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Optimizing Care for Older Adults With FLT3-Mutated AML

Announcer:
You're listening to *On the Frontlines of AML and ALL* on ReachMD. And now, here's your host, Ryan Quigley.

Ryan:
This is *On the Frontlines of AML and ALL* on ReachMD. I'm Ryan Quigley, and joining me to explore therapeutic strategies for older adults with FLT3-mutated acute myeloid leukemia, or AML, is Dr. Nicholas Short. He's an Associate Professor in the Department of Leukemia at the University of Texas MD Anderson Cancer Center in Houston.

Dr. Short, thanks so much for doing this. Really appreciate you being here today.

Dr. Short:
Thank you for inviting me.

Ryan:
So, Dr. Short, let's dive right in. What I'm curious about is, how do outcomes in older adults with FLT3-mutated AML differ from those in younger patients?

Dr. Short:
So, just like in patients with AML in general, older patients unfortunately still have worse outcomes. That's driven by a number of factors, including comorbidities and worse tolerance of intensive therapy, and therefore having to reduce the intensity of the therapy for those patients to deliver it safely. And the same is true for FLT3-mutated AML. The recent standard of care based on the VIALE-A study has been to treat older patients who are unfit for intensive chemotherapy with azacitidine-venetoclax. The standard right now is to do that whether they have a FLT3 mutation or not, but we know that those patients with FLT3 mutations who received that type of therapy, unfortunately, have poor outcomes.

So, it's still a really challenging group of patients to treat. But there are some new paradigms in this area and some new, exciting treatments for these patients that may be improving outcomes.

Ryan:
Absolutely. And looking at today's treatment landscape, what options are available for this older adult population?

Dr. Short:
The "standard of care," if we're just going based on randomized data for older patients, would generally be azacitidine-venetoclax, irrespective of the FLT3 mutation. Now, the caveats to that are, we're talking about patients who are unfit for intensive chemotherapy, but that's a very subjective concept. So, that applies to patients who are 75 years of age or older or have a very significant comorbidity. But we often lump patients over 60 years of age as older adults with AML, and so the question then is, how should we treat patients between 60 to 74? I think that's where the data are less clear. Those patients largely were not in the VIALE-A study that led to the approval of azacitidine-venetoclax.

But also, if we look, for example, at the QuANTUM-First study, which was the randomized study of seven plus three plus or minus quizartinib, they did allow older patients for that study; about 40 percent of patients were 60 to 74. But unfortunately, there was no benefit for that older population who received the seven plus three plus quizartinib, a FLT3 inhibitor. So, it's still definitely not settled. There's no good randomized data for what we should do for these patients.

I think the newer evolving paradigm is really to use these hypomethylating agent plus venetoclax plus FLT3 inhibitor-based regimens for

patients who are 60 years of age and older. That's what we do at MD Anderson. I think there's emerging data from our studies and others suggesting that the outcomes do look better for this older population with those regimens. But, of course, we'll need randomized data to confirm that.

Ryan:
Here's something I'm sure plays a pretty critical role in treatment. How does a patient's fitness or frailty influence your decision-making in this scenario?

Dr. Short:
Chronological age is important. So, is a patient 80 years of age? Well, with that patient, we're really never going to give intensive chemotherapy, even if they're in great shape. But, of course, you can have a patient who's 55 and who doesn't meet our typical definition of what we would call an older patient, but they may have significant comorbidities, like heart failure, COPD, et cetera. And then that patient is going to be more suitable for lower intensive therapy.

So, chronological age plays a role, but really, you have to think about the patient age, chronological age, and estimating their biological age based on other factors such as their comorbidities and other issues that they may have and ultimately tailor the treatment regimen.

So, in general, a patient who is under 60 who doesn't have any major comorbidities, we often would treat with intensive chemotherapy, and in the case of FLT3-mutated AML, add a FLT3 inhibitor. For patients who are 75 years of age or older who have a major comorbidity, it's a lower intensive regimen: HMA and venetoclax. We at MD Anderson and many other sites will add a FLT3 inhibitor. And then, I think the big question is, for those patients who may be a little bit younger but have a significant comorbidity, or maybe even a little bit older but don't, how should we treat those patients?

Based on some of the data presented at ASH this year, I think that many of us are moving towards, for patients over 60 years of age, largely using these lower intensive regimens, even if they seem like they're fit for intensive chemotherapy, because our assessment can be wrong. We can see a patient in front of us who's 65, and we think they're in great shape, but that patient is still going to have more likelihood of complications than someone who's in their 40s. So, to try to reduce the risk of those issues arising, I think many of us are moving towards lower intensive regimens, even for older patients who seem relatively fit.

Ryan:
For those just joining us, this is *On the Frontlines of AML and ALL* on ReachMD. I'm Ryan Quigley, and I'm speaking with Dr. Nicholas Short about key considerations for treating older adults with FLT3-mutated AML.

So, Dr. Short, from a clinical standpoint, what should clinicians keep in mind when it comes to monitoring and supportive care for these patients?

Dr. Short:
Well, of course, it depends on what kind of therapy you're giving them. But if we're talking about an older patient with FLT3-mutated AML, whether you're giving them azacitidine, venetoclax, or the triplet regimen with azacitidine, venetoclax, and the FLT3 inhibitor, obviously, those are myelosuppressive regimens. Even though we call them lower intensity, particularly in this older population, they're still very myelosuppressive. So, we're going to be watching their blood work very carefully. At MD Anderson, we admit the patient for the first cycle, for the first 30 days. I know that's not the case everywhere, but for induction, we admit them. And certainly, we're watching them very carefully.

And then, I think if we're specifically talking about these types of venetoclax-based regimens, there's a lot of both art and science to how many days of venetoclax you give. Talking about these triplet regimens, one of the strategies that we've adopted that I think has been very helpful is that in induction is we do a day 14 bone marrow, which is earlier than is typically done with lower intensive regimens, but we see that the vast majority of patients are already in some form of remission at that time. So, we stop both the venetoclax and the FLT3 inhibitor to allow them to have count recovery. I think that's allowed for very high CR rates. We've seen 90 percent CR rates essentially with these triplet regimens; that means full count recovery. And in part, that's because of this interim day 14 bone marrow where we stop the venetoclax and the FLT3 inhibitor.

And we also very liberally will give growth factors as well to mitigate the risk of prolonged myelosuppression and improve their counts. So those are some factors you need to consider when you're delivering those types of regimens.

Ryan:
If we look ahead, are there any promising clinical trials exploring treatment options for this population down the road that you're looking forward to?

Dr. Short:
I think that it really is more a refinement of what many of us are already doing. I would argue that the data are very compelling with these triplet regimens—azacitidine-venetoclax and gilteritinib or quizartinib. But I think a big question in the field, and I think a very reasonable question is, are we delivering this regimen correctly and optimally? Are we giving the right number of days of venetoclax? Do we need to continue the FLT3 inhibitor indefinitely, or should we stop it based on MRD, et cetera?

So, I think the next generation of clinical trials, rather than pointing to some really exciting new drug that we're going to be using in FLT3-mutated AML, at least in this context, I think it's really going to be just refining how we deliver these regimens. So, maybe stopping the FLT3 inhibitor after patients have a deep MRD response, or maybe using fewer days of venetoclax. I think that we have, in some ways, the tools needed to improve outcomes for these patients. It's just about delivering these regimens.

Looking forward to the future, I think many of these FLT3-mutated patients will have NPM1 mutations. So, I think that there are trials planned about how we can incorporate a menin inhibitor into the frontline setting. But I think those may be challenging just because it could be myelosuppressive trying to deliver all of these drugs, certainly in combination, so maybe sequencing them. So, I think that we have a lot of the tools, but it's really about just figuring out the best way to deliver them, and I think that's what the next generation of trials in this space will be focused on.

Ryan:
Dr. Short, what guiding principles would you like to share with clinicians navigating this quickly evolving treatment landscape?

Dr. Short:
I think that these patients should be treated at high volume centers—I think that that's a very important principle—and also ideally treated on clinical trials. If it's your first time delivering one of these regimens, I think it's very important to partner with an expert that you know in the field. And we'll all be very happy to help because there's a lot of nuances in terms of, when do I stop the gilteritinib or venetoclax? Or, how many cycles do I do? Or, what duration of drug per cycle? Et cetera.

But I think ideally, these patients, when possible, can come to a tertiary care center for their therapy and be treated by someone with a lot of experience because it's changing so much that I don't know how someone who sees more broadly in community practice can possibly keep up with this. But I'm very impressed with what many of our community physicians are able to do. We often partner with community physicians and co-manage. So, sometimes, the patient will come and see us every three to four months just to check in and make sure everything's going on track. There's a lot of different ways to do that.

So, I think that is an important guiding principle in the setting of this disease and really all of oncology with things just evolving very rapidly, and it takes more and more expertise to manage these patients optimally.

Ryan:
That's a great comment for us to think about as we come to the end of today's program. And I want to thank my guest, Dr. Nicholas Short, for joining me to share best practices in caring for older adults with FLT3-mutated AML.

Dr. Short, thank you so much for joining us today.

Dr. Short:
Thank you. My pleasure.

Announcer:
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