Is Your Patient Fit or Unfit for Intensive Therapy?

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Program Overview
Determining fitness for intensive therapy can be challenging to assess in patients with AML. In this activity, Dr. Kendra Sweet describes best practice in assessing fitness for intensive therapy for patients with newly diagnosed AML, the impact of comorbidities, and the available tools that should be utilized to determine a patient's fitness for intensive therapy. She will describe appropriate intensive and non-intensive treatment options for patients with AML based on their fitness.

How has the role of fitness evolved in terms of determining frontline treatment options for patients with AML?

Fitness is hard to assess, especially in the clinic, and especially at the time someone is newly diagnosed with AML. They can be weak and debilitated, but it's hard to know how much of that is their baseline status versus the disease causing them to become deconditioned very quickly. A patient may look pretty bad, but maybe just 4 weeks ago they were running 3 miles, 5 days a week—these things are not always obvious.

So there are two questions we have to ask when determining the frontline options. One is, *what treatment can they tolerate?* And two, is *what treatment is appropriate?* Fitness plays a role in answering both of those questions. To me, the question of what treatment is appropriate is important to answer first. You look at the cytogenetics, the mutational profile on next-generation sequencing, the patient's history—do they have a secondary AML? Have they had prior chemotherapy? Do they have MDS that has progressed? We take all of that into account—fitness aside—to determine what's the most appropriate treatment for this patient.

If intensive therapy options such as 7+3 induction chemotherapy or CPX-351 aren't appropriate, then fitness may not really be a relevant question. However, if you have a 62-year-old patient with a history of MDS progressing to AML who has never been treated with a hypomethylating

agent—basically someone who is appropriate for CPX-351 induction—then suddenly fitness becomes a very pertinent question: Is this someone who can tolerate spending a month in the hospital getting intensive chemotherapy or not?

So to me, the more important thing to look at first is to find the appropriate approach for their disease, and *then* ask if they can they tolerate that approach. Just because someone is fit enough to tolerate induction doesn't mean that they should get it. In the past, we used to just give 7+3 induction chemotherapy to anyone who could tolerate it, and if not, we'd give them azacitidine or low-dose cytarabine, and that was that. Now that we have many different treatment options for AML; jumping straight to intensive induction chemotherapy just because they are healthy or young is not always the right answer. We need to figure out what the appropriate treatment is based on the biology of their disease, and if intensive therapy is appropriate and we determine they're fit to handle it, we can do it. Just because we have established that they can tolerate it doesn't mean we should do it.

What are some of the key factors for determining a patient's fitness? Is this an objective or subjective process?

I wish it were more objective than it really is. Many have come up with algorithms based on objective criteria like albumin, creatinine, age, performance status, and others to determine who is fit for induction and who is not. They look at those objective criteria and then they come up with a risk score. Most of them are not used in day-to-day clinical practice. Instead, most of us use the "eyeball test" and then ask questions. In some cases, it's obvious—for example, if a patient arrives in a wheelchair, or they are on oxygen, or they tell you they require help getting in and out of the shower and are using a bedside commode. But others are not so obvious. Some people who at first glance you'd think are really fit and strong tell you that they struggle walking half a block or walking out to the mailbox every day.

When it comes to objective criteria, I think Eastern Cooperative Oncology Group (ECOG) performance status is probably what's used most commonly. At Moffitt, we're required to put ECOG performance status in our notes, and that's good, because at least it makes you think about it. It would be nice if there was something a little more standardized, but some of these assessment methods can be time-consuming and the data points aren't always available. So I don't know that we have any algorithms or calculators now that we could bring into a busy clinical practice setting.

In the recent clinical trials of venetoclax in combination with azacitidine or low-dose cytarabine, VIALE-A[1] or VIALE-C[2], they used the criteria proposed by Ferrara and colleagues, which again are not terribly objective—if the patient has severe liver or kidney dysfunction, or if they're over the age of 75 years, or any one of several other criteria that the patient's physician thinks is severe, that makes the patient ineligible for intensive induction chemotherapy.[3] So, the approval for those venetoclax regimens is based on that data, but even that isn't really what's

used in clinical practice—we're not treating only those patients with venetoclax regimens, we're using venetoclax in a lot of healthy patients who could tolerate more intensive regimens.

What goes into your thought process when you look at the patient's age in determining fitness?

The pathways we've developed here at Moffitt suggest that 75 years of age is the cutoff which we exclude intensive chemotherapy. It doesn't mean that you absolutely can't use intensive chemotherapy if you feel it's appropriate for your patient. There are, however, data from various SWOG and other studies showing that the older someone is, even if they look fit and healthy, their risk of dying from induction chemotherapy is much higher.[4] The early mortality rate with induction is significantly higher in older patients, irrespective of anything else. Biologically, their bodies are older, their organs are older, so their bodies can't tolerate intense therapy the way someone who is younger can.

Anecdotally, when I have tried induction therapy in someone over the age of 75 years, personally I have had bad experiences with it, which has reinforced my belief that it's not usually a good idea. So to me, 75 seems to be the cutoff, especially because we're unlikely going to be able to follow it up with an allogeneic stem cell transplant in a patient over the age of 75. If we can't send someone to transplant, then I don't know what the utility of inducing them is when we have alternatives that are less intense for getting them into remission and maintaining remission.

It's now frequently said that biologic age is not the same as chronologic age when it comes to health and fitness. Does that apply in AML as well?

Certainly, not all 60-year-olds are the same. You've got young 60-year-olds, old 60-year-olds, and 60-year-olds who actually *are* 60-year-olds. So you do have to look at each person as an individual, at their organ function, performance status, and try to get an idea what their functional status has been in the months leading up to their diagnosis. The disease itself can lead to a lot of deconditioning and debilitation, so you might not want to make your assessment based on how weak, inactive, or debilitated they've become in the past 3 or 4 weeks—that's likely related to their AML, not to their actual functional status. However, if they tell you that in the last year they've spent more than 50% of their time in bed or in a chair because they're weak, tired, and short of breath without any obvious cause, that's a different story. With that being said, by the time you get to 75, 80, 85 years of age, although you can have a very healthy person in this age group, I think you unmask their age, if you will, when you give them something like 7+3 or CPX-351.

How do comorbidities affect your assessment?

Comorbidities definitely play a role. Cardiovascular comorbidities play a role in treatment decisions for sure, especially when deciding on anthracycline-containing regimens, because in certain cardiovascular processes you would need to leave out the anthracycline. If someone has significant pulmonary issues, if they're on oxygen, that probably plays into their performance status. Those two things will likely go hand-in-hand. But just because someone has diabetes doesn't necessarily mean I wouldn't give them intensive therapy—if we can control their diabetes, they could do just fine. So the presence of comorbidities in and of themselves don't necessarily determine how I would treat someone, but specific comorbidities like cardiovascular disease and how they impact their performance status absolutely matter.

How do you view the current intensive and non-intensive frontline regimen options in terms of patient fitness?

We have 7+3 and CPX-351 as the intensive options, and there are other high-intensity regimens like FLAG-IDA, CLAG-M or CLAG, and MEC. Among the less intensive are the HMA-containing and low-dose cytarabine-containing regimens; glasdegib certainly falls into that category as well. HMA/venetoclax is classified as a lower-intensity regimen, but to me it falls somewhere in the middle; it is not the same as azacitidine or decitabine by itself—it is definitely harder for people to tolerate than an HMA alone. So there are people like the 90-year-old man who lives alone and who uses a walker and struggles to get around on his own and make his own meals—for him, I would think twice about giving HMA/venetoclax simply because it is so myelosuppressive and it requires very close follow-up. It's hard for some people to tolerate. Ivosidenib is a good option for less intensive frontline therapy. It is a very well-tolerated drug.

With many options available, deciding a frontline approach can be complicated. It's especially challenging when you have a patient who is fit for induction, but who would also be very appropriate for HMA/venetoclax. Take an intermediate-risk patient who's 70 years old—is that someone who should get intensive induction therapy or HMA/venetoclax? This would technically be off-label, because that's not somebody who would have qualified for the study, but if you extrapolate the data it looks like they could respond really well. For those patients, it's a lot harder to make a decision. Some are really obvious, like someone with secondary AML who's really fit and healthy, who would be a candidate for CPX-351. Likewise, in 79-year-old woman who has adverse-risk disease, the choice of HMA/venetoclax would be an obvious one. But with those intermediate-risk patients that are in their early 70s or late 60s, it's harder to know what to do.

And quite honestly, it's challenging even with some of the younger patients, like with a TP53 mutation—we know those people don't respond well to chemotherapy, but for that 47-year-old who's perfectly healthy with newly diagnosed TP53-mutated AML, if you don't have a clinical trial for that person, sometimes the best decision is tough to make. Are you going to

give that person HMA/venetoclax or are you going to give him CPX-351? For me, that decision is based more on biology than on fitness, because at the end of the day, I'd probably give that person HMA/venetoclax for their induction chemotherapy even though they are in their 40s and perfectly fit.

What are some of the other patient profiles you might encounter commonly in clinical practice that illustrate the complexity of considering fitness as a criterion?

For patients over 75, I'm usually not going to give induction, but where I struggle sometimes to decide is if I see a really fit, healthy 76- or 77-year-old with FLT3-mutated AML with significant leukocytosis on admission. Particularly if they present with tumor lysis syndrome or DIC, this is somebody who obviously needs to be in the hospital and needs treatment right away. With the FLT3 mutation, you could use HMA-venetoclax in this patient, but this is someone where I think that maybe 7+3 and midostaurin would be a good option as well. The RATIFY study that led to approval of midostaurin plus chemotherapy was conducted in patients up to the age of 59,[5] but it is approved for adult patients regardless of age.

So that's someone for whom I might decide to deviate from my stance on 75 and above, but I have also seen some unfortunate outcomes in the past in this setting, and have wished I made different treatment decisions. As I said previously, chemotherapy will unmask someone's age, and can do so very quickly. You can't undo 7+3 once you've given it. You give it, and then you just have to support them through the myelosuppression and wait until they recover and hope that they do. That's the hard part.

So to me, these are really complex patients for whom it's difficult to determine the best approach.

What are the most important take-home messages for clinical practice regarding the evaluation of fitness and disease features as part of frontline AML treatment decision making?

I think the most important idea is this: just because somebody can tolerate intensive therapy doesn't mean that they should get it. Make the decision first based on biology, and then if they can tolerate what's appropriate, give it. Biology and fitness need to both be looked at simultaneously, but biology I think needs to be determined before we start focusing on fitness.

References:

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