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Keeping Pace in Hematologic Malignancies: 2023
Contextualizing the Evidence: Newly Diagnosed AML in Difficult-to-Treat Subtypes

[Chapter 1]

Dr. Erba:
Acute myeloid leukemia, or AML, is the most common acute leukemia in adults. There have been exciting advances in molecular profiling of AML and the classification of AML subtypes. Are you up to date with the latest data of the treatment of newly diagnosed AML in difficult-to-treat subtypes?

This is CME on ReachMD, and I'm Dr. Harry Erba. Here with me today is Dr. Courtney DiNardo.

Dr. DiNardo:
Hi, thank you so much for having me.

Dr. Erba:
It's great to be doing this program with you, Courtney. Let's get started.

Courtney, to set the stage for this chapterized course, what can you tell us about biomarker and MRD [minimal residual disease]-driven approaches to newly diagnosed acute myeloid leukemia?

Dr. DiNardo:
I think one of the most important things to be aware of is that, you know, we should not be treating all AML patients as though they're exactly the same. Because the way I talk to my patients about it is that each AML patient has their own kind of genetic fingerprint that helps us identify, you know, now that we have more therapies, how to optimize, how to personalize, how to best approach that patient's leukemia.

And so I think, you know, when you have a newly diagnosed patient, you're seeing a new AML patient for the first time, the things you really want to make sure of is that you know the genomics, right? And so that's the cytogenetics, and that's their molecular characteristics. And I think we want to make sure that we're getting those results back within a reasonable time frame. Things should come back, optimally, within about 4 to 5 days, which is hard if you're sending them out, I know. But it is possible. And so I say that because I think it's really important that as a field, we're trying to make sure that this happens.

And the things that, in particular, I'm paying attention to in a newly diagnosed AML patient is do they have a favorable-risk leukemia that has a core-binding factor translocation? So that means an inversion 16 or a 8;21 translocation. If they do, then I want to make sure that I'm incorporating gemtuzumab ozogamicin to their intensive chemotherapy. Do they have a FLT3 mutation? If they have a FLT3-ITD or a FLT3-TKD mutation, we know that those patients are better served with the addition of a FLT3 inhibitor. And so I want to know that information as I'm deciding on their treatment course. Do they have, you know, a therapy-related phenotype? Meaning that they have underlying MDS-related changes. Do they have MDS-related mutations, splicing factor mutations, for instance? If they do, you know, then CPX-351, the liposomal 7+3 is a great option. And it has, in randomized studies, been shown to be more effective than standard
7+3.

So those are the types of things I'm thinking about as I'm seeing, you know, a new patient, in particular, a younger patient getting intensive chemotherapy.

The other thing that I think is really important to talk about is the genomics at the beginning so that you can then follow that patient over time. So then no matter what treatment you're giving that patient, you know, if that patient has an NPM1 mutation, for instance, that way you know that at various different time points, you know, after their first cycle of therapy, a few cycles, and you're following and you can be monitoring that patient for what we call measurable residual disease. So looking specifically at that marker, and does it disappear with time? And we know that if it does, that patient has a better outcome and that helps decide on posttreatment kind of maintenance-type approaches.

Flow cytometry is another way of measuring MRD, which doesn't depend on that specific mutation. And so that's another thing that is a very important thing that's available for all AML patients that you can be following at the time of remission to see do they become negative by flow? So those specific aberrant markers on the outside of the leukemia cells, do those disappear? And if they do, that's another really nice characteristic that we know leads to improved outcome. And so that flow MRD timing is often done at the end of the first cycle of therapy. So kind of postinduction is what we call it, with ongoing consolidation.

I'll just finish by saying MRD testing has become really important to help us decide and optimize transplant decision. So, you know, I mentioned core-binding factor. Leukemia patients, NPM1-mutated patients, those patients are considered favorable risk and often they don't need a transplant in their first remission. But if they stay MRD positive, for instance, you know, that may indicate a patient that would be better served with a transplant, because if we can't clear the lowest levels of leukemia with that chemotherapy the concern is that they would relapse.

So that's a lot of information about kind of genomics, cytogenetics, MRD-guided treatment planning decisions, but hopefully that was a helpful intro.

Dr. Erba:

Oh, that was great, Courtney. And I completely agree with what you laid out there in terms of the initial diagnostic studies. And of course, remembering to repeat those diagnostic studies, especially a mutational analysis, when you're suspicious of refractory or relapsed disease. Because the genomic changes may change. And the importance of following the disease by flow cytometry as well as MRD assays for the genomic changes that we can see.

I think one of the challenges that the practicing clinician will have is accepting this delay in starting treatment. For decades, we've been telling everybody, the leukemia experts have been telling everybody, don't let the sun set on a leukemia patient without writing for 3+7 or 7+3. And now we're saying it's okay to wait.

I think it is important, though, to consider the different subtypes and patients who are younger, who have a hyperleukocytosis or a high white count, they're in the hospital, and you're thinking about intensive treatment, which we'll talk about in the next chapter, you know, you can get intensive treatment started right away and add in other drugs that are shown to be beneficial, as that data comes back.

But for the majority of patients who may present with pancytopenia or leukopenia, you can wait. And so even if that patient is admitted to your hospital with febrile neutropenia or needing a transfusion, I think it's very reasonable and preferable to actually do exactly what Courtney said, that is, get the bone marrow, get the data, wait for the data; you can discharge the patient. After all, that patient probably came to your emergency room not expecting to be in the hospital for a month getting intensive therapy or less intensive therapy. So it's safe to do so in those situations. And that data, as we will talk about later on in Chapters 2 and 3, can be very helpful in guiding therapy.

So in Chapter 2, we'll be discussing how to approach the treatment of patients with newly diagnosed AML who are fit for intensive chemotherapy. So stay tuned.

[Chapter 2]

Dr. Erba:

Welcome back. We were just talking about biomarker and MRD-driven approaches to newly diagnosed AML. I'm going to start Chapter 2 off by discussing the approach to treating patients with newly diagnosed acute myeloid leukemia who are fit for intensive chemotherapy. Which, of course, begs the question: How do we define fitness?

Well, there is no perfect definition for fitness, and many of us are actually getting away from thinking of the patient as fit for intensive chemotherapy and may be thinking more about is that patient appropriate to give intensive chemotherapy? We've learned, of course, over the years that there are certain features of patients that will increase the risk of treatment-related mortality with intensive
chemotherapy. Advancing age, poor performance status, functional status, poor organ function, having a concomitant malignancy, comorbidities, and quite a few others that have been studied. But there's no perfect algorithm for deciding if a patient is fit to get an intensive chemotherapy regimen, especially in the days before 2018 when we had very few effective options for patients who are unfit for intensive chemotherapy.

In the next chapter, we'll be talking about what those options are. But let's focus on the patient that you've decided is fit for intensive chemotherapy. And the mutational background that I think is important in making those treatment decisions involves looking for the presence of FLT3-ITD or TKD mutations, core-binding factor rearrangements, as well as NPM1 mutation. We know, as Courtney mentioned in Chapter 1, that the addition of FLT3 inhibitors to intensive chemotherapy has improved the survival of patients with FLT3-mutated AML.

Before I get to that, let's delve into the core-binding factor rearrangements, that's the 8;21 also known as RUNX1-RUNX1T1 fusion and inversion 16, or the CBF [core binding factor] smooth muscle-myosin heavy chain 11 gene fusion. These account for about 10%, maybe 20% of younger patients with acute myeloid leukemia, and there have been a number of studies that have shown the benefit of addition of gemtuzumab ozogamicin to intensive chemotherapy.

In terms of NPM1 there are drugs being developed on the horizon that may someday be incorporated into intensive chemotherapy. But right now, it remains a prognostic marker and a marker that I use for selecting patients that I think should be considered strongly for intensive chemo, because they may be cured with intensive chemotherapy without the need for allogeneic transplant, especially if there isn't a FLT3 mutation.

Let's move on, though, to what we know about the addition of FLT3 inhibitors to patients with FLT3-mutated acute myeloid leukemia. About 30% of patients with FLT3 with AML will have mutations in FLT3. The majority, or about 20% to 25%, are internal tandem duplications. And then the other 5% to 10% are tyrosine kinase domain mutations. The internal tandem duplication has been shown to be impactful on prognosis. In most studies, remission rates are similar to those without a FLT3 mutation, but there is definitely a higher risk of relapse.

We now have 2 available options for our patients who are fit for intensive chemotherapy and have AML with a FLT3 mutation. We have been using midostaurin in combination with induction and consolidation chemotherapy for patients with FLT3-ITD and TKD-mutated disease based on the results of the RATIFY trial showing a survival benefit with the addition of that type 1 first-generation FLT3 inhibitor. However, recently, based on the results of QuANTUM-First, the FDA has approved quizartinib in the population of patients with AML and a FLT3-ITD mutation. Quizartinib is not active against the TKD mutation; however, the FLT3-ITD mutation is the one that has the biggest impact on survival with a higher risk of relapse. In the QuANTUM-First study, the hazard ratio for survival was 0.78 in favor of quizartinib. However, if you just evaluate the patients who were younger, such as the RATIFY trial, the hazard ratio was less than 0.7 in that population, and only included the high-risk ITD patients. Furthermore, there was a lower cumulative incidence of relapse with quizartinib compared to midostaurin at 2 years. And importantly for me and my patients, there was a benefit of quizartinib, not only if they went on to receive an allogeneic transplant in first remission, but also if they didn't receive an allogeneic transplant in first remission. This is in distinction to the data from the RATIFY trial showing the benefit being exclusively seen in patients who received midostaurin and then went on to allogeneic stem cell transplant.

However, there is added toxicity with the addition of a FLT3 inhibitor, especially a second-generation drug like quizartinib, and the others that are in development, gilteritinib and crenolanib. These will cause additional myelosuppression, and so we need to be able to manage patients through this intensive chemotherapy appropriately, often including prophylactic antibiotics, close monitoring of blood counts, close monitoring of the EKG for QT prolongation. But the benefit of a second-generation drug, and specifically now quizartinib clearly, in my mind, demonstrates that it is worth this additional risk with, of course, the appropriate monitoring and prophylactic therapies.

CPX-351 has been approved for patients with secondary AML and therapy-related AML. CPX-351 is a liposomal formulation of daunorubicin and cytarabine in a synergistic 1:5 molar ratio. This drug was shown to be superior to 7+3 in a phase 3 study. Interestingly, we have learned from 2 different data sets that patients that have mutations associated with myelodysplasia, the spliceosome mutations and chromatin modifier mutations, are the patients who seem to have the greatest survival benefit compared to 7+3 and, in a UK study, compared to IDA/FLAG. And so this mutational profile may identify patients best suited for CPX-351. CPX-351, however, is intensive chemotherapy. It targets the bone marrow and does cause more prolonged myelosuppression than is seen with 7+3. So again, we need to monitor blood counts closely and provide the appropriate supportive care with transfusions and prophylactic antibiotics as needed.

Courtney, I am sure I've left something out. Do you have anything to add?

Dr. DiNardo:
I think, you know, that was just such a nice comprehensive overview. I'll just reiterate, you know, that intensive chemotherapy is intensive, of course, so, you know, you need to be managing patients. Most of the time, these patients are admitted to the hospital, although not always at certain centers. But, you know, at least, you know, 3 times a week, if not every day, checking labs, giving transfusion support, monitoring for fevers, you know, it's the myelosuppression and the myelosuppression-related side effects that I think are the most prevalent and life-threatening with intensive chemotherapy.

And then when I think about intensive chemotherapy treatment options, right, and how do you, you know, you went through the gemtuzumab for the core-binding factor, CPX-351 for patients with therapy-related or MDS-associated mutations or leukemia, FLT3 inhibitors for patients with FLT3 mutations. And I would just add that, you know, I think there are a lot of clinical trials right now that are evaluating venetoclax. We'll talk about venetoclax with our lower-intensity strategies. But is there a way to achieve more remissions, deeper remissions with the addition of venetoclax to intensive chemotherapy. I'm excited about that. That's still very much in the realm of clinical trials right now. But hopefully, as time goes on, we'll see some of that data coming forward in a positive light as well.

Dr. Erba:
So in Chapter 3, we will be discussing how to approach the treatment of patients with newly diagnosed AML who are not fit for intensive chemotherapy. So stay tuned.

[Chapter 3]

Dr. Erba:
For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Harry Erba, and here with me today is Dr. Courtney DiNardo. We're discussing treatment plans for difficult-to-treat subtypes of patients with newly diagnosed acute myeloid leukemia.

Welcome back. I'm here with Dr. Courtney DiNardo. We just spoke about treating patients with newly diagnosed AML who are fit for intensive chemotherapy. Now we're considering our approach to patients who are not fit for such treatment.

Courtney, can you help us understand how we proceed once we determine a patient is not fit for intensive chemotherapy?

Dr. DiNardo:
So I think one of the first tenets is that has definitely shifted over time, who is fit and who is unfit, right? Because for a long time, we didn't really have effective therapy for people who weren't getting intensive chemotherapy. And so we tried to make anyone who was fit for intensive chemotherapy fit because we just didn't have good options.

But what has really changed are the combination therapies that we have now. And I'll focus primarily on azacitidine and venetoclax. That study was the VIALE-A study, which led to the approval of azacitidine and venetoclax for the older intensive chemotherapy-ineligible population, and it has just really kind of changed the overall landscape and expectations. Because instead of a remission rate of less than 20%, we're now seeing two-thirds of patients responding with either a true CR [complete remission], or a CR with incomplete count recovery. So 66%, two-thirds of patients will respond now to azacitidine and venetoclax. And more than just a response, you know, patients will recover their counts, become transfusion independent, and we saw an improvement in median survival up to about 15 months. And so 15 months is not a forever cure. So as you mentioned in earlier chapters, you know, even though it's much better, it's not a curative regimen, but I think it allows many patients an opportunity for a very durable remission which can be long-lasting in some.

So I'll kind of focus a little bit now on the populations of patients getting aza, then, who respond the best. And so the things that I pay attention to, we mentioned MRD in the first chapter, so about 40% of responding patients do become MRD negative by flow cytometry. And these populations of patients, regardless of underlying genomics, can do significantly better, have longer remissions, and longer expected overall survival. So that's something that, it's not required or mandatory to follow, but if you do follow it and you obtain knowledge of MRD negativity, that helps in terms of overall prognostication of your patient.

And also genomics is important. So it's not so much the ELN [European LeukemiaNet] classification that we know with intensive chemotherapy. But actually, there's a 4-gene classifier that helps to predict how well your patient is going to do. If they have a p53 mutation, unfortunately, they don't do that well. The median survival is unfortunately only about 6 months or so. Patients with signaling mutations that are often proliferative, like FLT3-ITD, KRAS, NRAS, PTPN11, those patients have an okay expectation, about a median survival of about 12 months. Anyone who didn't have any of those signaling mutations or p53 mutations, those patients do particularly well. And so that's something that I pay attention to.

The other thing that I think is really important is knowledge that it takes, on average, about 1 cycle to respond to azacitidine and venetoclax. So doing a bone marrow at the end of the first cycle, identifying if you've cleared the leukemia is really important, because if you've cleared the leukemia but the counts haven't recovered, then you hold ongoing venetoclax therapy, wait for that bone marrow to recover, counts to recover, and then continue with subsequent cycles. Most patients end up getting a 21-day, 14 to 21 days of...
venetoclax instead of a continuous 28-day venetoclax regimen to improve tolerability in patients who have obtained a remission.

The other thing I really want to talk about is a completely different clinical trial for patients with IDH1 mutations. This was the AGILE trial. And this led to the approval of azacitidine now with the IDH inhibitor, ivosidenib, for IDH1-mutated patient. So that's about 8% to 10% of older AML patients. And so it's certainly not the majority, but about 1 in every 10 patients will have an IDH1 mutation. And in the AGILE study we also saw a composite remission rate of about 60% or so. But what was particularly impressive is an overall survival in patients getting aza/ivo that initially was reported at 24 months, but we just saw updated long-term follow-up presented at ASCO and EHA, and it's now 29 months with longer follow-up. So patients with IDH mutations that receive azacitidine and ivosidenib can expect a greater than 2-year median overall survival with aza/ivo. So that's been a really nice new approval also for that specific targeted population.

There are other clinical trials that have led to approvals with low-dose cytarabine as a backbone, so LDAC, we call it low-dose cytarabine, with either venetoclax or with glasdegib, these are approved. I'm not going to talk about them too much, because they tend not to be the first choice of lower-intensity chemotherapy options, but they are available and potentially appropriate in patients, maybe, that have already received a hypomethylating agent. And so you're looking for a different backbone of therapy.

I'll finish what I'm talking about, patients not fit for intensive chemotherapy, with just a comment about transplants. So we don't tend to think about stem cell transplant for patients that have received lower-intensity therapy. They weren't fit for intensive chemo, are they fit for a transplant? But certainly, as the definitions are changing, as well as some patients just are sick from leukemia or sick from an infection because of the leukemia, and as they obtain a remission with lower-intensity therapy and do better and performance status improves, we absolutely should be thinking about transplant for these patients, because as I mentioned, you know, they tend not to be curative therapies. And so obtaining a nice remission and then transitioning to a transplant has, I think, a great long-term potential curative option for those select patients.

Dr. Erba:

Well, this has certainly been a fascinating conversation. Let me summarize.

First, it's important to gather all of the mutational data at the time of diagnosis because it helps to guide therapy and it can be used for measurement, for measurable residual disease. So that diagnostic evaluation is critical. And we now believe that it's safe and advisable to take the time to do that.

Second, it's not just 3+7 anymore. And I don't believe 3+7 should go away. There are patients who can be cured with intensive chemotherapy; those with core-binding factor leukemias, those with NPM1 mutations without a FLT3 or biallelic, or CEBP alpha mutations or the in-frame bZIP CEBP alpha mutations. And so those patients should be considered for intensive chemotherapy, if appropriate, and for the FLT3-mutated patients, if they have an ITD or TKD, they could receive midostaurin. If they only have an ITD, they can be treated with either midostaurin or quizartinib now.

And then the third, and the most important, I believe, is to remember the majority of our patients with AML are older with multiple comorbidities, and the VIALE-A trial that my colleague here, Dr. Courtney DiNardo, lead has improved the survival of older patients with acute myeloid leukemia. This is clearly practice changing. And we are already seeing improvements in survival in older patients with AML. But there's still yet a lot of work to be done.

That's all the time we have today. So I want to thank our audience for listening and thank you, Dr. Courtney DiNardo, for joining me and for sharing all of your valuable insights. It was great speaking with you today.

Dr. DiNardo:

It is always a pleasure to work with you. It was great to talk and thanks for the invitation.