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Antibody-Drug Conjugates: Targeted Treatments Providing Hope for Patients With Breast Cancer

The restrictive therapeutic index of chemotherapy has led to the emergence of antibody-drug conjugates (ADCs), medicines that combine the specificity of monoclonal antibodies (mAbs) with the cytotoxic effects of chemotherapy to deliver cytotoxic payloads to cancer cells. This targeted approach can reduce the side effects of chemotherapy and improve the effectiveness of treatment. Several ADCs, including ado-trastuzumab emtansine (Kadcyla), sacituzumab govitecan-hziy (Trodelvy), and fam-trastuzumab deruxtecan-nxki (Enhertu), are currently approved for treating some types of breast cancer (BC).

The ADC trastuzumab emtansine was approved specifically for treating human epidermal growth factor receptor 2 positive (HER2+) metastatic breast cancer (mBC) in patients who have previously been treated with trastuzumab and a taxane (paclitaxel or docetaxel) and who have already been treated for mBC or have developed tumor recurrence within 6 months of receiving adjuvant therapy. The US Food and Drug Administration (FDA) approval was based on the results of the EMILIA study, a phase 3 clinical trial that compared treatment with trastuzumab emtansine vs capecitabine + lapatinib in participants with HER2+, locally advanced, or metastatic BC. This trial emerged from the need for well-tolerated HER2-directed therapies for patients with this type of cancer. Trastuzumab emtansine consists of trastuzumab, a mAb that targets HER2 (which is overexpressed in about 20% of BCs), linked to emtansine, a cytotoxic payload that inhibits cell division. The trastuzumab emtansine group had a median overall survival (OS) of **29.9 months** vs 25.9 months in the capecitabine + lapatinib group, for a hazard ratio (HR) of 0.75 (95% CI: 0.64, 0.88). This trial emerged from the need for well-tolerated HER2-directed therapies for patients with this type of cancer.

Another ADC, sacituzumab govitecan, targets the Trop-2 protein, which is overexpressed in BC. This ADC includes a mAb that is linked to SN-38, a cytotoxic payload that inhibits DNA replication. Triple-negative breast cancer (TNBC) is a subtype of BC that does not have receptors for estrogen, progesterone, or HER2—making it more difficult to treat than other forms of BC. Sacituzumab govitecan is used to treat patients with metastatic TNBC who have received at least 2 prior therapies for metastatic disease. Sacituzumab govitecan is also approved for the treatment of patients with unresectable locally advanced or metastatic hormone-receptor–positive (HR+), and HER2-negative (HER2−) BC who have received endocrine-based therapy and at least 2 additional systemic therapies in the metastatic setting. Sacituzumab govitecan was the first Trop-2–directed ADC to demonstrate OS benefit in patients with HR+/HER2− mBC who had received prior endocrine-based therapy and at least 2 chemotherapies. It is now also recommended as a Category 1 preferred treatment for metastatic HR+/HER2− BC by the National Comprehensive Cancer Network, as defined in the Clinical Practice Guidelines in Oncology.

The results of the TROPiCS-02 study, which led to the FDA approval of sacituzumab govitecan, demonstrated a median OS of 14.4 months with sacituzumab govitecan vs 11.2 months with treatment of physician's choice (HR, 0.79; 95% CI: 0.65, 0.96; P = 0.02). This represents a 3.2-month improvement in survival and a 21% reduction in the risk for patient death. Before this medicine was approved, there were limited options to offer patients with BC after endocrine-based therapy and chemotherapy.

A third ADC, trastuzumab deruxtecan, targets the HER2 protein, like trastuzumab emtansine, but with a different cytotoxic payload. It consists of trastuzumab linked to deruxtecan, whose cytotoxicity inhibits

DNA replication. It is approved for the treatment of HER2+ mBC. Its FDA approval was based on the results of the DESTINY-Breast04 phase 3 clinical trial, which demonstrated that treatment with trastuzumab deruxtecan, when compared with standard-of-care chemotherapy, doubles progression-free survival among patients with mBC that expresses low levels of HER2. The median OS for patients in the HR+ group who received trastuzumab deruxtecan was 23.9 months vs 17.5 months for those who received chemotherapy. In the hormone-receptor–negative (HR−) group, the median OS for those who took trastuzumab deruxtecan was 16.6 months vs 10.3 months for those treated with chemotherapy.

The emergence of ADCs has shown promising advancements in the treatment of BC, particularly in patients with HER2+ or triple-negative disease. ADCs have given new hope to and prolonged life for patients living with pretreated HR+/HER2− mBC. ADCs also have the potential to provide a more effective and less toxic treatment option for patients with BC. However, further research is needed to fully understand their long-term effects and to develop new ADCs that target other types of BC.