BREAST CANCER IN FOCUS

Current Developments in the Management of Breast Cancer

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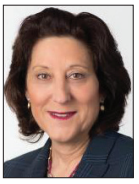
Management of Toxicities From Antibody-Drug Conjugates



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H&O Which antibody-drug conjugates (ADCs) are approved for use in breast cancer?

HR The first ADC to be approved for use in breast cancer was trastuzumab emtansine, also known as T-DM1 (Kadcyla, Genentech). T-DM1 was approved for use in human epidermal growth factor receptor 2 (HER2)–positive metastatic breast cancer in 2013 and received additional approval in 2019 for use as adjuvant treatment for patients with HER2-positive disease who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment. T-DM1 is effective as treatment for HER2-positive disease only, but the field has recently moved forward with highly effective novel ADCs that are effective across multiple breast cancer subtypes.

To date, 3 next-generation ADCs have been approved for use in breast cancer: trastuzumab deruxtecan (T-DXd; Enhertu, Daiichi-Sankyo/AstraZeneca), sacituzumab govitecan (SG; Trodelvy, Gilead), and, as of January of this year, datopotamab deruxtecan (Dato-DXd; Datroway, Daiichi Sankyo/AstraZeneca). T-DXd, a HER2-targeting ADC, is approved for patients with HER2-positive metastatic breast cancer, in whom it has been shown to produce superior progression-free survival and overall survival in comparison with T-DM1. T-DXd also has been shown to be superior to standard-of-care therapy following T-DM1. In addition, T-DXd is approved in the metastatic setting for the treatment of patients with HER2-low breast cancer who have received at least one line of chemotherapy, and most recently as first-line chemotherapy for patients with endocrine-refractory, hormone receptor–positive (HR+), HER2-low and HER2-ultralow disease. SG is approved as second- or later-line therapy for patients who have metastatic triple-negative breast cancer and endocrine-refractory, HR+/HER2-negative disease. T-DXd was recently approved for patients with endocrine-refractory, metastatic, HR+/HER2-negative breast cancer who have previously received 1 to 2 lines of chemotherapy for advanced disease.

H&O What toxicities are seen with these agents?

HR It is important first to understand the structure of ADCs because this can affect toxicities. ADCs are composed of an antibody that targets a receptor on the cell surface, a linker, and a payload. When the antibody binds to the receptor on the cell surface and is internalized by the receptor, the linker is cleaved and releases the payload, which then can kill the cancer cell. T-DM1 has a hydrophobic payload, so it kills primarily cells that express the target receptor. By contrast, most next-generation ADCs (and all 3 approved agents) have a more hydrophilic payload, so they can additionally cause the death of neighboring tumor cells that do not express the target receptor. The change in linker chemistry, the drug-to-antibody ratio, and the payload results in a "bystander" effect, in which effectiveness is seen in tumors that express the receptor at variable concentrations. Toxicity is variable among ADCs, even those with the same payload (or payloads with a similar mechanism of action) and different antibody targets, or with similar antibody targets and different payloads. These varied toxicities are thought to be related to a complex interaction between payload release and target expression on normal cells.

The most common toxicities associated with T-DXd are nausea and vomiting and modest hair loss. Bone

marrow suppression is relatively mild, with the rate of grade 3 or higher hematologic toxicities at less than 10%. Low-grade diarrhea occurs in fewer than 20% of patients. Fatigue may be dose-limiting in a subset of patients.

T-DXd is associated with interstitial lung disease (ILD), also referred to as pneumonitis, that is rarely fatal. The rate of ILD with T-DXd ranges from 11% to 15%. ILD is related to multiple factors, including dose size, presence of underlying lung disease, abnormal renal function, and a prior incidence of ILD or pneumonitis. In addition, the rate of ILD is elevated in Japanese patients. Most cases of ILD and pneumonitis are grade 1 or 2 but the mortality rate is approximately 1%, so that strict guidelines for monitoring and treatment have been developed. Interestingly, in the recent phase 3b/4 DESTINY-Breast12 study, which enrolled patients with and without brain metastases, the rate of any-grade ILD was 16%, and the mortality rate was 2.3%.[1] With further evaluation, it was discovered that 4 of the 6 patients (1.5%) with grade 5 ILD also had opportunistic infections. This finding provided a sobering reminder that prophylaxis for *Pneumocystis jirovecii* pneumonia is necessary with longer-term exposure to corticosteroids. Significant cardiac toxicity has not been observed with T-DXd, although ongoing monitoring is critical.

> The most common toxicity due to T-DXd is nausea, with relatively low rates of vomiting.

The toxicities of SG are related to its payload of SN-38, the active metabolite of irinotecan. The primary toxicities are neutropenia and diarrhea, with nausea of relatively less intensity and shorter duration. The rate of grade 3 or 4 neutropenia in heavily pretreated patients is 50% to 60% but this can be prevented and treated with granulocyte colony–stimulating factors. The rate of grade 3 diarrhea with SG across the 2 phase 3 trials ranged from 9% to 10%, and the diarrhea appears to be related to variable metabolism through the uridine diphosphate glucuronosyltransferase 1A1 (*UGT1A1)* pathway. Patients with homozygosity for the poorly metabolizing phenotype (*UGT1A1* *28/*28 polymorphism) in the ASCENT trial (in metastatic triple-negative breast cancer)[2] and the TROPiCS-02 trial (in metastatic HR+, HER2-negative breast cancer)[3] had more grade 3 or higher diarrhea and slightly more neutropenia. Because these patients are exposed to more of the payload, dose reduction can maintain efficacy and reduce toxicity. In addition, there is interest in whether we should begin SG treatment at a lower dose in patients who have poorly metabolizing phenotypes.

Dato-DXd is associated with unique toxicities as well. Although the rate of nausea is similar to that seen with T-DXd, ILD is rarely observed. This may be a consequence of the lower drug-to-antibody ratio (about half that of T-DXd) or of differential delivery due to receptor expression and targeting. Dato-DXd is associated with stomatitis, which may occur early or over the duration of exposure. Grade 3 stomatitis occurs in fewer than 10% of patients, but even grade 2 stomatitis can be quite impactful for patients. A second toxicity that is relatively unique among ADCs is ocular toxicity, specifically keratitis and dry eye. This appears to be relatively mild in most patients.

H&O How should toxicities with T-DXd be managed?

HR The most common toxicity due to T-DXd is nausea, with relatively low rates of vomiting. It is critical to start with prophylaxis, and a 3-drug antiemetic regimen is recommended. The intensity of the pre-medication regimen can be tailored to the observed toxicity over the course of treatment. T-DXd is also associated with delayed nausea that can be persistent. Rescue medications are critical to manage this adverse event. In addition to standard antinausea medications, we recommend low doses of the antipsychotic olanzapine, which is taken at bedtime. We recommend that patients start with 2.5 mg for the first 3 to 5 days and escalate (or de-escalate to 1.25 mg) as needed. Extending the use of antiemetics, including olanzapine, is important for patients with continued delayed nausea. Dose reduction is an effective strategy for persistent nausea despite adequate treatment. For fatigue, which is particularly common with T-DXd in older patients, dose reduction and dose delay can be very effective.

ILD remains a very important issue, with a known mortality rate. We believe that early identification and appropriate treatment are critical to optimize drug efficacy and minimize serious toxicity. Most cases develop in the first year of treatment, although late cases have been reported. Imaging of the lungs is recommended every 9 to 12 weeks to screen for asymptomatic ground glass opacities, indicating grade 1 ILD. The type of imaging is also important; diagnostic noncontrast computed tomography (CT) is the most sensitive testing modality. Fused positron emission tomography/CT should not be used for this purpose. Risk factors identified in a pooled analysis and a real-world study in France include a history

of ILD or pneumonitis, older age, and renal insufficiency. Screening for patients in Japan should be considered every 9 weeks. Screening should not be delayed until symptoms develop. An initial dose reduction should be considered for patients with renal insufficiency or a prior history of symptomatic ILD. Scans may be done less frequently after 1 year, but as previously noted, late cases have been described.

If grade 1 ILD/pneumonitis (asymptomatic ground glass opacities) develops, guidelines recommend holding the drug until radiographic recovery. Corticosteroids may be administered at 0.5 mg/kg with a slow taper (starting about 2 weeks after the start of corticosteroids) to hasten recovery, and existing data suggest that this is a successful strategy. I repeat the CT approximately 3 weeks after the held dose so that just one cycle is omitted, and treatment can be restarted in most patients. With repeated episodes of grade 1 ILD or very slow recovery, dose reduction is recommended.

If symptomatic ILD (grade ≥2) develops, T-DXd should be permanently discontinued and corticosteroids should be instituted at a dose of 1 mg/kg. Signs and symptoms include cough, shortness of breath, and occasionally fever, with associated radiographic changes. We recommend that management include a pulmonologist. The differential diagnosis includes infectious causes, but corticosteroids should be instituted unless infection is documented. Additional interventions for corticosteroid-refractory intervention are being evaluated and require a multidisciplinary team. Because opportunistic infections can occur in patients taking corticosteroids for more than 2 weeks and are a significant and life-threatening complication, it is important to prescribe preventive measures against *P jirovecii* pneumonia in this situation.

We conducted a pooled analysis of 9 prospective trials to evaluate the risks and benefits of T-DXd rechallenge after recovery from grade 1 ILD.[4] We found that rechallenging patients who have recovered from grade 1 ILD was safe, and some patients were able to stay on the drug for a long time with disease control. A small number of patients had recurrent ILD, but all but one case was grade 1. Some patients were rechallenged 2 or 3 times with continued clinical benefit and no significant toxicity.

H&O How should toxicities with SG be managed?

HR Given that neutropenia is the most common toxicity due to SG, careful management is critical to maintain efficacy and minimize complications. Although the clinical trials required an absolute neutrophil count (ANC) of 1500/μL to start a new treatment cycle, and at least 1000/μL at day 8, in practice we use an ANC of 1000/μL for both time points. Patients who have required prior myeloid growth factors for their treatment should receive prophylaxis with the first cycle. Otherwise, prophylaxis should be instituted if treatment is delayed owing to neutropenia, or of course with infectious complications. The schedule of short-acting myeloid growth factors is 1 to 2 doses on days 2 and 3. We have also given pegfilgrastim after day 8, which may take care of the entire growth factor need for each cycle. For persistent or complicated neutropenia despite growth factors, dose reduction should be included as part of the management strategy.

Myeloid growth factors are particularly important for patients with neutropenia and additional risk factors, such as diarrhea. These patients are at risk for infectious complications such as typhlitis and benefit from treatment with growth factors to reduce the duration and severity of neutropenia.

Diarrhea is a difficult toxicity for patients, so education and the use of loperamide are important for patients receiving SG. Loperamide is quite effective for grades 1 and 2 intermittent diarrhea, but patients with difficult-to-control or persistent grade 3 diarrhea despite appropriate interventions should receive reduced-dose therapy. Atropine is used for rare immediate cholinergic reactions during or after an infusion and is not effective for delayed diarrhea.

One recent study evaluated prophylaxis for neutropenia and diarrhea in patients receiving SG. The PRIMED study, which was presented at the 2024 American Society of Clinical Oncology Annual Meeting and updated at the 2024 San Antonio Breast Cancer Symposium, evaluated filgrastim and loperamide for the prevention of neutropenia and diarrhea.[5] The single-arm, phase 2 study enrolled 50 patients who were receiving SG for either triple-negative breast cancer or HR+, HER2-negative disease. Patients received filgrastim on days 3, 4, 10, and 11 of the first 2 cycles, and loperamide at 2 mg twice a day on days 2, 3, 4, 9, 10, and 11. The median follow-up was 9 months. The researchers saw markedly lower rates of both neutropenia and diarrhea than in ASCENT and TROPiCS-01, which is very encouraging. The rate of grade 3 neutropenia was only 24%, which is much lower than the 60% rate we expect to see without filgrastim. The rate of grade 3 or higher diarrhea was only 4%, a clinically important decrease in comparison with the 9% to 10% rate reported in the phase 3 trials. As expected, levels of constipation were increased.

We have experience with the use of octreotide in a patient who was a *28 heterozygote and had persistent diarrhea after dose reduction. The agent worked very well in this patient and allowed continued therapy with an ongoing clinical response for a number of months.

The nausea associated with SG is generally easy to control if a 2- or 3-drug premedication regimen is

combined with standard rescue medications. Nausea is generally short-lived following SG infusions.

H&O How should toxicities with Dato-DXd be managed?

HR To control the nausea from Dato-DXD, we use the same approach as that described above for T-DXd. Stomatitis can be a difficult side effect because it affects the ability to eat and is associated with hard-to-control pain or sensitivity. We are studying the use of corticosteroid mouthwashes to reduce both the grade and incidence of stomatitis, and our experience has been very favorable. Indeed, the US Food and Drug Administration approval label lists the use of corticosteroid mouthwash and ice chips during the infusion as strategies to reduce stomatitis. Higher-grade or persistent symptomatic stomatitis should be managed with dose reduction and dose delay as appropriate.

To prevent ocular toxicity with Dato-DXd, it is recommended that patients not wear contact lenses and that they use preservative-free eye drops 4 to 5 times a day. If symptoms develop, it is important to consult with an ophthalmologist for a detailed examination and recommendations for treatment.

H&O What other techniques can be used to manage general toxicities with ADCs?

HR Hair loss is variable with T-DXd and Dato-DXd and appears to be universal with SG. The effectiveness of cold caps is unknown, but anecdotally they seem to prevent hair loss from T-DXd. Ongoing studies are evaluating cold caps with current ADCs; there is concern that the long half-life of these agents would make cold caps less successful.

Another toxicity that has been reported is a possible increase in radiation necrosis when radiation is given concurrently with ADCs. The association so far is anecdotal but requires ongoing evaluation.

Disclosures

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