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Second-Line Solutions in Metastatic TNBC: ADC Selection, Sequencing, and Safety

Dr. Traina:
Welcome to this educational series on treating triple-negative breast cancer, including antibody-drug conjugate selection, sequencing, and management of toxicities.

This is CME on REACH MD, and I'm Dr. Tiffany Traina, breast medical oncologist at Memorial Sloan Kettering Cancer Center in New York.

Dr. Bardia:
Hello, and I'm Aditya Bardia, medical oncologist at UCLA.

Dr. Traina:
Thanks so much. So, Aditya, we're going to get started and we're going to do it in the context of a case. We'll start with a 42-year-old woman who has a family history of early-stage and early-onset breast cancer. Although her germline genetic testing is wild-type, BRCA1 and BRCA2 are negative. And about 3 years ago, she was found to have a T1CN0 triple-negative breast cancer.

That was HER2 0 at the time, and that was found just on routine screening mammography. She had up-front breast conservation surgery. She received adjuvant chemotherapy reasonably with dose-dense AC-T and radiation therapy and then entered observation. And 2 years after that, a CT scan, performed in the setting of a persistent nagging cough, found bilateral pulmonary nodules, quite large in size, as well as suspicious bone lesions and some adenopathy. So a lymph node biopsy was performed, confirmed metastatic breast cancer that was ER0, PR0, HER2 0 PD-L1, had a CPS of 20. She had some somatic sequencing done that was entirely unrevealing, and so she went on to first-line paclitaxel with pembrolizumab given her PD-L1–positive tumor. And she felt much better. Cough resolved. She did great for about 9 months. And then a routine follow-up CAT scan showed progression of disease with liver lesions. She had ctDNA sent off at that time, and again, no new actionable mutations.

So I guess with that all-too-familiar history and story. I'm wondering what you think we should be considering in terms of knowing the pivotal ADC clinical trial data that we have now that we're looking at a second-line setting for a woman with a metastatic triple-negative breast cancer.

Dr. Bardia:
Yeah, no, absolutely. As you said, this is not an uncommon scenario in a young patient with disease recurrence related to triple-negative breast cancer. And this patient did receive what we would recommend in the first-line setting, which would be chemo plus pembrolizumab for PD-L1–positive metastatic TNBC.

In the second-line setting, the preferred medication usually is sacituzumab govitecan, and that's based on the ASCENT study, which showed that SG was superior to standard of care chemotherapy in this setting, with improvement not only in progression-free survival, but improvement in overall survival as well. And if we look at different subgroups, including patients with PD-L1–positive disease, the benefit with SG was maintained. And now we have real-world data as well, confirming efficacy of SG in this setting.

For patients with HER2–low metastatic TNBC in the second-line and plus setting, there are 2 options. One would be T-DXd and the other would be SG. SG works regardless of the HER2 expression. And given what we've seen from phase 3 ASCENT clinical trial in general, that's the preferred agent. T-DXd and DESTINY-Breast04 were largely for hormone receptor–positive breast cancer.

Only approximately 10% of patients had TNBC in that study, and evaluation of T-DXd for patients with TNBC was an exploratory endpoint. It was not the primary endpoint. So from a level-of-evidence perspective, generally I prioritize SG over T-DXd, although that's certainly another option to consider and as per guidelines as well.

Dr. Traina:
Do you want to just spend a moment touching on what the toxicity is that we should be aware of?

Dr. Bardia:
Yeah, that's a great point. So with any drug, we talk both about efficacy as well as side effects. The efficacy with SG was established in the ASCENT study, and the trial also provided information in a phase 3 setting related to toxicities with SG as compared to standard chemotherapy. There are 3 toxicities that I usually counsel my patients about when I'm talking about the drug.

The first is diarrhea. Usually give a prescription of loperamide as well so they have that medication. The second is neutropenia, and I counsel patients that it's likely that your counts would decrease something that we'll monitor. And often, I do consider G-CSF generally as secondary prophylaxis for management of neutropenia.

And the third side effect is alopecia. The drug uniformly causes alopecia, so it's important to counsel patient about this side effect.

Now, in your practice, Tiffany, are there other AEs you've observed and what's your strategy when you talk about side effects?

Dr. Traina:
Yeah, I think it's very similar to what you've discussed already. The ones that you described are consistent with what we're experiencing in clinic and what was seen in the literature and in the clinical trials. So I think we very much share an experience and recommendations there. I think that one of the questions we get a lot about is how to choose patients for different agents in the second-line setting. And many times we're doing that primarily by efficacy as well as consideration of toxicity. So building on what you've talked about in the ASCENT trial, when we look at guidelines that are out there from NCCN and ESMO and ASCO, sacituzumab is there in that second-line setting as really a recommended agent, and that's regardless of biomarker.

But we also have other ADCs in this space, like trastuzumab deruxtecan, limited to those patients that have HER2–low expression, and so we struggle sometimes with thinking about, okay, how do we sequence these agents? I share your practice pattern of generally leading with sacituzumab in the second-line setting but also consider some of the real-world evidence we've seen around sequencing these agents. We know that the antibody-drug conjugate that's used first seems to do much better, has greater efficacy, and there is still some efficacy to the third-line antibody-drug conjugate. We eagerly await the prospective sequencing studies that are designed and that are ongoing right now, but I do sort of lean towards that preference for sacituzumab as my second-line choice, reserving T-DXd for third line in those patients that have HER2-low to help with that patient selection.

And building on the toxicity comments that you've made, sometimes toxicity is a limitation in which agents I might choose. So those patients that might have a compromised left ventricular ejection fraction, we remember that T-DXd does have that antibody against HER2, which can cause some issues with LV function. We're sensitive to the ILD toxicities. In the terms of sacituzumab, GI toxicity and diarrhea is one of the more common grade 3 adverse events seen. Although in the real-world evidence, we've seen G-CSF use be able to mitigate neutropenia and agents like Imodium be able to mitigate the diarrhea. So I think in making these choices around sequencing and patient selection, efficacy is usually my first driver for agent choice, and that is also then somewhat influenced by toxicity and sort of patient comorbidities.

Is that similar to your line of thinking?

Dr. Bardia:
Absolutely. It's very similar. So in the second-line setting, generally, SG. And then after that, if a patient has HER2–low disease, T-DXd. You brought up the point about the real-world evidence. And we do see that there is some cross-resistance between these agents, but for an individual patient, it's very tough to predict who will have cross-resistance. And given that T-DXd otherwise is a very active agent, it's very reasonable to consider that in this circumstance. But when I use ADC after ADC, with the second ADC, I generally get scans earlier because there's a concern that this patient might have disease progression, so I don't want to wait fo 4 months.

So usually somewhere in the range of 2 to 3 months, after 3 cycles or so, I tend to get scans just to ensure that the disease is under control with the second ADC. And as you nicely highlighted, sometimes the choice becomes evident based on the side effects. So if a

patient has cardiac dysfunction or pneumonitis, you cannot use T-DXd, and then SG is the preferred agent in that scenario.

We talked about SG; we talked about the side effects. You mentioned loperamide for diarrhea, but how about neutropenia? What's your practice in terms of primary or secondary prophylaxis related to neutropenia with SG?

Dr. Traina:
Yeah, that's a terrific question. I would say I'm sensitive to the risk of neutropenia. I tend to use sacituzumab earlier than the ASCENT population, which was a really heavily pretreated patient population. So I'm more inclined to incorporate growth factor as a secondary prophylaxis, and when I do that, I will often use pegylated G-CSF on day 8 to be able to have a better patient experience, fewer injections.

It helps to bridge them through that 2-week period so that they're ready for day 1, and it tends to carry them through day 8 as well. In the real-world evidence data that was presented not too long ago, upwards of 50% to 60% of clinicians using sacituzumab were using some degree of growth factor support, and so I have found that to be really successful, but I do it when needed.

How about you? Are you primary prophylaxis or secondary?

Dr. Bardia:
Mostly secondary prophylaxis, and that is what was done in the clinical trials as well. Generally, primary prophylaxis was not allowed, and that's what I do in clinical practice also. Now, here and there, there's an elderly patient, say, 82-, 84-year-old with metastatic TNBC, which can be seen, and I'm worried about neutropenic fever, I might consider primary prophylaxis, but for the most part, it's secondary prophylaxis.

How do you dose reduce or dose manage? So let's say there's a 62-year-old female with metastatic TNBC who gets SG, and then after the third dose she has grade 3 diarrhea that's there for more than 24 hours despite loperamide. How would you manage that?

Dr. Traina:
Yeah, I think, obviously, it's immediate supportive management with hydration and electrolytes, and I'm still using that Imodium support. But certainly we would hold sacituzumab at that point, allow our patient to recover. And then dose reductions are absolutely reasonable to incorporate, and we can reduce from 10 mg/kg down to 7.5 mg/kg. And I find that that can be highly successful in still providing some of the additional supports with Imodium as needed. But I would help to just aggressively manage and support those symptoms before rechallenging with the dose reduction.

Dr. Bardia:
That was great. And usually that tends to work. I think we covered the key elements regarding AEs. Maybe the other thing I can add is pneumonitis management related to T-DXd, which is a serious side effect that can be seen with T-DXd. And the key becomes early recognition and management for anyone who has grade 1 toxicity, which is asymptomatic. Even for asymptomatic AE, the recommendation is to hold the drug, but for anyone who's symptomatic—so that's grade 2 or higher—the recommendation is to permanently discontinue T-DXd, and usually with that, at least in our experience, we can manage this side effect.

Anything else to add, Tiffany?

Dr. Traina:
No, I would agree. I think, as you said, it's early detection and monitoring and more intense monitoring with T-DXd because of that ILD risk. Absolutely.

And this has been great. The time went so quickly. I think just before we wrap up, is there any sort of one key takeaway for folks listening today that you'd want to share?

Dr. Bardia:
I think it's AE management. It's great to have these ADCs that are efficacious. The key is AE management related to these drugs.

Dr. Traina:
That's right. And I would say I'm super excited that there are not only these highly effective ADCs but more on the horizon. So our challenges now are really understanding mechanisms of resistance and understanding how to best use all these tools that we have for our patients now. So it's an exciting time.

So I think that's all we have for today. I want to thank our audience for listening in. Thank you so much, Aditya, for joining me and for sharing all your really valuable thoughts. It was really great speaking with you today.

Dr. Bardia:

Thank you.