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What Is the Evidence Supporting TROP-2 Directed Therapy in Current Clinical Practice of Patients With TNBC?

Announcer:
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Dr. Bardia:
Hello, I'm Aditya Bardia, attending physician at Mass General Hospital Cancer Center. Associate professor Harvard Medical School. I'll be reviewing what's the evidence supporting TROP-2 directed therapy in current clinical practice for patients with triple negative breast cancer. TROP-2 is an attractive therapeutic target because it's a pan-epithelial cancer antigen that's over expressed in tumor, but not so much in normal tissues. And thus it's an excellent target for antibody drug conjugates. The concept behind antibody drug conjugate is that of targeted payload delivery. The idea is that the antibody drug conjugate would bind to an antigen that's over expressed in cancer cells and not so much in normal tissues. Get internalized, get degraded in the lysosome and release payload which causes apoptosis of the cancer cell. Newer ADCs also have an additional mechanism of action, the bystander effect. Which allows the ADC to exert its effect even in cells that do not express the antigen.

Sacituzumab Govitecan is a first in class TROP-2 directed antibody drug conjugate. It's distinct from other antibody drug conjugate in that the antibody is highly specific for TROP-2. It has a high drug to antibody ratio, and finally, internalization and enzymatic cleavage is not required for liberation of SN-38 from the antibody. Hydrolysis of the linker can also release SN-38 cytotoxic payload extra-cellularly in the tumor microenvironment, providing a bystander effect.

Sacituzumab Govitecan was evaluated in the pivotal phase three trial comparing Sacituzumab Govitecan was a treatment of physician's choice for pretreated patients with metastatic triple-negative breast cancer. Primary outcome being progression free survival. The trial met its primary endpoint. It showed that patients who received Sacituzumab Govitecan and had an improvement in progression free survival. 5.6 months was a standard of care chemotherapy, 1.7 months. And this corresponded to a hazard ratio of 0.41. Furthermore, patients who received Sacituzumab Govitecan had an improvement in overall survival about doubling of overall survival with Sacituzumab Govitecan as compared to standard chemotherapy. This corresponded to a hazard ratio of 0.48. Patients who received Sacituzumab Govitecan had a median overall survival of about 12 months as compared to about six months with standard chemotherapy. Similar results were also noted with additional follow up on final database log presented at ASCO 2022. In terms of response rate, again, the response rate was higher with Sacituzumab Govitecan. A response rate of 35% with Sacituzumab Govitecan, versus 5% with standard chemotherapy.

In terms of side effects, the treatment-related adverse events noted with Sacituzumab Govitecan were predominantly due to the toxic payload SN-38. Neutropenia, anemia, diarrhea, nausea, and alopecia being the common side effects. Neutropenia being the most common side effect seen with Sacituzumab Govitecan. The incidence of febrile neutropenia was low, less than 10%. And patients were allowed to receive GCSF for management of neutropenia. And that's something that's recommended in routine clinical practice as well. There were no cases of severe cardiovascular toxicity, grade two neuropathy, or grade three interstitial lung disease with Sacituzumab Govitecan. And finally, in terms of biomarkers the drug targets TROP-2. So in the ascend trial, TROP-2 expression was analyzed and essentially the benefit with Sacituzumab Govitecan was seen regardless of TROP-2 expression. Even in tumors with low TROP-2 expression, patients who receive Sacituzumab Govitecan did better as compared to standard chemotherapy. And that's why in routine clinical practice TROP-2 expression is not required. Regardless of TROP-2 expression, patients derive benefit with Sacituzumab

Govitecan as compared to standard chemotherapy. And thus, it's not a biomarker that needs to be evaluated in routine clinical practice.

How about other drugs? There's another TROP-2 directed antibody drug conjugate called Datopotamab Deruxtecan. It's a TROP-2 directed antibody drug conjugate, has a topoisomerase, one inhibitor payload called Deruxtecan, and has a tetrapeptide-based cleavable linker. It has demonstrated activity in non small cell lung cancer. And in 2021, we saw results in metastatic triple negative breast cancer as well. Impressive clinical activity seen with Datopotamab Deruxtecan. And in terms of side effects, the common side effects being nausea and stomatitis. The incidence of diarrhea, and hematologic toxicity was lower in Datopotamab Deruxtecan as compared to Sacituzumab Govitecan, and thus has a differential toxicity profile as compared to Sacituzumab Govitecan.

And besides these there are multiple other antibody-drug conjugates in development, including Patritumab Deruxtecan, Trastuzumab Deruxtecan, and a host of other antibody-drug conjugates in clinical development.

Summary, Sacituzumab Govitecan, a first-in-class TROP-2 directed antibody-drug conjugate is the preferred treatment for patients with metastatic TNBC in the second line and beyond setting. You know, ongoing studies which are evaluating Sacituzumab Govitecan and other indications combination with immunotherapy as well as early breast cancer. Datopotamab Deruxtecan, or Dato-DxD, is another TROP-2-directed antibody-drug conjugate that has demonstrated activity in pretreated metastatic TNBC. And there are other targeted therapies in development that would target other genomic pathways and antigens overexpressed in breast cancer. Thank you so much for your attention.

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