Are patients who relapse after first-generation FLT3 inhibitors likely to respond to second-generation FLT3 inhibitors?

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Welcome to *Managing AML*. My name is Dr. Nicholas Short and I'm frequently asked, “Are patients who relapse after first-generation FLT3 inhibitors likely to respond to second-generation FLT3 inhibitors, and should these inhibitors be given alone or in combination?”

First of all, when the studies were performed of gilteritinib, which is a second-generation FLT3 inhibitor, most patients had not yet been receiving midostaurin as standard of care in the frontline setting. Most of the data that we have from the ADMIRAL study, which is a randomized study of gilteritinib versus chemotherapy for patients with relapsed FLT3-mutated AML, most of the patients in that study did not have prior FLT3 inhibitor exposure.

That said, we know that treatment with gilteritinib compared to chemotherapy improves response rates and improves overall survival, with a median survival a little over nine months in the gilteritinib arm. There has been a subgroup analysis looking at those patients who did receive midostaurin in that study. It was still shown that those patients had significantly better response rates and median overall survival.

We've also seen in retrospective analyses that now, while the response rate does decline with subsequent lines of FLT3 inhibitors, that you can still get response rates of around 50% when patients are treated with a second-generation inhibitor such as gilteritinib even after prior FLT3 inhibitor exposure, most commonly midostaurin in the frontline setting. Still, we'd give midostaurin for a patient with relapsed/refractory AML, even if they had midostaurin in the frontline setting.

Now, should these agents be given alone or in combination? It's important to note that the FDA approval is for monotherapy of gilteritinib. That was what the randomized phase 3 study was evaluating. However, there's a number of retrospective studies that have evaluated combination therapy versus a FLT3 inhibitor as single agents. What we've seen in these studies is that the combination of a FLT3 inhibitor with either hypomethylating agent or intensive chemotherapy does seem to improve response rates and survival compared to the use of FLT3 inhibitors as a single agent. Many of us in practice do like to combine gilteritinib, for example, with appropriate backbone regimen for the patient, either some intensive chemotherapy backbone or hypomethylating agent.

Those are not, again, standard of care, but we do have a lot of data to support this use. I think it's certainly reasonable to try because we know that these patients need to get to transplant. Combination therapy does lead to higher response rates and therefore should, in theory, lead to more patients being able to be bridged to potentially curative stem cell transplant. Thank you very much for viewing this activity.