BREAST CANCER IN FOCUS

Current Developments in the Management of Breast Cancer

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Sequencing Antibody-Drug Conjugates in Patients with Hormone Receptor–Positive, HER2-Negative Metastatic Breast Cancer

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H&O How do you determine whether breast cancer is endocrine-resistant?

JC An endocrine-sensitive patient is someone who has never received or has gone at least a year without endocrine-based therapy. In endocrine resistance, a tumor progresses during or after exposure to endocrine-based therapy. In the great majority of our patients with metastatic breast cancer, resistance has developed to at least one line of endocrine treatment, so the key question becomes how to determine whether a patient could benefit from a subsequent line of endocrine treatment. To determine this potential benefit, we look at 3 factors: (1) whether estrogen and progesterone receptors are present, (2) the amount of metastasis, and (3) the time from prior endocrine-based therapy to disease progression. Someone with a single liver metastasis is different from someone with 100 liver metastases, and someone whose disease progressed within 3 months after endocrine-based therapy is different from someone whose disease progressed after 12 months. If we determine that a quick response is required and the patient is unlikely to benefit from endocrine treatment, we need to move on to antibody-drug conjugates (ADCs) or chemotherapy.

H&O For patients who have endocrine-resistant hormone receptor–positive (HR+), human epidermal growth factor receptor–negative (HER2–) metastatic breast cancer, what is the optimal sequencing of ADCs with standard chemotherapy?

JC We should use ADCs as soon as possible in eligible patients, for 2 reasons. First, ADCs have been shown to be superior to chemotherapy after endocrine resistance. Second, we cannot guarantee that the patient will be able to receive further lines of therapy, so the earlier the better. Eligibility for ADCs depends on the tumor type. From examination of the biopsy specimen, we learn whether the tumor is triple-negative and the level of HER2 expression: HER2-positive, HER2-low, HER2-ultra-low, or HER2-null. If a tumor is endocrine-resistant and HER2-low, the US Food and Drug Administration (FDA) has approved the use of trastuzumab deruxtecan, also known as T-DXd (Enhertu, Daiichi-Sankyo/AstraZeneca) in the second-line setting, as well as in the first-line setting if the tumor is HER2-low or HER2-ultralow. I may consider capecitabine for certain patients because of the good toxicity profile, but overall I think that ADCs are a better option than standard chemotherapy on the basis of the results of the phase 3 DESTINY-Breast04 and DESTINY-Breast06 trials.[1,2] Of course, that depends on the country where you are practicing; in Spain, we need to wait until the second line to use T-DXd.

Sacituzumab govitecan (SC; Trodelvy, Gilead) is currently a second-line option for patients with metastatic HR+/HER2– (immunohistochemistry [IHC] 0, IHC 1+, or IHC 2+/in situ hybridization [ISH–]) breast cancer who have received endocrine-based therapy and at least 2 additional systemic therapies in the metastatic setting. The FDA approval was based on the results of the phase 2 TROPiCS-02 study.[3]

The phase 3 ASCENT-07 trial is examining the efficacy and safety of SG in patients with endocrine therapy–resistant HR+/HER2– breast cancer who have received endocrine therapy and are eligible for their

first chemotherapy for advanced or metastatic disease (NCT05840211).

Finally, datopotamab deruxtecan, also known as Dato-DXd (Datroway, Daiichi Sankyo/AstraZeneca), has received FDA approval for patients with metastatic HR+/HER2–breast cancer who have received prior endocrine-based therapy and chemotherapy for unresectable or metastatic disease. Approval was based on the results of the phase 3 TROPION-01 trial.[4]

> Some patients may benefit from a second ADC regardless of whether they benefited from a first one.

H&O How do you sequence T-DXd with SG and Dato-DXd in patients with HR+/HER2– metastatic breast cancer?

JC Treatment guidelines from the National Comprehensive Cancer Network (NCCN) recognize sequencing as an option to treat these patients.[5] Dato-DXd has not been approved in Europe, however, so we do not have any experience sequencing it with T-DXd or SG. I think that it would make sense in at least some cases to sequence T-DXd followed by SG followed by Dato-DXd, or else to sequence T-DXd followed by Dato-DXd followed by SG. I have 2 comments to add here. First, we know that the activity of the second ADC is shorter than that of the first ADC. Still, some patients may benefit from a second ADC regardless of whether they benefited from a first one. My second comment is that we do not know whether a second ADC should be used immediately after the first or whether chemotherapy should be used between the 2 ADCs. That question has yet to be answered. I think that both approaches are reasonable, but we need to explain to the patient the limitations of the data we have, along with the pros and cons of the toxicity profile of the drugs. We do not have guidelines to tell us exactly what to do, however.

H&O What considerations do you factor in when determining the best treatment?

JC We need to look at everything, including survival, patient comorbidities and preferences, treatment schedule, and adverse events. A patient who lives far from the treatment center may have to receive a different treatment than one who lives nearby. The most important factors are the activity of the drug—basically, progression-free survival and overall survival—and the preferences of the patient, with comorbidities and the patient's ability to get to the treatment center taken into account.

H&O What studies are underway that will further inform sequencing?

JC Dozens of clinical trials are examining ADCs with various payloads, so that is exciting. Regarding trials of existing drugs, the most exciting one is the ongoing phase TRADE DXd clinical trial, which is being led by Dr Ana Garrido-Castro of the Dana-Farber Cancer Institute. This trial is comparing the sequencing of T-DXd followed by Dato-DXd vs the sequencing of Dato-DXd followed by T-DXd in estrogen HER2-low or HER2-negative metastatic breast cancer (NCT06533826). Also interesting is the phase 2 SATEEN trial, which is evaluating the safety and effectiveness of SC plus trastuzumab in patients with metastatic HER2+ breast cancer who have previously received or been exposed to T-DXd (NCT06100874). This trial is being led by Dr Adrienne G. Waks, also of Dana-Farber.

H&O Do you think that we can accurately differentiate between HER2-ultralow and HER2-null disease?

JC T-DXd is approved in the United States in the first-line setting in both HER2-low and HER2-ultralow disease, so we need to be able to differentiate between HER2-ultralow and HER2-null disease. Unfortunately, the discordance between IHC 0 and IHC 1+ is somewhere between 30% and 50%, so we can imagine that the discrepancy between HER2-null and HER2-ultralow is also going to be significant. That is something we need to optimize so that we know which patients can receive T-DXd.

H&O Is there anything you would like to add?

JC The exciting world of ADCs has clearly changed the prognosis for all breast cancer phenotypes, but how to sequence them remains tricky. One reason why sequencing is tricky is that except for trastuzumab emtansine, also known as T-DM1 (Kadcyla, Genentech), all the ADCs we have now for use in the breast cancer setting have a topoisomerase I inhibitor as the payload. A second reason is that we do not yet have prospective clinical trials that

have explored clinically whether a later payload-based antibody conduit works after an earlier one. As a result, we are working only with real-world evidence when it comes to sequencing.

I would like to see future studies address sequencing of these agents. I would also like to see research on different mechanisms of resistance, some of which might involve mutations in the TROP2 antigen, also known as TACSTD2. If we understood the different mechanisms of resistance, we could optimize the sequencing with a similar antiviral conduit.

Disclosures

Dr Cortés has served as a consultant or advisor to Roche, AstraZeneca, Seagen, Daiichi Sankyo, Lilly, Merck Sharp & Dohme, Leuko, Bioasis, Clovis Oncology, Boehringer Ingelheim, Ellipses, Hibercell, BioInvent, Gemoab, Gilead, Menarini, Zymeworks, Reveal Genomics, Scorpion Therapeutics, ExpreS2ion Biotechnologies, Jazz Pharmaceuticals, AbbVie, BridgeBio, Biontech, Biocon, Circle Pharma, Delcath Systems, Hexagon Bio, and Bliss Bio; has received honoraria from Roche, Novartis, Eisai, Pfizer, Lilly, Merck Sharp & Dohme, Daiichi Sankyo, AstraZeneca, Gilead, Streamline Therapeutics, and Zuellig Pharma; has received research funding to his institution from Roche, ARIAD Pharmaceuticals, AstraZeneca, Baxalta GmbH/Servier Affaires Médicales, Bayer HealthCare, Eisai, F. Hoffmann-La Roche, Guardant Health, Merck Sharp & Dohme, Pfizer, Piqur Therapeutics, Iqvia, and Queen Mary University of London; has stock in MAJ3 Capital and Leuko (relative); and has received travel, accommodation, or expenses from Roche, Novartis, Eisai, Pfizer, Daiichi Sankyo, AstraZeneca, Gilead, Merck Sharp & Dohme, and Streamline Therapeutics. He also has the following patents: Pharmaceutical combinations of a PI3K inhibitor and a microtubule destabilizing agent. Javier Cortés Castán, Alejandro Piris Giménez, Violeta Serra Elizalde. WO 2014/199294 A (issued). HER2 as a predictor of response to dual HER2 blockade in the absence of cytotoxic therapy. Aleix Prat, Antonio Llombart, Javier Cortés. US 2019/0338368 A1. (licensed).

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