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AML Care: Examining the Efficacy and Safety of a Triplet Combination Therapy

Announcer:
You're listening to *Project Oncology* on ReachMD, and this episode is sponsored by Stemline, a Menarini Group company. Here's your host, Dr. Charles Turck.

Dr. Turck:
Welcome to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and here with me today is Dr. Anthony Stein, who is a Professor in the Department of Hematology and Hematopoietic Cell Transplantation at City of Hope in Duarte, California where he's also the Associate Director of the Gehr Family Center for Leukemia Research at the Hematologic Malignancies Research Institute. Together, we'll be discussing a recent Phase 1B trial that examines the use of tagraxofusp, or 'tag', and azacitidine with or without venetoclax in patients with acute myeloid leukemia, or AML for short. Dr. Stein, thanks for being here today.

Dr. Stein:
Thank you for inviting me.

Dr. Turck:
So if we start with some background on tagraxofusp and azacitidine, Dr. Stein, what have previous studies looking at these AML treatment options found?

Dr. Stein:
Once tagraxofusp binds to the leukemic cell, the toxin is released and internalized into the leukemic cell, causing cell death. Around 2010 or 2011, there were studies done looking at tagraxofusp as a single agent for patients with relapsed/refractory AML, and at that time, it was shown to have single agent activity in the setting of relapsed/refractory AML.

Learning further about the drug and doing in vitro testing, it was learned what causes resistance to tag. And unlike other immunotherapies, when a patient's leukemia stops responding to tagraxofusp, the CD123 expression is not changed. Rather, it's a resistance mechanism affecting the way the diphtheria toxin works against the cell. And it's been basically found that the resistance to tagraxofusp is mediated by methylation and downregulation of diphthamide genes, and then this eliminates the diphthamide target for the diphtheria toxin. What's been found is that by adding azacitidine to tagraxofusp, this will increase the diphthamide expression and restore the diphtheria toxin target. And then in xenograft models, it's also shown that combining tagraxofusp with azacitidine, you get a better overall survival.

Dr. Turck:
So with that background in mind, let's zero in on the recent Phase 1B trial. What could you tell us about the study design?

Dr. Stein:
So the study design started off looking at the doublet combining azacitidine with tagraxofusp, and this was done as a Phase 1 study with dose-escalation of the tag. The ultimate safe dose that was determined was giving azacitidine for 7 days at a standard dose and giving the tagraxofusp for 3 days—not 5 days as when it's given as a single agent. And this was found to be the dose that was taken forward.

Then, while that study was going on, we also found that the leukemic cells have an altered mitochondrial apoptosis threshold and an increased propensity to undergo cell death in the setting of a BCL2 inhibitor. And at that time, it was decided to add venetoclax to the doublet, so we basically created a triplet. Again, we went through a dose-finding study, and it was found that azacitidine/venetoclax,

again, combined with tagraxofusp that's given for 3 days on day 4, 5, and 6 was the best-tolerated regimen.

Dr. Turck:
And as a follow-up to that, what could you tell us about the patients who were included in this study?

Dr. Stein:
So the patients included in the study were basically patients with newly diagnosed AML that, by ELN criteria, had adverse cytogenetics or they had relapsed/refractory AML.

Dr. Turck:
For those just joining us, this is *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Anthony Stein about recent research on a potential combination treatment for acute myeloid leukemia.

Now if we take a look at the results of the study, Dr. Stein, how effective were azacitidine, venetoclax, and tagraxofusp, or 'tag', when combined?

Dr. Stein:
So the triplet seems to be superior to those results that were previously seen with azacitidine/venetoclax studies. Obviously, this is not a randomized study, but just comparing one study to the other, it seems that by using the triplet combination, the relapse-free and overall survival seem to have improved.

Most of the patients in the study had adverse cytogenetics, including TP53 abnormalities. But again, the only way you're going to be able to find out whether this triplet is better than just azacitidine/venetoclax alone is through a randomized study.

Dr. Turck:
And turning to safety, what adverse events did patients experience when receiving these treatments?

Dr. Stein:
So the major adverse events were cytopenias that we normally encounter when treating patients with azacitidine and venetoclax, but these were manageable with transfusional support and infection-preventing medications. But as far as toxicities that are attributed to tagraxofusp, such as liver function abnormalities and capillary leak syndrome, the frequency and severity of these were much lower, and this may be related to venetoclax's effect on the endothelium that's preventing capillary leak syndrome. The other reason may be because the tagraxofusp is only given on day 4, 5 and 6, so patients are already seeing 3 days of venetoclax/azacitidine, and this may reduce the tumor burden before exposure to tag.

Dr. Turck:
As we come to the end of our program, Dr. Stein, let's look ahead for just a moment. What are the next steps for this line of research?

Dr. Stein:
Before you can say tagraxofusp adds additional benefit to azacitidine/venetoclax, either a Phase 2 randomized or a larger Phase 3 randomized study would need to be performed.

There is another rare disease entity called blastic plasmacytoid dendritic cell neoplasm, which also highly expresses CD123, and there's currently a trial going on, again, using the triplet therapy for this disease. We expect to present some results this coming year, but so far, using the triplet seems to be very promising. We see less toxicity than when you use single-agent therapy. We're just waiting to see if the overall response rate, relapse-free survival, and overall survival have been improved by the triplet.

Dr. Turck:
Well, with those forward-looking insights in mind, I want to thank my guest, Dr. Anthony Stein, for joining me to discuss how tagraxofusp, azacitidine, and venetoclax might impact patients with acute myeloid leukemia. Dr. Stein, it was great having you on the program.

Dr. Stein:
Thank you.

Announcer:
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