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**How should patients with relapsed mutant FLT3 AML be treated?**

Welcome to *Managing AML*. I am Dr. Richard Stone. I am frequently asked, "How should patients with relapsed mutant FLT3 AML be treated?" This is actually a very difficult question because there is no standard of care for such patients. Moreover, now that we have a newly approved drug to be used in the upfront setting for patients with mutant FLT3 AML, the landscape is likely to be changed. The patient's leukemia is likely a little bit different now in that context of patients having received a FLT3 inhibitor in the upfront setting, and perhaps also a stem cell transplant. The most important point here about relapsed mutant FLT3 AML in the relapsed setting is whether it is still mutant FLT3 AML. You have a patient in the upfront setting, you have diagnosed FLT3 AML by a genetic test, they have been treated one way or the other, perhaps with a FLT3 inhibitor nowadays, or maybe they were treated before the FLT3 inhibitor was approved, and now they have relapsed.

There are many questions to ask. The first is, are they still mutant FLT3 positive? We know that patients who are diagnosed with mutant FLT3 AML may relapse without mutant FLT3 AML. The clone may be extinguished and the AML may be driven by other mutations. Secondly, if a patient has mutant FLT3 AML at relapse, they may have not had it at diagnosis. In other words, we have to redo the mutational testing at the time of relapse to see if they picked up a FLT3 mutation if they have not had it, or if they have lost a FLT3 mutation that they did have, because that will influence how you approach the patient.

Right now, there is no standard of care for relapsed AML treatment. One of the most important general features to know about is whether or not they are fit for intensive chemotherapy. That is really the first step because many patients may be older, they may have comorbid disease, they may have a poor performance status, they may be frail, and you would not want to subject them to the difficulty of myelosuppression and mucosal toxicity of a typical relapsed regimen. This regimen would be either high-dose AraC and mitoxantrone, or possibly what is called FLAG-IDA which is fludarabine, idarubicin, and cytarabine, or MEC which is mitoxantrone, AraC, and etoposide. All these regimens are very tough. So, you might say, okay, let's say I do have a relapsed FLT3 AML patient. I have gone through the trouble of reassessing their mutational pattern now. They still have the mutation or they picked it up. Should I give MEC plus midostaurin, should I give MEC plus other FLT3 inhibitors like sorafenib? That is the only other one that is approved now, and that is not approved as a FLT3 inhibitor but rather in renal

cancer as a VEGFR inhibitor. The answer is we do not know, and it is very important to try to enroll such a patient on a clinical trial if possible.

There are two types of clinical trials you can think of. One is chemotherapy plus placebo (or alone) versus chemotherapy plus a novel FLT3 inhibitor. Some of those trials are ongoing. For example, in Germany right now, they are doing a trial of high-dose AraC/mitoxantrone versus high-dose AraC/mitoxantrone plus crenolanib, a second-generation or more specific FLT3 inhibitor.

There are also patients who are unfit for chemotherapy. For those, you might want to consider using hypomethylating agent. Hypomethylating agents together have about a 10% or 11% response rate in relapsed AML overall. Of course, that is generally given to patients who are not deemed to be fit for chemotherapy. There is interesting data from MD Anderson where azacitidine is combined with sorafenib, the aforementioned kinase inhibitor that also has FLT3 inhibiting activity. That is an interesting trial to use. Again, it is not approved for that, but you could consider azacitidine plus sorafenib in an unfit relapsed mutant FLT3 AML patient. I think we really need a lot more research in this area. The summary points are: please re-measure the mutational profile of your patient when they relapse; please consider a clinical trial; please assess the patient for the degree of fitness; and right now the standard of care is either intensive chemo alone or non-intensive chemo without the addition of a FLT3 inhibitor. We also have to think about that in terms of developmental therapeutics.

Finally, there are two very important clinical trials going on now that are testing whether a single-agent specific FLT3 inhibitor (in one case gilteritinib and in the other case quizartinib) might be better than ”dealer’s choice” chemotherapy in relapsed mutant FLT3 AML patients. I think it would be very relevant to consider enrolling your relapsed mutant FLT3 AML patients on one of those two trials if at all possible. Thank you very much for viewing this activity.

*Gilteritinib trial:* https://clinicaltrials.gov/ct2/show/NCT03182244
*Quizartinib trial:* https://clinicaltrials.gov/ct2/show/NCT02039726