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https://reachmd.com/programs/cme/clinical-innovation-in-aml/14103/

Released: 09/30/2022
Valid until: 09/30/2023
Time needed to complete: 30 minutes

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Clinical Innovation in AML

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[CHAPTER 1]

Dr. DiNardo:
We all know that risk stratifying and identifying potential targets for acute myeloid leukemia [AML] is complex, and busy clinicians are challenged to select the correct assessments in order to match the right patients to the right treatment.

This is CME on ReachMD. I am Dr. Courtney DiNardo at MD Anderson, and here with me today is Dr. Marina Konopleva.

Dr. Konopleva:
Hello, thanks for having me today.

Dr. DiNardo:
Of course. So let's go ahead and get started. Dr. Konopleva, let's set the stage for what will be this chapterized CME course. If you can please tell us about some of the key targets and pathways in AML.

Dr. Konopleva:
Certainly. So in the past we all knew that the AML is driven by chromosomal abnormalities and multiple chromosomal changes. But most recently, we have identified a lot of novel genetic aberrations, mostly mutations, and of course rearrangements as well. And some of them have become therapeutic targets for which we have drugs available.

So I would like to bring some examples of that. I think the well-established target is epigenetic modulators for which we have had hypomethylating agents quite a while ago used in patients ineligible for chemotherapy and having a response rate of about 20%. But recently, we have identified mutations in IDH1 and IDH2, which are actually metabolic enzymes that also alter epigenetic makeup of the cells. And fortunately, we have inhibitors of IDH1 and IDH2, ivosidenib and enasidenib, that both have entered clinical trials; both are approved for relapsed/refractory acute myeloid leukemia harboring specific mutations. But most importantly, they are now moving into the frontline based on the results of the recent study. Combination of azacitidine and ivosidenib has shown survival advantage and can now be used for all the patients unfit for the chemotherapy. And preliminary data from the intensive chemotherapy studies, 7+3 + ivosidenib, have also looked very encouraging.

The second large target that I would like to mention are signaling mutations, and the most well studied is mutation in FLT3. This is the cytokine receptor, and the mutations in that confers poor survival in acute myeloid leukemia and results in patients needing allogeneic stem cell transplantation.

We have now a range of different molecules, small molecule inhibitors of this pathway. And the first approved drug was midostaurin that

showed advantage when combined with 7+3 chemotherapy in intensively treated patients with AML in the randomized phase 3 study. Recently, the results of the study with quizartinib have also been positive in the same setting. And there are other inhibitors such as gilteritinib, which is right now approved in the relapse setting, but is also going into the frontline hopefully soon. So this is another pathway which we can target with the specific agents.

The next large target that was perhaps more recent is BCL-2. BCL-2 is pro-survival anti-apoptotic protein that is widely expressed in leukemic blasts and stem cells across different subsets of AML. And the inhibitor BCL-2 venetoclax has shown tremendous efficacy when combined with the low-intensity chemotherapy and, again, all the patients unfit for chemotherapy, which now has become a standard of care for the subset of patients.

But moreover, the addition of venetoclax is highly effective, also, when added to the chemotherapy, intensive chemotherapy such as 7+3 or FLAG-Ida. And the clinical trials are ongoing. The preliminary data indicate improved depth of response with this particular agent.

And finally, the target that we still don't know how to deal with is a mutant p53, which is commonly happening in patients who have complex cytogenetics, poor-risk AML, therapy-related acute myeloid leukemia. We still do not have specific agents that target this mutant p53, and this is an area of active investigation.

Dr. DiNardo:
So that was a fantastic overview. So just to kind of highlight a bit, you know, when we're talking about key targets and pathways, we're thinking about them in the context of our standard intensive chemotherapeutics and our epigenetically active remodeling agents, the hypomethylating agents. And then, so now we're thinking about, you know, signaling targets like FLT3 inhibitors in combinations. We're thinking about the IDH1 and the IDH2 mutations, the epigenetic and metabolic mutations. We're thinking about menin inhibitors, which are not currently FDA-approved, but are epigenetically active and relevant for patients with NPM1 and KMT2A-rearranged leukemias. And then not specific, you know, molecular targets, but as AML as a whole, the importance of BCL-2 inhibition and the new effectiveness of venetoclax in various combinations.

So a lot of key targets and a lot of really important pathways that we are developing great treatments for, and then still some areas of really unmet need, like patients with p53 mutations.

So, that wraps up our first chapter.

In Chapter 2 we'll be discussing optimal molecular testing for patients with AML, so stay tuned.

[CHAPTER 2]

Dr. DiNardo:
All right, welcome back. We were just discussing the important pathways in AML, and now we're going to move on to how and when we should be testing for various different molecular alterations.

So we have Dr. Konopleva with us. Tell us what molecular markers do you think we need to consider in AML, and when should we be testing for them?

Dr. Konopleva:
Thank you, Dr. DiNardo. So obviously, the question of when we should be testing those, the most important time is at diagnosis. But some of them are also important to be tested at the time of remission for assessment of minimal residual disease. And of course, at the time of relapse because the biology and genetics of leukemia may be changed, and that can dictate our therapy.

So what are the most molecular relevant markers for acute myeloid leukemia? Of course, we do get cytogenetics on every patient because complex cytogenetics defines the poorest patients who are a candidate for allogeneic stem cell transplantation.

As far as molecular testing, we routinely get the rearrangements. And then on top of that, the third test that we are getting molecularly are the mutations in the DNA coding genes. So there are multiple mutations that we'll look for, but as far as most significant ones, FLT3, that when mutated confers poor survival prognosis. IDH1 and IDH2 because we have targets and we can use the specific inhibitors for those. NPM1 is important, again, more as a prognostic marker because patients with NPM1-mutated AML without FLT3-mutated AML and without complex cytogenetics, they have what we call good prognosis, and they may not require allogeneic stem cell transplantation.

Dr. DiNardo:
When we talk about different mutations and when we should be testing them, I think that was actually really informative. So of course, we want to know mutations at diagnosis. We also want to know about changes in mutations at relapse, right? Because it can change, especially signaling mutations, FLT3 mutations, these can change, you know, at different treatment time points. And so you want to

know how to optimally treat your patient.

You know, and as you mentioned, in remission, too, it's actually really interesting, and I think more and more people are realizing the importance of checking for mutations in remission. You know, NPM1, for example, is a fantastic MRD marker. And in patients in remission who have persistent NPM1 that's lasting multiple cycles during consolidation, that's a high-risk feature, and that actually can change the risk category and make you think about a transplant.

So then when it comes to, you know, which mutations should we be testing for, you know, we look to our guidelines and our algorithms, especially the ELN AML classification guidelines. So we're looking for, you know, you want to know those different mutations that will tell us is our patient favorable risk and likely to be cured with chemotherapy alone? Or are they adverse risk, including those 8 to 9 mutations that you've identified that are MDS associated as well as p53? These patients have much higher risk. And we should be thinking about transplant for these patients if possible, once in remission. So these are the important mutations to be thinking about and really kind of the important times to be assessing them.

All right, so next we're going to focus on treatment considerations for AML. Stay tuned.

[CHAPTER 3]

Dr. DiNardo:
For those of you who are just tuning in, you are listening to CME on ReachMD. Dr. Courtney DiNardo here. Here with me today is Dr. Marina Konopleva. We are discussing the clinical innovations and the latest data on the use of BCL-2 inhibitors for the treatment of AML.

Welcome back. Now that we have discussed the complexity of genomics, so cytogenetics and molecular testing, let's explore some of the treatment considerations for our patients.

Dr. Konopleva:
Yes, Dr. DiNardo, the treatment landscape for AML has dramatically changed over the past 4 to 5 years. Can you please describe to us some of the treatments that are now available and how they fit into the complex clinical setting in AML?

Dr. DiNardo:
It's a great question, because things have gotten really complicated, which is great, because we have all these new treatment options for our patients, right? But it's challenging to make sure that you know exactly what is the best option for any particular patient that you're about to see in clinic.

So I still think about 2 different backbones of therapy for my AML patients. I'm assessing them, and I think, "Are you kind of a young patient who's fit for intensive chemotherapy?" And if so, I'm going to think about, you know, an intensive chemotherapy, so a cytarabine and anthracycline-based therapy. And if my patient is older, frail, a lot of comorbidities, then I'm going to think about a lower-intensity hypomethylating agent-based therapy. But a lot has changed within these 2 different cores and treatment backbones.

So, you know, for our younger intensive chemo-eligible patients, I think the most important updates are to be thinking about incorporating a FLT3 inhibitor if your patient is FLT3 mutated. So the standard of care right now is still midostaurin. But as Dr. Konopleva alluded to in the first chapter, there's actually a recent randomized phase 3 study that identified quizartinib as also a very effective FLT3 inhibitor in combination with 7+3. So we may be seeing kind of updated second-generation FLT3 inhibitors added in combination here.

Gemtuzumab ozogamicin is a CD33 monoclonal antibody, and we know in patients who are favorable-risk core-binding factor leukemia, which is an inversion 16 or an t(8;21), that we want to be adding gemtuzumab ozogamicin to our intensive chemotherapy to best give our patients the best chance of cure with favorable-risk disease.

And then I want to highlight the liposomal 7+3 formulation CPX-351, which is approved for fit patients with therapy-related disease or AML with MDS-related changes. That population is where the randomized study identified CPX-351 to be particularly effective.

So those are the things right now I'm thinking about. I'm also, you know, really excited about the incorporation of venetoclax with intensive chemotherapy. And those are some of the clinical trials that Dr. Konopleva and myself are both involved in. Right now, those are not kind of FDA-approved treatments. But I do think that, you know, as time goes on, we're going to see improved remissions, improved MRD-negative remissions with the incorporation of venetoclax with intensive chemotherapy.

And then about half or more of our newly diagnosed AML patients are really in that older, unfit, frail, comorbid group where we're thinking about an azacitidine or decitabine-based therapy. And this is where venetoclax has really changed the game. So venetoclax combinations with either azacitidine or decitabine, you know, are leading to two-thirds of patients obtaining a composite remission, improvement in overall survival. So this is my kind of standard for most patients.

And then, you know, the challenge, right, is what to do with your patients with p53 mutations? This is about 15% to 20% of our patients. Oftentimes, they're older; oftentimes, they have therapy-related disease. And these ones are particularly challenging. Right now, you know the standard is still the standard for them, but we know they don't respond as well. So I'm really looking forward to new treatment options, hopefully, in the future for these patients.

Dr. Konopleva:
This was a great summary. So the only thing I would like to add to that, that of course a lot of prognostic factors would determine the consideration for the stem cell transplantation. And so traditionally, we send patients for the allogeneic stem cell transplant if the risk of relapse is more than 40%. And then now, of course, we know which patients perhaps have the space in more granular fashion. For example, we know that patients with NPM1, if they have complex karyotype, they do not do very well. So they also need to undergo perhaps stem cell transplantation if they're eligible for that. And also patients with MDS-defining mutations, generally their outcomes are inferior. And as Dr. DiNardo mentioned, p53-mutated AML are clear candidates for allogeneic stem cell transplantation; we essentially have no cures without that.

I think these are all great summaries, and that will help us to stratify the patients and have perhaps personalized medicine that we've been talking about for such a long time.

Dr. DiNardo:
Thank you. So that was a great segue into our fourth and final chapter, where we will discuss some of the latest data in AML, and most specifically BCL-2 inhibition. Stay tuned.

[CHAPTER 4]

Dr. DiNardo:
And welcome back. After hearing about some of the treatments to consider for the management of AML, let's get a better understanding of the BCL-2 inhibitors and how this class is playing a role in clinical practice.

Dr. Konopleva:
This is clearly one of the most exciting agents that we have the luxury of working with over the last few years. And Dr. DiNardo, if you can review some of the latest data for venetoclax in AML, and put it into the context for our listeners.

Dr. DiNardo:
Yes, happy to do so. And really everyone should know that Dr. Konopleva was really instrumental in getting this combination of azacitidine and venetoclax approved for our AML patients. And I've been fortunate to work with her on some of the clinical trials.

So essentially, you know, azacitidine and venetoclax was evaluated in a randomized clinical trial, placebo-controlled phase 3 study looking at azacitidine with venetoclax compared to azacitidine with placebo. And it confirmed kind of what we've been seeing in our phase 1 and phase 2 clinical trials, where, you know, this combination really has changed the standard of care for our older AML patients not fit for standard intensive chemotherapy. You see a composite remission rate of two-thirds of patients, which is far greater than the 20% to 30% response rate that you could expect to see with azacitidine alone. We saw an improvement in overall survival to over a year median, which doesn't sound like a lot, but when you think about the fact that we have been treating AML the same way for over 40 years, and in these older, intensive chemo-ineligible patients, there had never been a study where the median survival had extended beyond that 12-month mark. And so this was really clinically meaningful. And even more so is that kind of regardless of the underlying genomics, you know, patients are benefiting more with a combination of venetoclax in addition to azacitidine than with azacitidine alone, meaning that there isn't really a population that you didn't see improved remission and response rates with. And so it really is appropriate across the board compared to azacitidine alone.

And what you see is that responses happen really quickly, too. The median time to response is about 1 cycle. So as opposed to waiting, you know, 4 to 6 cycles with azacitidine alone, you know, your patient is hopefully going to respond within the first 1 to 2 cycles.

And we talk a lot, you'll hear a lot about the VIALE-A's data and azacitidine with venetoclax. And that was the approved regimen based on the phase 3 study. But I think it's also really important to know that decitabine, which is the other hypomethylating agent, was also evaluated in the earlier studies and showed equivalent response rates as a backbone, as azacitidine did. And so actually, the approval is either decitabine or azacitidine, and in my clinical practice, I feel perfectly comfortable using either azacitidine or decitabine.

I think one of the most important things is, as more and more people I think are using these combinations, is that it's an easy regimen to give, but it requires a little bit of understanding how to optimize the therapy. And so I think the most important thing for clinicians that are listening to this to know is it's really important to do a bone marrow at the end of the first cycle because, again, many of your patients are going to have already obtained a response at the end of the first cycle. And if their counts haven't recovered yet but their leukemia is

gone, then that means that actually you should stop the venetoclax, wait a week or 2 before you start the second cycle, because you don't want to compound toxicity if their counts haven't recovered and the leukemia is gone.

So most of my patients that are on these therapies are typically getting, you know, their week of the hypomethylating agent, you know, about 14 days or so of venetoclax ends up being their happy place. I go from the continuous 28 days down to 21 days. Many patients stay there, but oftentimes they'll have to go down to 14 days for optimal tolerability.

And one thing that actually I presented at the European Congress this past June was the importance and the safety of using GCSF. So many patients have kind of ongoing neutropenia as part of their treatment course on a venetoclax combination. And it is safe and appropriate to use GCSF in those patients to prevent neutropenia, prevent neutropenic-related infections; it does not negatively impact their duration of remission or their overall survival. And if anything, actually, those patients receiving GCSF did the best.

And so I think those are some of the most important things to keep in mind when you're thinking about using a venetoclax/hypomethylating agent regimen.

Dr. Konopleva:
Thank you, Dr. DiNardo. This was a fantastic summary of hypomethylating agent/venetoclax trials. But of course we, as a field, are moving beyond that. And we hear a lot now about what we call triplet regimens under investigation. Can you please elaborate on the trials? What data can we derive from them from our patients? What are the challenges and advantages?

Dr. DiNardo:
Yes, absolutely. So I kind of alluded to that a little bit when I was talking about how – so most patients, you know, two-thirds of patients, right, are going to respond to azacitidine and venetoclax. And really it is regardless or independent of the genomics to a sense. But actually the durability of remission actually matters a lot in terms of what the patient's underlying genetics were. Patients with p53 mutations, patients with signaling mutations, like FLT3 mutations, these patients actually don't tend to respond as long. The durability of remission is lower; the median overall survival is lower. And so we really want to think about optimizing our therapy. And so adding something that's going to help, you know, adding something that we would call a triplet to try to improve the depth of remission and the durability of remission. So certainly, you know, FLT3 inhibitors make natural sense to think about incorporating with azacitidine and venetoclax to try to improve responses in patients with FLT3 mutations.

IDH1 and IDH2 inhibitors also exist, right? And so even though IDH-mutated patients do well with azacitidine and venetoclax, you know, can they do even better when we incorporate an IDH inhibitor into their regimen? And I think that's particularly relevant for the IDH1-mutated patients that don't do quite as well as the IDH2-mutated patients on just the doublet therapy of venetoclax and a hypomethylating agent.

p53-mutant patients, for sure, are an obvious area where we should be thinking about adding something, because as we've been referencing throughout this activity, these patients have really suboptimal responses and durability of responses with combinations.

So these are the things we're thinking about. You want to kind of add something that's going to improve effectiveness but not kind of augment side effects or toxicity. And so many, many clinical trials are under evaluation right now trying to do just that, identify other agents that can improve upon responses.

So, Dr. Konopleva, you know, in addition to triplets, another thing I think that's really important and has really changed in terms of how we think about our AML patient and the pathway that we go through in treating them is the idea of maintenance. And so what do you think about maintenance in terms of trials and, in particular, when you're thinking about venetoclax? And tell us about what your thoughts are on some of that data.

Dr. Konopleva:
I think maintenance will be very important in acute myeloid leukemia. Obviously has been tried with the different agents with different regimens for quite some time and has not been successful. I would pose that this is because we did not have good agents that could really perform in the maintenance setting, which means that they have to be effective and ideally not toxic to the patients, not having too many side effects.

So from historical data, the first agent that has shown efficacy in the maintenance setting was azacitidine in the trials done in Germany, in the randomized trials. Addition of azacitidine was shown to have a survival advantage in patients in AML. And most recently, the oral form CC-486 has shown, again, survival advantage for patients who were unable to proceed towards allogeneic stem cell transplantation in the maintenance setting given every 14 days out of 1 month. So this is a great success already. So we already have these hypomethylating agents as maintenance drugs that are approved.

The next drug that has been tried and perhaps will show hopefully success is a FLT3 inhibitor. In the original RATIFY study midostaurin

was used in the maintenance setting after allogeneic stem cell transplantation. But the data were not as clear as far as superiority of and need of using midostaurin in that setting. However, in the subsequent trial with the gilteritinib, the subset analysis of patients who received gilteritinib after allogeneic stem cell transplantation has shown survival advantage. And we're hoping that this year we will have the results of the randomized study where gilteritinib is used in the maintenance fashion that perhaps will show the improvement in survival and then will become a standard of care.

The other clear agent that can be used in the maintenance setting is inhibitor of IDH1 or IDH2. Again, we do not have the data yet. But there's a large study of HOVON [Dutch-Belgian Cooperative Trial Group for Hemato-Oncology] and German AMLSG group that will be testing ivosidenib or enasidenib in the maintenance setting of the patients who received the induction consolidation and followed by maintenance in genotype-specific manner.

And finally, of course, venetoclax has a great promise in maintenance because of its activity. There are several trials ongoing both post allogeneic stem cell transplantation where venetoclax is combined with azacitidine. And the second setting is where venetoclax is combined typically with hypomethylating agents IV or oral formulations in patients who are unable to proceed towards allogeneic stem cell transplantations.

These studies have not yet been reported. They are ongoing. I believe we will hear about some of them at this next ASH meeting. But one caveat to those, venetoclax, as we all know, as Dr. DiNardo mentioned, has a potential to reduce neutrophil count. And therefore, this maintenance that is – requires a lot of tweaking of the dose and duration of both agents in order for them to be viable, sustainable, and long term. But I believe we're certainly moving in that direction.

Dr. DiNardo:
Perfect. Well this has been just such a great conversation.

So, to summarize, I think the best way to think about it is we have now kind of what I've heard people refer to as a total therapy approach for AML. So it's not just induction consolidation. We're also thinking about, you know, are we consolidating with a stem cell transplantation, and even in patients who are not going to transplantation, we now have identified that maintenance therapies with well-tolerated, oral, outpatient therapies are effective. And as you mentioned, CC-486, the kind of oral azacitidine version, is now approved for patients that have received standard induction consolidation therapy who are not going to transplant, and that has improved their relapse-free survival and their overall survival. So this is now our standard.

And so we're looking continually at ways to improve upon the outcomes for all of our patients. And so I think maintenance is just one of the kind of new avenues of this total therapy that really is important to be aware of right now. As mentioned, CC-486 is the approved therapy. Certainly, patients with targets like FLT3, IDH1, IDH2-mutated patients, we're thinking about maintenance with those. And studies are ongoing. And of course, we know how effective azacitidine is with venetoclax for older unfit patients. Should we be thinking about maintenance approaches with CC-486 and venetoclax as soon as we identify that that is not only an effective but also easy, well-tolerated, oral outpatient approach? You know, I think that likely will modify our current standards as well.

So that's all the time we have for today. I want to thank you all so much for listening in and thank you, Dr. Konopleva, for joining me and for sharing all of your valuable insights. It was great speaking with you today.

Dr. Konopleva:
Thank you. It was a real pleasure for me, too. Thanks so much.

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