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Trastuzumab deruxtecan in the treatment of adult patients with HER2-positive breast cancer

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ABSTRACT

In 2020, approximately 18,000 women in Poland were diagnosed with breast cancer, and 6,000 of them died. In recent years, we have witnessed significant progress in the diagnosis and treatment of breast cancer patients. When detected early and treated appropriately, the prognosis is very good, and even some patients with distant metastases have experienced long-term survival. The most common biological subtype is hormone receptor-positive breast cancer, accounting for about 70% of diagnoses, showing expression of estrogen and progesterone receptors. Triple-negative breast cancer and HER2-positive breast cancer each make up approximately 15% of all cases. In the treatment of advanced HER2-positive breast cancer, a combination of docetaxel with pertuzumab and trastuzumab is used in the first line. In subsequent lines of treatment, options include trastuzumab deruxtecan (T-DXd), trastuzumab emtansine, lapatinib, tucatinib, margetuximab, and trastuzumab.

Trastuzumab derukstekan is an immunoconjugate that, upon entering the cell, releases a cytostatic agent that destroys its genetic material and neighboring cells (the "bystander effect"). It significantly prolongs the time to disease progression and overall survival compared to standard treatments used in the second and subsequent lines of treatment. It represents an effective and valuable therapeutic option for patients with early-stage HER2-positive metastatic breast cancer.

Keywords: breast cancer, HER-positive breast cancer, trastuzumab deruxtecan

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Introduction

Breast cancer (BC) is the most common malignancy diagnosed in women in Poland and worldwide, and second, after lung cancer, cancer-related cause of death. In 2020, approximately 18,000 women in Poland were diagnosed with breast cancer and 6,000 died from it. The incidence of breast cancer is increasing in all age groups, which is primarily related to changes in women's lifestyles [1]. Postponing the first birth, childlessness, sedentary lifestyle, obesity, smoking, drinking alcohol, and prolonged hormone replacement therapy (HRT) are just some of the modifiable factors that contribute to the increased incidence of breast cancer [2].

Enormous progress in the diagnosis and treatment of breast cancer has been observed in recent years. If this disease is detected early and treated appropriately, the prognosis is very good, and long-term survival is observed even in some patients with distant metastases. There are several specific biological subtypes of BC distinguished in daily clinical practice, based on the status of estrogen, progesterone, and HER2 receptors, as well as Ki-67 proliferation index value.

The most common biological subtype is hormone-dependent BC, with positive expression of estrogen (ER) and progesterone receptors (PR), accounting for approximately 70% of cases. Both triple-negative (TNBC) and HER2-positive BC account for approximately 15%

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of all cases. They are characterized by an aggressive course, rapid cell proliferation, increased risk of disease recurrence, metastasizing to parenchymal organs, and development of treatment resistance [3].

HER2 receptor

The *HER2* gene is located on chromosome 17, and its amplification leads to overexpression of the HER2 receptor. There are various interchangeable terms in the literature, which describe this receptor. The name of HER2 results from its similarity to the human epidermal growth factor receptor (HER1). The HER2 receptor was derived from glioblastoma multiforme cell lines, one of the neuronal tumors, hence the name Neu. In turn, the name ErbB-2 is related to *HER2* gene similarity to the avian erythroblastosis oncogene B, encoding epidermal growth factor receptor (EGFR). Gene cloning showed that HER2, Neu, and ErbB-2 are encoded by the same ortholog.

The epidermal growth factor receptor family includes 4 receptors: HER1/EGFR, HER2, HER3, and HER4. The receptor is composed of an extramembrane part that binds to the ligand, a lipophilic transmembrane part, and an intramembrane part with tyrosine kinase activity. HER2 overexpression leads to its dimerization and activation of proliferation and repair pathways, including PI3K-AKT-mTOR, mainly in a ligand--dependent or independent manner. Activation of HER2-dependent mechanisms is one of the most important factors leading to growth and regeneration of breast cancer cells and apoptosis inhibition [4].

The *HER2* gene was discovered in 1984 by Weinberg's group. Subsequently, Dennis Slamon described the overexpression of the *HER2* gene protein product on the surface of aggressive BC subtype cells. In the mid-1990s, clinical trials were initiated with use of trastuzumab, a human monoclonal antibody that inhibits the dimerization of the HER2 receptor with other EGFR family receptors in patients with advanced HER-positive breast cancer [5]. In 2005, the results of a study involving approximately 10,000 patients with early breast cancer were published, showing that the use of trastuzumab in adjuvant treatment reduced the risk of recurrence by half and risk of death by approximately 30%. In addition to inhibiting signal transduction, trastuzumab stimulates antibody-dependent cytotoxicity and the immune system to destroy cancer cells; it also has anti-angiogenic effects and shows additive or synergistic activity with chemotherapy [6–8].

There are ongoing studies on new drugs that inhibit HER2 receptor: monoclonal antibodies (pertuzumab) and tyrosine kinase inhibitors (lapatinib, tucatinib, neratinib), which will significantly improve the prognosis of patients with early and advanced breast cancer [9–12]. Recently, immunoconjugates, i.e. a combination of an antibody with a cytostatic drug, which is called a "Trojan horse", are gaining more and more importance. After binding to the cellular surface receptor, the molecule penetrates the cell, releases a cytostatic agent that damages the genetic material and leads to cell apoptosis. In the next step, it leads to damage to neighboring cells, which is called the "bystander effect".

Advanced HER2-positive breast cancer

Based on the results of the Cleopatra study, chemotherapy combined with dual HER2 blockade with pertuzumab and trastuzumab is the standard of care in the treatment of patients with metastatic HER2-positive breast cancer. In patients with newly diagnosed metastatic or recurrent breast cancer, docetaxel was used in combination with two antibodies at least 12 months after completion of definitive treatment. After 6 courses of combination therapy, treatment with pertuzumab and trastuzumab was continued until disease progression or unacceptable side effects prevented further therapy. Among 808 enrolled patients, 402 patients were randomly assigned to triple therapy, and 406 patients received docetaxel in combination with trastuzumab and placebo. After a median follow-up of approximately 99 months, median overall survival (OS) in the experimental arm was 57.1 months and in the control arm 40.8 months [hazard ratio (HR) = 0.69; 95% confidence interval (CI) 0.58–0.82], and the risk of death was reduced by approximately 30% [10].

Until recently, the standard of care in the next treatment line was the use of trastuzumab emtansine. According to the results of the EMILIA study, which enrolled 991 patients, therapy with trastuzumab emtansine was associated with prolonged progression-free survival (PFS) compared to lapatinib and capecitabine (9.6 *vs.* 6.4 months; HR = 0.65; 95% CI 0.55–0.77; $p < 0.001$), as well as prolonged OS (30.9 *vs.* 25.1 months; HR = 0.68; 95% CI 0.55–0.85; $p < 0.001$) and a better objective response rate (43.6%, *vs.* 30.8%; $p < 0.001$). Trastuzumab emtansine showed not only greater effectiveness but also a more favorable safety profile and better tolerability in patients previously treated with taxanes and trastuzumab [13].

In patients previously treated with pertuzumab and trastuzumab in combination with docetaxel and trastuzumab emtansine, the use of tucatinib in subsequent line prolonged PFS (7.8 *vs.* 5.6 months, HR = 0.54; 95% CI 0.42–0.71; p < 0.001) and OS (21.9 *vs.* 17.4 months; HR = 0.66; 95% CI 0.50–0.88; p = 0.005) as compared with placebo with trastuzumab and capecitabine. Previous studies indicated the activity of tyrosine kinase inhibitors in combination with capecitabine in patients with central nervous system (CNS) metastases; however, adverse events limited treatment initiations. Blockade of the extramembrane and intramembrane domains in the experimental arm improved the prognosis of patients with stable and progressive brain metastases, with acceptable tolerance [12].

Subsequent treatment lines include a combination of lapatinib with capecitabine, trastuzumab with capecitabine, or another cytostatic. Due to the low objective response rate (9–27%) and short PFS (3.3–6.1 months), the search for a therapy with higher effectiveness was extremely important [11, 14–16].

Trastuzumab deruxtecan

Trastuzumab deruxtecan (T-DXd) is an immunoconjugate, a combination of trastuzumab with a cytostatic agent — a topoisomerase I inhibitor. The effectiveness of T-DXd was established in the phase II DESTINY-Breast01 study, which enrolled patients with advanced HER2-positive breast cancer after progression on trastuzumab emtansine therapy. The study showed an objective response rate of 61% and a benefit in terms of PFS prolongation [17].

Phase III DESTINY-Breast02 study was designed to confirm the effectiveness of T-DXd in patients previously treated with trastuzumab emtansine compared to the investigator's choice therapy. It enrolled 608 patients, of whom 406 were randomly assigned to the experimental arm and 202 to the lapatinib or trastuzumab with capecitabine arm. The median patient age was 54 years, and ER expression was detected in approximately 60% of patients in both arms. Fewer than 80% of patients had previously received pertuzumab-based therapy, almost 80% had metastases to parenchymal organs, and almost 20% had CNS metastases. The median of prior treatment lines, excluding hormone therapy, was 2 in both groups. Median PFS was in favor of T-DXd (17.8 *vs.* 6.9 months; HR = 0.36; p < 0.0001). Clinical benefits were observed in all subgroups, regardless of ER status, prior pertuzumab therapy, as well as parenchymal organ and CNS metastases. Median OS in the experimental arm was significantly longer than in the control arm (39.2 *vs.* 26.5 months; HR = 0.66; p = 0.0021). Objective responses were observed in 70% of patients treated with T-DXd and in 29% of patients in the investigator's choice therapy arm. Notably, 6% of patients in the T-DXd arm and 27% in the control arm received T-DXd after progression.

In the subgroup of patients with stable CNS metastases (18% in each arm), prolonged PFS was observed, and further analysis will help to precisely determine the effectiveness of T-DXd in this special patient population.

In total 14% of patients receiving T-DXd therapy and 5% of patients receiving therapy of the investigator's choice required treatment discontinuation due to adverse events. In the T-DXd arm, the predominant symptoms were pneumonia (6%) and interstitial lung disease (4%), while in the control arm, it was hand-foot syndrome (2%). There were 4 treatment-related deaths in patients receiving T-DXd: pulmonary complications occurred in 3 patients and acute myeloid leukemia in 1 patient. The most common adverse events were: nausea, vomiting, fatigue, alopecia, and hand–foot syndrome.

Interstitial lung disease (ILD) occurred in 42 (10%) patients in the T-DXd group and 1 (< 1%) patient in the control arm. The median time to ILD onset was 29.9 and 2.9 months, respectively.

Left ventricular dysfunction was observed in 18 (4%) patients treated with T-DXd and in 3 (2%) patients receiving therapy of the investigator's choice. Treatment was discontinued for this reason in 2 (< 1%) and 1 (< 1%) patients, respectively [18].

Median PFS in the DESTINY-Breast02 study was significantly longer than median PFS achieved in other studies using new therapies in previously treated patients with advanced HER2-positive breast cancer. In studies with trastuzumab emtansine, margetuximab, neratinib, and tucatinib, median PFS was 5.6 to 7.8 months. Obviously, it is important to remember that this is only a numerical comparison of the duration of response (DoR), and not a head-to-head comparison [12–15].

Encouraging results of T-DXd use after trastuzumab emtansine therapy in previously treated patients prompted researchers to evaluate the effectiveness and safety of this drug in earlier stages of BC. The DESTINY-Breast03 study compared the effectiveness of two immunoconjugates: trastuzumab emtansine and T-DXd. Trastuzumab emtansine consists of an antibody and a cytostatic agent — a microtubule inhibitor, while T-DXd contains a topoisomerase I inhibitor. The number of cytostatic molecules in relation to the antibody is more than twice as high in the case of T-DXd than in the case of trastuzumab emtansine (8 *vs.* 3.5).

Patients were qualified for the study after progression on trastuzumab and taxanes perioperative therapy due to advanced or recurrent disease during or up to 6 months after its completion. In total 261 patients were qualified for the experimental arm and 263 for the trastuzumab emtansine arm. The median age was approximately 54 years in both arms. Median PFS was over 4-fold longer in the T-DXd arm (28.8 months *vs.* 6.8 months; HR = 0.33; 95% CI 0.26–0.43). Median OS was not reached in the experimental arm, and the risk of death was reduced by approximately 35% (HR = 0.64; 95% CI 0.47–0.87; p = 0.0037). Objective responses were observed much more often in the experimental arm (79% *vs.* 35%). Complete responses were observed in 21% of patients treated with T-DXd and in 10% of patients receiving trastuzumab emtansine. The effectiveness of therapy was observed in all analyzed subgroups, regardless of ER status, use of pertuzumab, metastases in parenchymal organs, and CNS.

In 20% of patients in the T-DXd group and 7% of patients in the trastuzumab emtansine group, treatment was discontinued due to adverse events: pneumonia and interstitial lung disease, and thrombocytopenia and pneumonia, respectively. Pulmonary complications occurred in 15% of patients receiving the experimental drug and in 3% of patients receiving standard therapy, and no death due to these AEs was observed in either group. The median time to complication was 8.1 months for T-DXd and 11.7 months for trastuzumab emtansine. The remaining AEs were consistent with the drug's safety profile. Trastuzumab deruxtecan was used in subsequent treatment lines in 2% of patients in the experimental arm and 7% of patients in the control arm [19].

In the EMILIA study, the median follow-up was 19.1 months, and median OS was 30.9 months, while after 2 years of follow-up in the DESTINY-Breast03 study, median OS for the experimental arm was not achieved, and PFS achieved in this study was the longest achieved so far in patients with HER2-positive advanced breast cancer [13]. The results of previous studies have varied, with median PFS of approximately 10 months, and even the results of the CLEOPATRA study, using dual HER2 blockade combined with chemotherapy in the first treatment line were not so encouraging (PFS 18.7 months) [10].

The exceptional effectiveness of T-DXd in the treatment of patients with advanced breast cancer makes it revert to earlier stages of the disease. Currently, the DESTINY-Breast09 study is ongoing, with previously untreated patients with advanced HER2-positive breast cancer randomly assigned to 3 arms: docetaxel in combination with pertuzumab and trastuzumab, T-DXd in combination with pertuzumab, and T-DXd. The results of this study may be very interesting, especially considering safety profile and tolerability, with expected extraordinary effectiveness [20].

Conclusions

Trastuzumab deruxtecan is an effective and valuable therapeutic option for patients with advanced HER2-positive breast cancer at an early stage of treatment. In addition to the well-known gastrointestinal and hematological side effects, which are manageable in daily clinical practice, pulmonary complications constitute a new challenge and will require good cooperation of an interdisciplinary team including an oncologist, a radiologist, and a pulmonologist. The benefits resulting from previous experience encourage attempts to introduce the drug at an early stage of therapy, including perioperative treatment.

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Supplementary material

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