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Chairperson Perspective: Improving HR+/HER2- Breast Cancer Outcomes with TROP2 Antibody-Drug Conjugates

Announcer:
Welcome to CME on ReachMD. This activity, titled “Chairperson Perspective: Improving HR+/HER2- Breast Cancer Outcomes with TROP2 Antibody-Drug Conjugates” is provided by AXIS Medical Education.

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Dr. Bardia:
Hello. I'm Aditya Bardia, Medical Oncologist at UCLA, and I'm excited to talk about this important topic, which is improving the outcomes of patients with hormone receptive-positive, HER2-negative metastatic breast cancer with TROP2-directed antibody-drug conjugates.

Let's start with a case, a common scenario we see in clinic. A 55-year-old female with metastatic hormone receptor-positive, HER2 IHC 0 metastatic breast cancer, who's had disease progression on various endocrine-based regimens, also received one line of chemotherapy with capecitabine, good performance status, no actionable genomic alterations, germline BRCA-negative, has a history of inflammatory bowel disease. And the question is, after capecitabine, what would you consider for this patient? Eribulin, navelbine, sacituzumab govitecan, or trastuzumab deruxtecan, or datopotamab deruxtecan.

So it's a common scenario we are faced with the clinic. We have all these drugs that are FDA approved now, so I'll review how to select these agents and how to sequence these agents.

Let's start with sacituzumab govitecan. It was the first in class TROP2-directed ADC. It targets TROP2. It has SN38, the active metabolite of irinotecan as the payload, also has a bystander effect, so it can even impact cells with low or no expression of TROP2. This was evaluated in the TROPiCS-02 study, a pivotal phase 3 trial that demonstrated that sacituzumab govitecan was superior to standard chemotherapy for patients with hormone receptor-positive, HER2-negative breast cancer, so that was both HER2-low as well as HER2 IHC 0 metastatic breast cancer.

There was improvement in progression-free survival. And impressively, there was improvement in overall survival as well the median overall survival 14.5 months with sacituzumab govitecan versus 11 months or so with standard chemotherapy. So this led to the FDA approval for sacituzumab govitecan. And as per label, it was for patients who've received at least two prior lines of systemic therapy in this setting.

Now, how about biomarkers? Should we look for TROP2, the drug targets TROP2? Should we measure for TROP2? And the answer in clinic is no. We do not look at TROP2 expression for selection of sacituzumab govitecan at this time based on the FDA label. In TROPiCS-02, as well as other trials like ASCENT, the team looked at the correlation between TROP2 and outcomes, and even in patients with low expression of TROP2, the benefit with SG was maintained, so the outcomes were better with SG as compared to standard chemotherapy. So measurement of TROP2 does not influence clinical decision-making, and that's why we don't use it in clinic at this time.

How about AEs? Three common AEs seen with sacituzumab govitecan; the first one is neutropenia, close to 50% so 1 in 2 patients will have grade 3 or grade 4 neutropenia. Generally recommend secondary prophylaxis, although for certain patients, such as elderly, you could consider primary prophylaxis as well. The second side effect is diarrhea, generally grade 1/grade 2, although you can see grade 3/4 diarrhea as well. Generally recommend prophylactic antidiarrheal, secondary prophylaxis with the use of loperamide. And the third side effect is alopecia. The drug uniformly causes alopecia, so it's important to counsel patients regarding this side effect.

The AEs we do not see with sacituzumab govitecan include cardiovascular toxicity, neuropathy, or interstitial lung disease. And this becomes important as we have multiple agents in this setting. And how do we select between the different agents? The AE profile can be an important factor to consider when selecting the ADC.

The other point to note is sacituzumab govitecan is given Day 1, Day 8, every 21 days in terms of schedule.

The second ADC, that's now FDA approved, is datopotamab deruxtecan, which targets TROP2. It's a different antibody than sacituzumab govitecan. It's datopotamab. It's a different payload as well, deruxtecan as opposed to SN38 which is much more potent in terms of TOP1 inhibition. And the linker is different as well. It's a tetrapeptide-based cleavable linker. The drug is given every 3 weeks, so it has a different schedule as well, as compared to sacituzumab govitecan.

In terms of efficacy, this was evaluated in the phase 3 TROPION-Breast01 study, where there was improvement in progression-free survival, median PFS of about 7 months with Dato-DXd versus about 5 months with standard chemotherapy. Hazard ratio of 0.63. So improvement in progression-free survival was seen with this agent. Statistically significant, clinically meaningful as well.

In terms of overall survival, the team did not see an improvement in overall survival in this clinical trial with a hazard ratio of 1. However, this study was done in an era where trastuzumab deruxtecan was also approved, and so the team did additional sensitivity analysis, adjusting for the use of T-DXd, or balancing the use of T-DXd in both the arms so there was no imbalance. And then you could see a trend towards improvement in overall survival with Dato-DXd, a hazard ratio 0.86, 19 months of median OS with Dato-DXd was a 17.5 with investigator's choice of chemotherapy. So it appears that at least some of the difference in OS was because of imbalance in the use of subsequent ADC like T-DXd. And also speaks to the challenge in interpreting overall survival in the current era, when there are multiple effective agents.

In terms of side effects, the side effect of Dato-DXd, while it targets TROP2, is different from sacituzumab govitecan. In the clinical trial, the incidence of grade 3/grade 4 AEs were actually lower with Dato-DXd as compared to standard chemotherapy. So overall, it's well tolerated. The percentage of dose reduction interruptions were lower with Dato-DXd as compared to standard chemo. Generally does not cause much neutropenia, unlike sacituzumab govitecan. And the rate of neutropenia with Dato-DXd is lower as compared to standard chemo as well. But the drug does have side effects. Two important side effects to note; one is stomatitis, or mucositis, which can be seen with Dato-DXd, usually grade 1/grade 2, recommend primary prophylaxis with the use of a steroid mouthwash, and usually with that, you can manage the mucositis. The second side effect is pneumonitis, not to the degree as seen with T-DXd, but it is a side effect that can be seen with Dato-DXd, so it does require monitoring as well.

How do you manage these side effects? Let's talk about ocular toxicity. The median onset of ocular toxicity is about 2 months from the start of Dato-DXd. Generally recommend primary prophylaxis with a preservative-free lubricant eye drop and ophthalmology visit as well. If it's severe, you can hold the drug. In very severe cases, discontinue Dato-DXd.

In terms of mucositis, as I mentioned, this is a side effect seen with Dato-DXd. Usually the first cycle, you'll see the side effect. Recommend steroid mouthwash three to four times a day, ice chips or ice water during infusion can also be considered. Again if it becomes severe, grade 3/grade 4, hold Dato-DXd, which would then allow this AE to recover, and then you can resume generally at a lower dose.

Now, besides this, there are other drugs that are in development or even approved. For example, T-DXd is another drug that's approved for HER2-low and ultralow metastatic breast cancer that's hormone receptor-positive. There are other drugs in development, like sacituzumab tirumotecan, patritumab deruxtecan. So multiple ADCs in development.

And a question for the field is, how do we sequence the different ADCs? At this time, we don't have any biomarkers to guide sequencing of ADCs, but conceptually it'll be based on resistance. So for example, we know that some tumors develop mutations in TOP1, which is the target of the payload, both sacituzumab govitecan and datopotamab deruxtecan. And if you have emergence of TOP1 mutation, that'll cross resistance between SG and Dato-DXd and even T-DXd. All these three ADCs that are FDA approved have TOP1 payload, so there's TOP1 mutation that could result in cross resistance.

On the other hand, if the resistance is more because of the antigen, then you can use T-DXd and then Dato-DXd. Because one targets HER2, the other targets TROP2.

So better understanding of resistance could help with sequencing. It's not ready for prime time yet because we need the clinical assays, but conceptually as a field, that's where we are going.

So what's the current guideline? This is my recommendation for management of hormone receptor-positive HER2-negative metastatic breast cancer. In the first-line setting, I would recommend endocrine therapy, plus a CDK4/6 inhibitor, ribociclib, palbociclib, abemaciclib, those are the three ones that are FDA approved. In the second-line setting, strongly recommend genotyping, because it's actionable. If a patient has ESR1-mutant breast cancer or detection of ESR1 mutations, generally by a blood-based assay, elacestrant is the drug that's approved for a patient who has PIK3CA mutation. Fulvestrant plus alpelisib, or fulvestrant plus capivasertib would be an option for a patient who has detectable alterations in the AKT pathway. So that's PIK3CA mutation, or PTEN mutation, or AKT mutation, then you can use fulvestrant plus capivasertib as well. For patients with germline BRCA mutations, PARP inhibitors, olaparib and talazoparib, would be options to consider. If a patient does not have any actionable genomic alteration that's detectable, you can use fulvestrant with/without switching the CDK4/6 inhibitor. So if in the first-line setting, ribociclib was used; in the second-line setting, you could consider abemaciclib or consider the use of everolimus. The approval of everolimus is not linked to any genomic alteration. So certainly something you can use in this setting. In the second-line, third-line setting, usually we sequence these endocrine-based options. So if you've started with fulvestrant/capicitabine, then after that, you could consider everolimus or abemaciclib. Or if a patient has both ESR1/PIK3CA mutation, you could consider elacestrant as well. So generally, we use endocrine-based options.

Once endocrine-based options have been exhausted, that's when we go to ADCs and chemo. Based on DESTINY-Breast06, T-DXd, or trastuzumab deruxtecan, is an option to consider in this setting for both HER2-low or ultralow metastatic breast cancer. For some patients, capecitabine could be an option before T-DXd, it's an older drug. If you use T-DXd first, then you can use capecitabine after that. If you use capecitabine first, then you can use T-DXd after that. Generally, that's the preferred regimen to consider for a patient with HER2-low or ultralow disease. And then after that, we consider sacituzumab govitecan. And now we have datopotamab deruxtecan as well. For a patient who has HER2 IHC 0 disease, two or three biopsies, all HER2 IHC 0, 00, not even ultralow, then as per label, the option would be sacituzumab govitecan or datopotamab deruxtecan. You cannot use T-DXd as per the label.

So that's my algorithm. I generally sequence these ADCs. I prioritize ADCs over chemo based on what we've seen from the clinical trials. If there's a good clinical trial option available, that's always something to consider.

It's good to do shared decision-making with the patient based on their priorities based on the comorbid conditions they have. Sometimes it requires multidisciplinary management as well. So if a patient has history of pneumonitis with T-DXd, involving a pulmonologist. Or like the case we reviewed a patient with inflammatory bowel disease, working with a GI specialist. So having a multidisciplinary team and involving the patient as well. So more of a patient-centered, person-centered decision-making, is critical when there are multiple options.

Schedule. SG is Day 1, Day 8 every 21 days, while Dato-DXd is every 3 weeks. So all of those factors come into picture in terms of looking at these drugs. And the key components are to foster the patient-clinician relationship, ensuring that we are engaged in a patient-centered communication, understanding their preferences, understanding the different comorbid conditions, and providing the right drug.

So to summarize, TROP2 ADCs have revolutionized the care for patients with hormone receptor-positive metastatic breast cancer. Datopotamab deruxtecan is now approved for hormone receptor-positive HER2-negative metastatic breast cancer after one prior line of chemo, as per label. Sacituzumab govitecan also approved for hormone receptor-positive breast cancer after two prior lines of systemic therapy. And sacituzumab tirumotecan, not approved yet, is being evaluated in phase 3 clinical trials. Besides this, there are other drugs and development as well. So for the field, the question is going to be, how do we sequence these agents? How do we move them to earlier lines? As well as, how do we build with combinations that are ADC based?

Thanks so much for joining today. Hope this was helpful.

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