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Venetoclax and Palbociclib in AML: Exploring New Findings

Announcer:
You're listening to *On the Frontlines of AML and ALL* on ReachMD. And now, here's your host, Ryan Quigley.

Ryan Quigley:
Welcome to *On the Frontlines of AML and ALL* on ReachMD. I'm Ryan Quigley, and today, I'm joined by Dr. Jeffrey Tyner and Dr. Melissa Stewart, who recently led a study on the use of venetoclax and palbociclib in the treatment of acute myeloid leukemia, or AML. Dr. Tyner is the George Ettelson Endowed Professor of Medicine and Co-Leader of the Translational Oncology Program at the OHSU School of Medicine and Knight Cancer Institute.

Dr. Tyner, it's a pleasure having you with us.

Dr. Tyner:
Thanks so much for having me. It's great to be here.

Ryan Quigley:
Also joining us from OHSU is Dr. Stewart, who's a Research Assistant Professor at the School of Medicine and Knight Cancer Institute.

Dr. Stewart, thank you for being here.

Dr. Stewart:
Hi. Thank you for having me.

Ryan Quigley:
So, Dr. Tyner, to start us off, could you walk us through the current treatment landscape for AML and why drug resistance remains such a major challenge in patient care?

Dr. Tyner:
Well, for much of the past 50 years or so, for AML, there had been only one single drug regimen that was available to patients, and this was an intensive chemotherapy regimen that combined alkylating agents with nucleoside analogs. And patients who received this regimen oftentimes could go into a remission, but unfortunately, the majority of patients would subsequently relapse, and treatment options and outcomes thereafter were quite dismal.

In addition to that, a large percentage of AML patients weren't even eligible for this intensive chemotherapy regimen. More elderly patients or patients who had less fitness, which describes maybe as much as half of AML patients, were not even eligible for this intensive chemotherapy regimen. And they received less intensive versions, which really had poor outcomes.

The good news is that over the last 10 years or so, the landscape has begun to change quite dramatically, with a number of new agents coming into play. One of the most prominent of these is a BCL2 inhibitor called venetoclax combined with a class of drugs called hypomethylating agents. And this regimen has become available for those more elderly, less fit patients who could not receive the intensive chemotherapy regimen. This came with great improvements in remission rates for these more elderly patients. But unfortunately, almost all of these patients do subsequently relapse with, again, not good outcomes after that relapse.

And then the other drugs that have been approved have been more targeted to specific mutational subsets of disease, again, with some good initial response rates. But again, invariably, most patients develop disease relapse and drug resistance.

So the good news is that we have an expanding universe of drug regimens that are options for AML patients used sometimes as single

agents, used sometimes in combinations. This has definitely expanded the options for patients, and while many of these drugs are successful initially, unfortunately, the vast majority of patients will develop drug resistance and disease relapse eventually. We really need new options that will provide more durable responses, more durable remissions, and better outcomes for patients.

Ryan Quigley:
Now, Dr. Stewart, your team identified venetoclax paired with palbociclib as a promising coupling in AML treatment. How did you arrive at that combination?

Dr. Stewart:
Our lab has been studying drug sensitivity and resistance in AML for many years. As part of this work, we routinely receive peripheral blood and bone marrow samples from patients with AML and evaluate how their leukemia cells respond to different therapies in ex vivo drug sensitivity assays. So basically, to do this, we isolate the primary cells from the patient sample and plate them on these 384-well plates that contain a library of small molecule inhibitors, and the tumor cells from the patient are exposed to those inhibitors in culture for three days. And then we measure the cell viability and obtain IC50 and AUC values, which allow us to quantify how sensitive a patient's tumor cells are to those individual inhibitors, or a combination of inhibitors.

So, as Jeff mentioned, the combination of venetoclax plus the hypomethylating agent azacitidine has become the standard of care for elderly AML patients who cannot receive intensive chemotherapy. However, the relapse and resistance continues to be a major problem. So, in an effort to find improved therapies, colleagues in our lab published a study in 2023 where they used the ex vivo platform that I described to compare venetoclax in combination with azacitidine to 25 novel ven-based drug combinations. And in this study, they found that several of those combinations performed similarly to standard of care venetoclax plus azacitidine. Surprisingly, most combinations actually showed greater potency and efficacy in killing the tumor cells in this assay. Among those combinations that were tested in this study, venetoclax and the CDK4/6 inhibitor palbociclib was among the most effective and potent combinations. So, this was the initial motivation to study this combination in greater detail.

And interestingly, what we found with single-agent venetoclax or palbociclib was these drugs were more effective on the AML cells that are of a more primitive, undifferentiated cell state. And when you use venetoclax in combination with palbociclib, this actually switches to a greater efficacy of the combination on the more monocytic differentiated cell types, which are typically the cell types that are resistant to venetoclax and still present at relapse.

Ryan Quigley:
For those just tuning in, you're listening to *On the Frontlines of AML and ALL* on ReachMD. I'm Ryan Quigley, and I'm speaking with doctors Jeffrey Tyner and Melissa Stewart about early findings on pairing venetoclax with palbociclib in AML.

So, Dr. Stewart, sticking with you here, your findings suggest that AML cells exposed to venetoclax alone may adapt by increasing protein production. Can you explain that survival mechanism and how palbociclib interrupts that?

Dr. Stewart:
In our paper, we show that primitive AML cells, which, as I mentioned, are more sensitive to venetoclax, have a higher basal rate of protein synthesis compared to monocytic AML cells, which are typically resistant to venetoclax. So, when we exposed cells to venetoclax alone, we saw an increase in protein synthesis. However, because the primitive cells are already operating at a relatively high level of protein synthesis at their baseline, they have a limited capacity to further increase protein synthesis following exposure to venetoclax. So, because this adaptive pathway isn't available to the primitive cells, this likely contributes to their sensitivity to venetoclax alone, and the addition of palbociclib would not provide an added benefit to these primitive cells.

In contrast, the monocytic AML cells have a lower basal protein synthesis rate, and following venetoclax exposure, they would be able to increase protein synthesis as an adaptive mechanism, which makes them resistant to single-agent ven. But the addition of palbociclib blocks the ven-induced increase in protein synthesis, which leads to synergy with the combination. Mechanistically, we found that venetoclax treatment also increased protein expression of some translational regulators that are downstream of mTOR, including 4E-BP and phospho 4E-BP, and palbociclib was able to block that increase in those translational machinery proteins.

And we also looked at MCL-1 protein expression, which is commonly upregulated in cells that are resistant to venetoclax and is also regulated by mTORC1 cap dependent translation. And in our study, we found that venetoclax in combination with palbociclib greatly reduced the expression of MCL-1 as well.

So moving forward, we're very interested in looking more closely at this mechanism and are planning some additional studies to get some further information about how this might be working in patient samples.

Ryan Quigley:

And Dr. Tyner, turning to you now, palbociclib is currently approved for breast cancer, but these findings suggest it could also have a role in AML. What does this tell us about shared biological pathways across these different types of cancer?

Dr. Tyner:
I think at a basic level it tells us that these shared pathways absolutely exist. CDK4/6 is clearly an important target in breast cancer. These drugs clearly work very well there. But CDK4/6 expression is not limited to breast tissue. These genes are expressed, these proteins are expressed pretty ubiquitously, certainly in myeloid and in white blood cells. And what our data suggests is that there is dependence on these pathways in AML cells in a very similar way as there is dependence in the breast cancer cells. As Dr. Stewart mentioned, one thing that's really enticing here is that this CDK4/6 dependence appears to exist in some of the disease subsets of AML that are most problematic for some of the existing therapies, such as venetoclax and hypomethylating agents.

I think this shows us that these commonalities absolutely exist. And I think it also tells us that we need to be sometimes maybe a little more open-minded about opportunities for drug repurposing. I think there sometimes in research can be a proclivity to continue studying drugs in a bit of a narrow fashion and to continue studying the same drugs that are already existing and approved in a particular cancer type. And that way of doing things is really, I think, a great way of not discovering new uses for drugs and drug repurposing opportunities. So, I think it's important to be open-minded about drugs, even though they might be used in a very different cancer setting; there could still be a great opportunity to repurpose those drugs in a setting of different interest.

Ryan Quigley:
Now, Dr. Stewart, something else that's interesting is you used genome-wide CRISPR screening to better understand how venetoclax and palbociclib interact. So, what did that approach reveal about the synergy between the two treatments?

Dr. Stewart:
We used the approach with the CRISPR screen to really support what we had already found in our patient sample data, which was that in the patient samples which showed synergy with venetoclax and palbociclib in our ex vivo drug assays, when you look at the genes that were downregulated in that patient cohort, there was a large downregulation in genes and pathways that were involved in protein synthesis.

We thought in our CRISPR data we would also look for genes that when lost would uniquely confer sensitivity to venetoclax, but would show no evidence of an effect from the combination treatment. This would suggest that loss of these genes could sensitize cells to venetoclax.

So, the pathway analysis showed the most highly enriched pathways were related to cell cycle, which was a nice proof of principle since the primary function of palbociclib is to inhibit the cell cycle, and the other most highly enriched pathways were related to protein synthesis. The data from the patient samples and the CRISPR screen were both leading us to mechanisms involving protein synthesis, which is what we went on to show. So, our data does suggest that CDK4/6 inhibitors not only work through cell cycle inhibition, but that they also have an ability to affect protein translation by decreasing the translational machinery, which is an added benefit in this context when used in combination with venetoclax.

Ryan Quigley:
Thank you for that. And finally, if we look ahead for a moment, Dr. Tyner, what are the next steps for translating this research into clinical trials?

Dr. Tyner:
This is an area that we're actively pursuing. We have been having a lot of conversations with clinical colleagues, and we're hearing a great deal of interest and enthusiasm about parlaying these findings into a clinical trial. We're running into a few hurdles, you might call them business development hurdles, in that the existing FDA-approved CDK4/6 inhibitors, including palbociclib, are drugs that were developed some time ago and are therefore nearing the end of their patent life. There are newer drugs that are targeting CDK4 and other CDK family members that are also of interest, but those are very early in the development stage and probably not yet candidates for an AML clinical trial.

Nonetheless, there do appear to be some routes through the National Cancer Institute that might make some of these drugs available as well as looking at some of these newer drugs that are coming into play. So, we are pursuing all possible avenues, and we're really excited about trying to get a clinical trial off the ground testing venetoclax with a CDK4/6 inhibitor, probably in combination with hypomethylating agents as a novel triplet.

Ryan Quigley:
And that's a great look ahead as we come to the end of today's program. I want to thank my guests, Drs. Jeffrey Tyner and Melissa

Stewart, for joining me to discuss their research on combining venetoclax with palbociclib in AML.

Dr. Tyner, Dr. Stewart, it was great having you both on the program.

Dr. Tyner:
Thanks so much, Ryan.

Dr. Stewart:
Yes. Thank you so much for having us. We appreciate the opportunity.

Announcer:
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