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Evaluating a Treatment for HER2-Positive Metastatic Breast Cancer

Dr. Chalasani:
For patients with HER2-positive metastatic breast cancer, there have been significant improvements in treatment with pertuzumab/trastuzumab and T-DM1, but more recently, a new drug, trastuzumab/deruxtecan, or T-DXd for short, has been making waves. It has been shown to be very effective in the third-line setting. However, most recently there have been studies exploring it earlier on, and today we'll dive into the study exploring the efficacy and side effects from this treatment in the second-line setting.

Welcome to *Project Oncology* on ReachMD. I'm Dr. Pavani Chalasani. And joining me today to talk about the DESTINY Breast03 trial is Dr. Erika Hamilton, the Director of the Breast Cancer and Gynecologic Cancer Research Program at Sarah Cannon Research Institute at Tennessee Oncology.

Dr. Hamilton, thanks for joining us today.

Dr. Hamilton:
Thank you so much for having me.

Dr. Chalasani:
All right. So, let's begin with some background on the DESTINY Breast03 trial. Can you tell us about the study design?

Dr. Hamilton:
Absolutely. So, trastuzumab/deruxtecan is not a new drug for us in breast oncology. As we know, it was initially approved for patients that had seen at least two previous regimens for HER2-positive breast cancer, so in other words, it was for third line and beyond. And specifically, the DESTINY Breast03 trial looked at trastuzumab/deruxtecan versus T-DM1, so the so-called standard second-line regimen at that point, and the results were previously reported resulting in a 72 percent reduction in the risk of progression with trastuzumab/deruxtecan compared to standard T-DM1. And what was updated at ASCO 2022 was essentially follow-up and more safety information comparing trastuzumab/deruxtecan to traditional T-DM1.

Dr. Chalasani:
Great. Thank you. So, I know you briefly mentioned about the results, but in general, when the results were announced, had it changed your practice?

Dr. Hamilton:
Yeah. So, you know, it had already been presented in terms of the 72 percent reduction in the risk of progression. What we updated at ASCO was—now with a longer median duration of treatment for trastuzumab/deruxtecan, so the treatment duration is now over 16 months—we looked at in general grade three or higher treatment-emergent adverse events, and really, they were quite similar between trastuzumab/deruxtecan and T-DM1: 53 percent with T-DXd, 50 percent with T-DM1. We also looked at side effects leading to the drug being stopped, and that was a little bit more frequent for trastuzumab/deruxtecan. About 14.8 percent of patients had to have drug stopped versus only 7.3, but this was largely driven by the about 8 percent of patients receiving trastuzumab/deruxtecan that had to stop drug due to ILD or pneumonitis. We also looked at side effects kind of across the board, so nausea, vomiting and alopecia, or in other words hair loss, was more common with trastuzumab/deruxtecan whereas fatigue was actually quite similar between the arms.

I think one of the new things we looked at that I wasn't as familiar with is something called exposure-adjusted incidence rates, or EAIRs. And really, exposure-adjusted incidence rates are looked at for trials where the treatment duration and follow-up may be different between the arms to really kind of, in other words, standardize what we see in terms of adverse events based on how long somebody

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may stay on drug. We know that our patients on trastuzumab/deruxtecan had a much higher treatment duration than those with T-DM1. And when we looked at these exposure-adjusted incidence rates, everything was actually lower with trastuzumab/deruxtecan compared to T-DM1 except for that adverse event leading to treatment discontinuation that was driven by the ILD pneumonitis.

Dr. Chalasani:
Yes, that was something, I was not familiar with until I heard you talk about that during the ASCO, so thank you for going in detail and explaining that even further. So, digging a little bit deeper into the ILD that you were mentioning, but any other, you know, ILD or any other adverse events or special interests which were unique to this class of agents?

Dr. Hamilton:
Yeah. I think that there are two adverse events that it's probably important to understand. So let's tackle the ILD pneumonitis first. So about 8 percent of patients had to discontinue due to ILD pneumonitis, and that's really because of the increased awareness and recommendations around ILD pneumonitis with trastuzumab/deruxtecan. I think we all remember back in the initial DESTINY Breast01 trial that there were cases of fatal pneumonitis that I think worried us about bringing this drug, you know, up into earlier lines. Luckily, in DESTINY Breast03 with these increased recommendations—that I'll dive into in a second—we saw a 10.9 percent ILD pneumonitis rate but no grade four or grade five, and grade three was actually only 0.8 percent, so we've managed to eliminate these serious cases of ILD pneumonitis. And again, this is around the recommendations that the drug be discontinued for grade 2 ILD pneumonitis or higher. And a little bit different from some other drugs, like immunotherapy, etc., we even hold the drug for grade one pneumonitis. If the pneumonitis resolves on imaging within four weeks, we can rechallenge the patient. If it does not, then we don't rechallenge the patient. And so, what this has taught us is that when we're a little bit more vigilant and a little bit more strict with our holding around trastuzumab/deruxtecan, that we can very safely give this drug and eliminate the more serious cases of ILD.

The other side effect that I think is pretty important to have awareness around is the nausea and vomiting that I spoke to. You know, this is more common with trastuzumab/deruxtecan than, say, another drug like T-DM1. In general, it tends to be mild and manageable, but what's important is, when we were initially enrolling patients in DESTINY Breast03, there were no mandatory antiemetic, you know, in a prophylactic fashion. Now, because we recognize that trastuzumab/deruxtecan is moderately emetogenic, it's actually recommended to use a multidrug regimen up front to prevent nausea and vomiting in our patients before it occurs, and so, most often in the United States, and in my practice, this is a three drug regimen. This is a 5HT3, dexamethasone or a steroid, as well as an NK1. And I think now that we're doing this, now that it's part of trastuzumab/deruxtecan's label, we're really doing an even better job treating nausea in our patients.

When we looked in the assays of the study kind of over time, it looks like nausea, vomiting, as probably would be expected, peaks in the first or second cycle, but it really stays pretty consistent over time. It doesn't get worse. It also doesn't go away. And so I normally start with this 3-drug regimen for my patients. If they're not having any nausea, we can drop things out. If they are having nausea, we can add things on. But I think that the three drug regimen is a good place to start.

Dr. Chalasani:
Yeah, great. Thank you. Yes, that is definitely something we should definitely take into account because that is something the patients experience as they're getting treatment.

For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Pavani Chalasani, and I'm speaking with Dr. Erika Hamilton about the DESTINY Breast03 trial for HER2-positive metastatic breast cancer. So, one other quick thing just to ask and follow up for the ILD. Do you routinely recommend the testing, like pulmonary function tests, like prior to patients starting on therapy, you know, if they have any prior history, or why lung therapy? Is it something you do in your practice?

Dr. Hamilton:
Yeah, that's a great question. I think that's a question that a lot of people have been having. You know, is there a way to predict this before it happens, or is there a way to pick out individuals that may be high-risk? It doesn't look like pulmonary function testing helps us much. You know, there's been a lot of analyses across studies about, you know, maybe people with a smoking history or do they have higher rates. We really can't figure out who it is that gets interstitial lung disease pneumonitis. And the mechanism is still a little bit unknown. The best way for us to manage this and monitor it really is with routine CT scans, and so, for many of our patients, this happens at the restaging scans that we're doing anyway for their treatment. So, certainly, you know, grade one is asymptomatic pneumonitis ILD that's only picked up on a scan. Grade two is any symptomatic ILD. So, if a patient's complaining of new cough or shortness of breath, that's a grade 2 event, and so that's somebody that the drug should not be restarted in.

How this plays out in my clinic is that with trastuzumab/deruxtecan, you know, for a drug that somebody may be on for two years, etc., a CDK 4/6 inhibitor, often times I may space out the scanning interval a little bit. For trastuzumab/deruxtecan, because I kind of need

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those scans to find this early grade one pneumonitis ILD before it gets more severe and the patient wouldn't be able to go back on therapy, I tend to not stretch their scans out much beyond two months, and so I really kind of keep my scanning interval pretty consistent as a way to find this pneumonitis ILD in about 10 percent of patients that it will happen for before it becomes problematic for the patient.

Dr. Chalasani:
Thank you for that. So, one of the things that I just wanted to ask is in the context of clinical practice, how have you been applying these results in the treatment strategy for patients with HER2-positive metastatic breast cancer?

Dr. Hamilton:
Yeah. It's always a, you know, a little bit of an interesting spot when we get a trial result but yet we don't quite yet have the expanded label. It's always easier to get the drug for that indication if it's already an approved drug, like trastuzumab/deruxtecan is, and so I have been successful going ahead and getting it for patients in second line. We anticipate seeing an approval and expanded label and, you know, as part of NCCN/ASCO/ESMO guidelines, etc., shortly. But, you know, I think that this really was pretty impressive in its magnitude of benefit compared to T-DM1 in the second-line setting, and so I do think that this is going to become our new standard for second line. Certainly, our current standard for first-line metastatic HER2-positive disease is a taxane in combination with trastuzumab and pertuzumab, and then we certainly have other drugs available in neoadjuvant, adjuvant setting, etc.

I think it's important to note, you know, where will trastuzumab/deruxtecan end up. We certainly have approval third line and beyond. We now have this result in second line. There are a host of trials looking at trastuzumab/deruxtecan in the first-line setting. There are trials looking in so-called KATHERINE setting, so for patients that have neoadjuvant therapy and have residual disease where we would typically think of T-DM1, there's a head-to-head T-DM1 versus trastuzumab/deruxtecan trial. And then there are also neoadjuvant trials, asking, you know, whether we can give trastuzumab/deruxtecan for several cycles up front and avoid traditional chemotherapy, or as I like to tell my patients naked chemotherapy that isn't targeted specifically to the cell.

Dr. Chalasani:
Oh, great. Is there anything else you wanted to comment on or speak or expand on?

Dr. Hamilton:
I guess the one other important thing to maybe just mention about trastuzumab/deruxtecan is obviously the plenary presentation at ASCO, in June of 2022, for our HER2-low patients, and I think this is really a paradigm shift. You know, we certainly have had trials testing trastuzumab or other HER2 agents in patients that may not be HER2-high or traditional FISH-positive or 3-plus by IHC but have some HER2 expression, and they've been negative, but trastuzumab/deruxtecan in DESTINY Breast04 was certainly positive by a landslide. And I think this really just speaks to the different mechanism of action, the antibody drug conjugate in particular, and also the bystander effect of a drug like trastuzumab/deruxtecan where it may only take a very little amount of HER2 expression to get the drug in and then influence cells around it to die. So I think that there's a few action points from that.

You know, certainly this spans across what we would typically consider triple-negative and hormone receptor-positive disease, and really, this is probably about 50 percent of our breast patients that this is actionable for. And so I think, you know, our job in the community as oncologists, you know, across the United States is to make sure that we're having these conversations with our pathologists, that an IHC of 1-plus or 2-plus is now actionable, and to make sure that this information is in our notes. I have to admit that some of my notes, you know, would say kind of, you know, HER2-negative by FISH and maybe dismiss the IHC, and over the past year or so, I've definitely been going back and making sure that I capture this information as this is very soon going to be actionable for our patients that we would traditionally consider triple-negative or hormone receptor-positive that have some low HER2 expression.

Dr. Chalasani:
With that information in mind, I want to thank my guest, Dr. Erika Hamilton, for sharing her insights on the DESTINY Breast03 trial for HER2-positive metastatic breast cancer. Dr. Hamilton, thank you for being here today.

Dr. Hamilton:
Thank you so much for asking me to be here. I enjoyed it.

Dr. Chalasani:
I'm Dr. Pavani Chalasani. To access this and other episodes in our series, visit reachmd.com/projectoncology, where you can be a Part of the Knowledge. Thanks for listening.

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