BREAST CANCER IN FOCUS

Current Developments in the Management of Breast Cancer

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Antibody-Drug Conjugates in Breast Cancer

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H&O What are antibody-drug conjugates (ADCs)?

AB ADCs are drugs that contain an antibody linked to a chemotherapy agent. Accordingly, they have 3 components: an antibody corresponding to a specific antigen, a linker, and a chemotherapy agent (toxic payload).

H&O How do they work?

AB The idea behind ADCs is that they can deliver high doses of chemotherapy to cancer cells while sparing normal cells. Scientists begin by selecting an antigen that is highly expressed on cancer cells and minimally expressed on normal cells. The goal is for the antibody to bind to the antigen on the cancer cells, become internalized, and only then release the toxic payload to the cancer cells. Linkers are designed to break inside the cancer cells under certain conditions, such as exposure to a specific pH or a proteasome.

The poster child for this approach is trastuzumab emtansine (T-DM1; Kadcyla, Genentech). Trastuzumab (Herceptin, Genentech) is a monoclonal anti–human epidermal growth factor receptor 2 (anti-HER2) antibody, and emtansine (DM1) is the chemotherapy component. T-DM1 received US Food and Drug Administration (FDA) approval for the treatment of patients with HER2-positive metastatic breast cancer after prior treatment with trastuzumab and a taxane on the basis of results from EMILIA (A Randomized Phase 3 Study of the Antibody-Drug Conjugate T-DM1 Versus Capecitabine + Lapatinib in Participants With HER2-Positive Locally Advanced or Metastatic Breast Cancer).

H&O What are the advantages and limitations of using ADCs?

AB The advantage is being able to deliver high doses of chemotherapy to cancer cells while reducing the toxicity of the chemotherapy; these drugs have a high efficacy-to-toxicity ratio. For example, DM1 was initially developed in the 1970s and then abandoned because it was too toxic. However, when DM1 is a component of an ADC intended for selective delivery to cancer cells, its toxicity becomes an advantage—it has highly potent effects against HER2-positive cancer cells.

The main limitation of this approach is that only the antigen targeted by the agent is affected. So if you have a tumor cell that does not express the targeted antigen, or the tumor cells exhibit significant heterogeneity, the agent will not work the way it is designed to work.

H&O How much toxicity is seen with these agents?

AB In a perfect world, there would be no toxicity because the chemotherapy agent would be entirely absorbed by the cancer cells. In practice, we do see some toxicity, for various reasons. First, some of the chemotherapy agent may be released into the blood as the cancer cells die. Second, normal cells may take up the ADC. We sometimes see an increase in liver enzymes with T-DM1, possibly because of uptake by hepatic cells. Third, if the linker breaks before the ADC makes its way into the cancer cells, the chemotherapy agent will leak into the blood, resulting in toxicity.

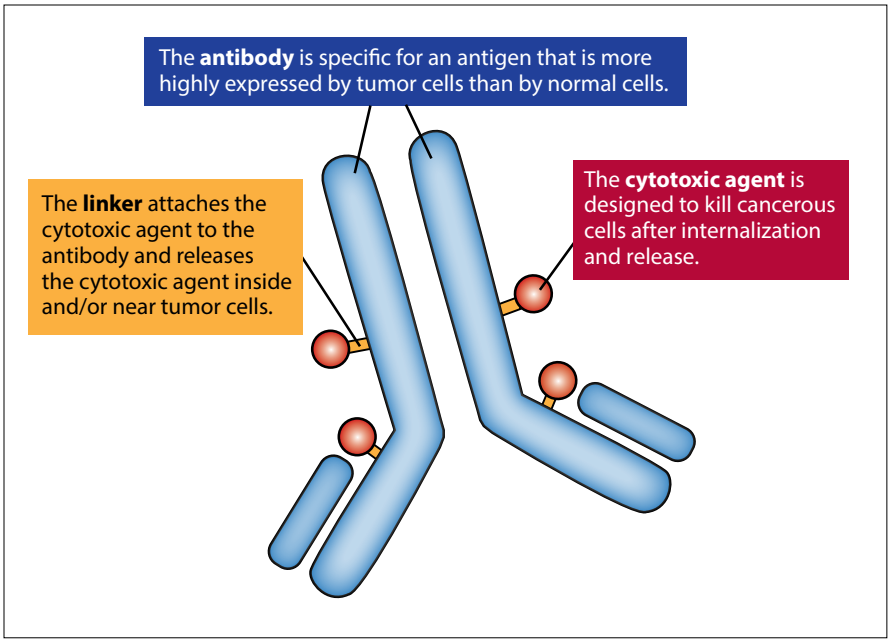

Figure. Elements of an antibody-drug conjugate.

H&O What ADCs are available besides T-DM1?

AB The only other one that has been approved is brentuximab vedotin (Adcetris, Seattle Genetics), which is used in Hodgkin lymphoma after autologous stem cell transplant.

H&O How many ADCs are being developed for use in breast cancer?

AB At least 2 ADCs for breast cancer are in advanced stages of development: sacituzumab govitecan and glembatumumab vedotin. Several additional agents are in phase 1 trials.

H&O Could you discuss sacituzumab govitecan in more detail, including your own study?

AB Sacituzumab govitecan, which is also known as IMMU-132, targets Trop-2, which is an epithelial antigen overexpressed in many solid tumors. Approximately 80% to 85% of triple-negative breast cancers express Trop-2. The chemotherapy component is SN-38, which is the active metabolite of irinotecan, a chemotherapy agent that targets topoisomerase I, resulting in DNA damage and cellular apoptosis. The linker is pH-sensitive, so it will release the drug within cancer cells and/or near tumor cells if the microenvironment is acidic, which often happens in cancer. Thus, although the drug is designed to be released inside cancer cells, release adjacent to cancer cells also is effective.

In a phase 2 study that was presented at the 2016 San Antonio Breast Cancer Symposium, we looked at 69 patients with metastatic triple-negative breast cancer who had received a median of 5 prior lines of therapy. Patients received sacituzumab govitecan at a dose of 10 mg/kg. The objective response rate was 30%, with 2 confirmed complete responses. The median progression-free survival was 6 months, and the median overall survival was 16.6 months. The updated results are scheduled for publication in an academic journal. The tumors of most of the patients in the study overexpressed Trop-2, and we are conducting an analysis to determine any correlation between the degree of Trop-2 overexpression and clinical outcomes. These results have not yet been presented. In addition, we anticipate opening a phase 3 trial this year.

H&O What were some of the side effects seen in the trial?

AB The most common side effect was neutropenia. Other common side effects were nausea, diarrhea, and hair loss.

H&O Is there anything else you would like to highlight about the trial?

AB Chemotherapy tends to produce early responses when it works, but the responses are usually not durable. With sacituzumab govitecan, most of the responses were also early. What was different was that they tended to be durable. The reason for this is probably the

antibody component of the ADC, although we need more research to better understand this finding.

Another notable finding is that the incidence of diarrhea was much lower than what one would anticipate with irinotecan. That speaks to the major advantage of ADCs—you can deliver higher drug doses with less toxicity.

Finally, because this was a single-arm trial, we cannot draw definitive conclusions from the results. The median progression-free survival of 6 months was approximately double that seen in historical cohorts with standard chemotherapy agents, but this was not a randomized trial, and conclusions should be drawn accordingly.

This finding is especially important because triple-negative breast cancers are the cancers that we worry about the most.

H&O Could you talk about what we have learned about glembatumumab vedotin?

AB Glembatumumab vedotin, which is also called CDX-011, is an ADC that targets glycoprotein NMB (gpNMB), which is a transmembrane protein that is expressed at higher levels in several malignant tissues than in normal tissues. It is a poor prognostic marker in breast and lung cancer, and it is overexpressed in triple-negative breast cancer. The toxic payload in glembatumumab vedotin is monomethyl auristatin E (MMAE), which is a microtubule inhibitor. The ADC binds to the antigen gpNMB, becomes internalized, and releases MMAE following proteasomal cleavage. This sequence of events results in inhibition of the microtubules.

In a clinical trial called EMERGE (A Randomized Phase II Study of the Antibody-Drug Conjugate Glembatumumab Vedotin in Advanced Glycoprotein NMB-Expressing Breast Cancer), which was published in the *Journal of Clinical Oncology* in 2015, patients with metastatic breast cancer were randomly assigned to glembatumumab vedotin or the standard of care. A subset analysis revealed that the ADC was most active in tumors that were triple-negative and that overexpressed gpNMB. Median progression-free survival in this subset of patients was significantly better with glembatumumab vedotin than with standard treatment.

Moving forward, the phase 3 METRIC trial (Study of Glembatumumab Vedotin [CDX-011] in Patients With Metastatic, gpNMB Over-Expressing, Triple Negative Breast Cancer) is looking at glembatumumab vedotin vs capecitabine for triple-negative breast cancers that are gpNMB-positive (NCT01997333). This trial is specifically studying women with advanced breast cancer who have had no, 1, or 2 prior lines of therapy, whereas sacituzumab govitecan received breakthrough designation status in February of 2016 for patients who have received 2 prior lines of therapy. In other words, glembatumumab vedotin is being studied for use earlier in therapy than sacituzumab govitecan is used.

H&O What is the significance of the finding that these drugs appear to work best in patients with triple-negative breast cancer?

AB This finding is especially important because triple-negative breast cancers are the cancers that we worry about the most. They tend to affect younger and African American patients, and they tend to be associated with brain and visceral metastases. Triple-negative breast cancer carries a poor prognosis, and no FDA-approved targeted therapies for it are available, so these agents have the potential to meet an unmet need.

H&O What other ADC trials are ongoing in breast cancer?

AB A few other ADCs are being investigated in breast cancer. For example, the agent SGN-LIV1A, which is designed to bind to LIV-1 proteins and release MMAE, is being investigated in a phase 1 trial that is currently recruiting patients with LIV-1–positive metastatic breast cancer (NCT01969643).

There is also interest in next-generation agents after T-DM1 that target HER2. Examples include DS-8201 and XMT1522, which are being investigated in clinical trials of advanced breast cancer that overexpresses HER2 (NCT02564900, NCT02952729). However, efficacy after T-DM1 can be a difficult bar, as witnessed in HERMIONE (A Randomized, Phase 2 Trial of MM-302 Plus Trastuzumab Versus Chemotherapy of Physician's Choice Plus Trastuzumab in Patients With Previously Treated, Anthracycline-Naïve, HER2-Positive, Locally Advanced/Metastatic Breast Cancer). This trial, which investigated the use of MM-302 to target HER2, was terminated on the basis of futility analysis.

H&O How about ADCs in other cancer types?

AB Sacituzumab govitecan is being tested in other

epithelial cancers, such as lung, bladder, and endometrial cancers, and several studies are examining the use of glembatumumab vedotin in lung cancer, melanoma, and osteosarcoma.

Rovalpituzumab tesirine is also being tested in lung cancer. This ADC targets delta-like protein 3 (DLL3), which is overexpressed in more than 80% of small cell lung cancers. In a presentation at the 2016 American Society of Clinical Oncology annual meeting, Dr Charles M. Rudin reported that rovalpituzumab halted tumor growth in 89% of 26 patients whose tumors overexpressed DLL3.

The agent inotuzumab ozogamicin is being tested for use in several types of cancer, including non-Hodgkin lymphoma and acute lymphoblastic leukemia. Gemtuzumab ozogamicin was withdrawn for use in acute myelogenous leukemia but was resubmitted to the FDA in February of this year. Vadastuximab talirine is being studied for use in acute myeloid leukemia and myelodysplastic syndromes.

H&O Do you see ADCs being used in conjunction with other agents?

AB Yes, there is interest in combining them with targeted therapies or immunotherapy, especially programmed death 1 (PD-1) inhibitors.

H&O Do you see them being used in earlier lines of therapy?

AB Absolutely, and we have already begun to see T-DM1 being evaluated in early breast cancer alone and in combination with other agents (NCT02073487, NCT01772472, NCT01966471) as the preferred HER2 backbone instead of trastuzumab.

Disclosure

Dr Bardia has consulted for Novartis, Pfizer, Genentech, and Immunomedics.

Suggested Readings

Bardia A, Diamond JR, Mayer IA, et al. Safety and efficacy of anti-Trop-2 antibody drug conjugate, sacituzumab govitecan in heavily pretreated patients with TNBC. Paper presented at: 39th Annual San Antonio Breast Cancer Symposium; December 6-10, 2016; San Antonio, TX. Abstract PD3-06.

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