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Updates in AML Care: Evolving ASH Guidelines for Older Adults

Announcer:

You're listening to *On the Frontlines of AML and ALL* on ReachMD. And now, here's your host, Dr. Shelina Ramnarine.

Dr. Ramnarine:

This is *On the Frontlines of AML and ALL* on ReachMD. I'm Dr. Shelina Ramnarine, and joining me to review the updated American Society of Hematology treatment guidelines for acute myeloid leukemia in older adults is Dr. Mikkael Sekeres. He's a Professor of Medicine and Chief of the Division of Hematology at the Sylvester Comprehensive Cancer Center at the University of Miami Miller School of Medicine.

Dr. Sekeres, thanks for being here today.

Dr. Sekeres:

Thanks so much for having me. What a privilege it is to be here.

Dr. Ramnarine:

So, Dr. Sekeres, before we dive into specific recommendations, can you tell us about what motivated the ASH panel to revisit and update the AML guidelines for older adults?

Dr. Sekeres:

Believe it or not, the AML guidelines for treating newly diagnosed older adults with acute myeloid leukemia were the first hematologic malignancy guidelines that ASH put out, and we put these out in August of 2020. Now, whenever you create guidelines, it's actually a multi-year process. It's really complicated if you do it rigorously. And we tried to do this rigorously with methodologists from McMaster University using what's referred to as a grade approach to evaluating evidence and then finally giving recommendations.

When these guidelines came out, we knew they would be outdated, and the reason was that they were actually published the exact same month as the publication of a treatment regimen, azacitidine and venetoclax, that became the new standard of care for patients who were considered "not fit" for intensive chemotherapy. So, upon arrival, we knew we would have to revise these guidelines.

Since then, there were some other publications that came out where we thought to ourselves, "You know what? We are not sure that the recommendations in the 2020 guidelines are perfectly accurate the way we need them to be to help advise people in treating older adults with AML." So, those additional studies that came out really motivated us to have a reboot of these guidelines, and we're so thrilled that we were able to do that within about a year and a half.

Dr. Ramnarine:

Now, with that context in mind, one notable shift in the guidelines is moving away from the traditional intensive versus non-intensive framework. How should clinicians think differently about treatment intensity in older patients with AML?

Dr. Sekeres:

So, that study that I mentioned was from August of 2020. The first author was Courtney Denardo from MD Anderson. It showed that patients who received azacitidine and venetoclax compared to azacitidine monotherapy for newly diagnosed AML in people considered "not fit" for intensive chemotherapy, there was a significant survival advantage for the combination versus azacitidine monotherapy and that survival advantage was substantial. It was a few months on average.

Now, that treatment regimen is often given as an outpatient, but as soon as we started using it inpatients, we recognized that it's pretty aggressive therapy. And we knew that both because we saw the degree of cytopenias that patients were experiencing with the

combination, and also the fact that these patients were contracting fungal infections as if they had received the standard 7+3 intensive chemotherapy that they ordinarily would have gotten in the hospital. So, understanding that, we realized that drawing a line in the sand between traditional 7+3 intensive chemotherapy, calling that intensive, and other regimens, saying they are not intensive, was disingenuous. It wasn't accurate. Patients who are receiving combination drugs, like azacitidine and venetoclax, are getting pretty intensive therapy. They're just getting it as an outpatient. So, we wanted to remove that nomenclature entirely so that treating physicians, nurses, and pharmacists wouldn't erroneously conclude that combination therapies with a venetoclax backbone were non-intensive.

Dr. Ramnarine:

The guidelines strongly recommend antileukemic therapy over best supportive care for most older adults. What factors should guide that initial conversation with patients and families?

Dr. Sekeres:

I think this is one of the most challenging conversations that I have with patients. We structured the guidelines so they would go in order of the conversations that doctors, nurses, and pharmacists have with patients as patients are making decisions about therapy. And the very first decision that a patient has to make about therapy is, "Should I be treated at all?" And that is really closely tied to a patient's goals.

So, a typical scenario is an older adult, let's say someone who's 77, is diagnosed with acute myeloid leukemia and is referred to see me or somebody like me in our offices. That person will show up often with a partner, if they have a partner, and often with children, and they're told they have acute leukemia. Often, they're told before they even come into our office that they should get their affairs in order. So, we have a conversation about what the treatment options are like and what the potential benefits and risks are of those treatment options. We talk about things like going into remission and prolongation of survival, particularly if somebody does go into remission. We also talk about the chances that they won't go into remission and that the treatment may not prolong their survival. We talk about average survival if they don't get treated. And for older adults with acute myeloid leukemia, that average survival is really scary. It's only two or three months.

Then we talk about what their goals are. And I have some patients who will say to me, "I have a grandchild who's graduating high school or college coming up. There's a wedding on the horizon. There's a 50th or 60th wedding anniversary that's coming up. I really want to live for that, and I will do anything to get to that point." That's very concrete; we have a goal. We know what we're all working for; we're all in it together. I've also had patients who, at age 77, say to me, "I've lived a really good life, and I don't want to spend the rest of it seeing you here in the clinic or being in a hospital." And those are folks who choose not to receive any therapy.

So, we recommend that if a patient decides that he or she wants to be treated, that person gets treated. That person will likely live longer if they get treated than if they don't get treated. However, it's all predicated on that initial decision that a patient makes that's aligned with that person's goals.

Dr. Ramnarine:

For those just joining us, this is *On the Frontlines of AML and ALL* on ReachMD. I'm Dr. Shelina Ramnarine, and I'm speaking with Dr. Mikkael Sekeres about the updated AML treatment guidelines from the American Society of Hematology.

So, Dr. Sekeres, if we continue to look at the recommendations, venetoclax-based recommendations appear repeatedly. How did the panel weigh the benefits against concerns about myelosuppression and infection risk?

Dr. Sekeres:

That myelosuppression and infection risk with venetoclax-based regimens is real. Before we got started on identifying the questions we were going to ask of patients and providers and how we were going to answer those questions to provide recommendations in the guidelines, we actually had the panel go through a rigorous process. This is part of the grade methodology of identifying what's important to patients, caregivers, and providers, like doctors, nurses, and pharmacists, and how should we rank the importance of those different factors?

So, for every one of these questions, we went through this process of identifying important factors to consider in making decisions and factors that were less important in making that decision, and that's how we came to make our recommendations, whether they involved treating patients with venetoclax or other questions in the ASH AML guidelines.

For venetoclax-based combination regimens, frankly, I think a lot of what drove our recommendations were the survival advantages and the impression that, yes, things like myelosuppression and infection risk were probably higher if a patient got venetoclax plus, for example, azacitidine, as opposed to getting azacitidine alone or not getting treated at all. But leukemia itself leads to enough

myelosuppression and enough infection risk that it wasn't looked at as a risk that was higher substantively compared to the advantage in overall survival that patients would be able to appreciate.

Dr. Ramnarine:

Now for patients with actionable mutations, how do the guidelines recommend integrating targeted agents into frontline therapy?

Dr. Sekeres:

Well, we recommend that everybody with a new diagnosis of acute myeloid leukemia undergoes cytogenetic testing to see if there are any chromosomal abnormalities that can be identified in the AML cells and that they undergo next-generation sequencing analyses looking for specific molecular mutations, particularly potentially actionable molecular mutations. And I would put into that category patients who have a FLT3 mutation, an IDH1 mutation, and an IDH2 mutation, and increasingly, we're looking at patients who have KMT2A or NPM1 mutations who would be amenable to therapy with menin inhibitors.

Now, there are very strong data supporting the use of adding a FLT3 inhibitor to standard 7+3 remission induction therapy with a survival advantage for those patients who received a FLT3 inhibitor such as midostaurin or quizartinib versus those who didn't get a FLT3 inhibitor for that initial intensive chemotherapy. So, we made a very clear recommendation that patients should receive FLT3 inhibitors when they have a FLT3 mutation.

For patients with IDH1 and IDH2 mutations, the literature was a little murkier. Now, there was a very well done study that looked at treating patients with an IDH1 mutation with azacitidine and ivosidenib, an IDH1 inhibitor, versus azacitidine alone with a survival that was actually tripled in that study for those who got the combination that included ivosidenib versus those who didn't get the combination—in other words, who got the azacitidine monotherapy. So, we made a strong recommendation that when considering azacitidine versus azacitidine and ivosidenib, patients should get the targeted therapy in addition to the azacitidine. The data were not as clear for the IDH2 inhibitor enasidenib, so we did not make that recommendation for patients with IDH2 mutations and their AML. Now, in the end, I think a question that people would ask is, "If you have an IDH1 mutation, should you get azacitidine and venetoclax, or should you get azacitidine and ivosidenib? And frankly, the literature doesn't guide us at all with answering that question, so we made the comment that either combination therapy would be acceptable to treat somebody with a new diagnosis of AML and an IDH1 mutation.

Dr. Ramnarine:

So, once an older adult achieves remission, what guidance does the ASH recommendations offer regarding post-remission therapy and treatment duration?

Dr. Sekeres:

This is another area where the literature is not straightforward, which is surprising. We've been giving induction chemotherapy to patients with AML and then post-remission or consolidation therapy to people with AML for decades, yet there really aren't great randomized trials in which some patients received post-remission therapy and other patients didn't receive post-remission therapy. So, we had to use the data a little bit indirectly to answer this question. And the indirect answer to this question is that patients who survived long term with their AML all received at least two treatment regimens. In other words, they either received a double induction regimen or induction chemotherapy followed by some type of post-remission therapy. So, we did recommend that patients receive some sort of post-remission therapy after receiving their induction chemotherapy and after they were in a remission. But we didn't give a high level of evidence to support that recommendation because the evidence simply wasn't out there.

Dr. Ramnarine:

And finally, Dr. Sekeres, as clinicians begin applying these guidelines in practice, what's the single most important mindset shift you hope they take away?

Dr. Sekeres:

We had two patients who were on our panel as well, and I can't emphasize enough how important their contributions were to how we thought about generating the questions that we would ask and the answers that we provided. Those patients told us over and over again how important it was that their healthcare team communicated to them about their goals at every step of a treatment decision throughout their leukemia course.

It is so important that we as healthcare providers align our recommendations with our patients' goals so that we're truly meeting our patients' needs.

Dr. Ramnarine:

That's a great comment for us to think about as we come to the end of today's program, and I'd like to thank my guest, Dr. Mikkael Sekeres, for joining me to share key updates to the AML treatment guidelines.

Dr. Sekeres, it was so great to have you on the program.

Dr. Sekeres:

And it was such a pleasure to join you. Thank you for the outstanding questions.

Announcer:

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