 25% in older patients receiving an HMA plus venetoclax and a 3-year survival rate of less than 50% in PARADIGM.

H&O What further studies would you like to see conducted?

HK I would like to see randomized trials that compare CLIA-VEN with 3 + 7 or HMA/venetoclax in younger patients, and randomized trials that compare the CLADILLAC regimen with HMA/venetoclax in older patients.

H&O What are your recommendations in the meantime for the various types of patients?

HK For younger patients, I recommend using CLIA-VEN or FLAG-IDA-VEN and avoiding 3 + 7 and

HMA/venetoclax. For older patients, my classification is very simple: younger than 60 vs age 60 and older. Why is age the best cutoff? On the basis of the Surveillance, Epidemiology, and End Results (SEER) Program data on 37,000 patients with AML presented at the most recent American Society of Hematology Annual Meeting and Exposition, overall mortality in the first months with intensive chemotherapy is 30% in patients aged 60 to 75 years and 15% in younger patients.[6] Given that mortality doubles when patients are aged 60 and older, age is what is relevant—not whether the patient is fit or unfit. For older patients, we always use CLADILLAC. As a leukemia center of excellence that has a lot of expertise and provides extensive supportive care, we have been able to reduce the induction mortality rate to 2% in both younger and older patients.

Disclosures

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