How are the drugs approved for AML in 2017 changing the therapeutic landscape?

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Welcome to *Managing AML*, I am Dr. Naval Daver. Today I will be talking about four new therapies that have been approved for acute myeloid leukemia in 2017, and how these are changing the management and therapeutic landscape of AML very rapidly. In 2017, there were four drugs approved for AML. The first of these was a FLT3 inhibitor called midostaurin. The approval of this agent was based on a large phase 3 multicenter, multinational randomized trial. The primary endpoint of the study was overall survival, and patients were randomized to receive either standard induction of 3+7 or 3+7 induction in combination with the FLT3 inhibitor midostaurin given from day 8 through 21 of induction, consolidation, as well as maintenance. The study reached its primary endpoint with improved median overall survival with the addition of midostaurin to 3+7 induction. The results were published in the *New England Journal of Medicine* earlier last year and this led to the approval of the agent. Importantly, this will impact clinical practice as this study now requires that we check the FLT3 mutation at baseline for all newly diagnosed acute myeloid leukemia patients who are below 65 years of age. If they do have a FLT3 mutation, whether it is a FLT3-ITD or a FLT3-D835 mutation, we recommend the addition of midostaurin on day 8 through 21 of induction and subsequent consolidations followed by maintenance with midostaurin for one year. This is now no longer research but is a standard clinical practice in FLT3 mutated. The second important note is that sometimes it may take 8 to 10 to 14 days to get the results back for the mutational testing. In that case, it is okay to go ahead and start the induction, especially if you have a patient with proliferative acute myeloid leukemia, and to add the midostaurin whenever it is available, so this may be on day 10 or 12 or 14. The addition of the FLT3 inhibitor is more important than the timing of starting the FLT3 inhibitor, so we recommend using it later after the mutational analysis, and still trying to get the benefit.

The second drug that was approved was an IDH2 inhibitor called enasidenib. The IDH2 mutation is less common than the FLT3 and is seen in about 8% to 10% of all acute myeloid leukemia cases. The study that led to the approval of the IDH inhibitor was an expanded phase 2 study in relapsed/refractory acute myeloid leukemia with about 200 patients. The patients in the study received the IDH inhibitor and the overall response rate that included CR/CRi partial responses was about 40%. Interestingly, the median overall survival in a salvage population, which included patients from salvage 1 through salvage 8, was 10 months, which is quite encouraging in such a relapsed acute myeloid leukemia population. Based on this data, the FDA approved the agent to be used in relapsed/refractory acute myeloid leukemia patients who had an IDH mutation. One of the things to note with this drug is that it may result in a differentiation

syndrome similar to what we had seen with ATRA and arsenic in patients with acute promyelocytic leukemia. The differentiation syndrome may present within one to two months of starting treatment, and usually these patients will come in with shortness of breath, skin rash, frequently with leukocytosis. The differentiation syndrome is managed by treatment with steroids, and we often are able to continue the IDH inhibitor in patients who have the differentiation syndrome.

A third drug that was approved was an agent called CPX-351. This was approved based on a phase 3 study that randomized the CPX-351 to standard 3+7 induction in elderly patients over the age of 60 who had secondary AML. Secondary AML was defined as patients who have AML that arises from chemotherapy or radiation or a prior tumor such as lung, colon, breast, or ovarian cancer, or patients who have AML with background MDS-MPN changes. In this phase 3 study, the CPX-351 significantly improved both the response rate and overall survival over 3+7. Based on this, it should be considered standard induction for patients with secondary AML. Again, the change in practice that is going to come about because of the approval of CPX-351 is to look at your patients and get a good history, try to figure out if it is a secondary AML, and the patient did have a prior malignancy treated with chemoradiation, or if they have MDS or MPN-like changes in the background, and if they do, then I would favor using a CPX-351-based induction over 3+7-based induction followed by transplant. In most cases, we do know that patients with secondary AML even with CPX-351 therapy continue to be high-risk and so following up CPX-351 with a stem cell transplant is probably the ideal scenario to try to optimize survival of the patients.

The fourth drug that was approved in 2017 was an immune therapy which was an antibody-drug conjugate targeted toward CD33 on the surface of leukemia cells. The drug is called gemtuzumab ozogamicin, and it is an antibody that targets CD33 and is conjugated to a bacterial toxin, calicheamicin. Gemtuzumab has been evaluated in multiple phase 3 studies in Europe and in five large phase 3 studies done in five European countries. It showed that the gemtuzumab was able to significantly improve overall survival, especially in patients with favorable cytogenetics such as inversion 16 or 8;21, as well as patients with intermediate cytogenetics, without significantly increasing toxicity. Based on these, gemtuzumab is now approved for front-line treatment in combination with 3+7-based induction therapy and is being used in the United States and Europe. There has been a significant shift in the treatment of acute myeloid leukemia based on these four approvals, and this is a very exciting time. A number of new drugs are also entering the arena to look out for.