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TRASTUZUMAB - REVIEW OF USE AND EFFECTIVENESS IN THE TREATMENT OF HER2-POSITIVE NEOPLASM

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ABSTRACT

Treating cancers is a challenge that many scientists from around the world face every day. Thanks to the scientific advances, cancers are now divided not only by the organ they affect, but also into subtypes such as histological and molecular. Small molecules present on cancer cells have become the target of molecular drugs, making cancer treatment even more personalized for specific type. One of them is the use of trastuzumab - a targeted monoclonal antibody used in the treatment of cancers with overexpression of the HER2 protein on cell membrane. Trastuzumab inhibits the growth of cancer cells by blocking HER2 receptors. This mechanism is used in the treatment of HER2-positive breast and stomach cancer. In clinical trials, trastuzumab has been shown to have significantly higher rates of disease-free survival, absolute survival rate, median overall survival, progression-free survival and the duration of response than similar therapies without it. This makes it promising and useful in anticancer therapy in some neoplasm types. In addition, the safety profile has been checked and assessed in many respects, taking into account the side effects that this drug causes.

KEYWORDS

Trastuzumab, Cancer, Breast, Stomach, HER2

CITATION

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Introduction

Recent years have seen a dramatic increase in cancer incidence. It is estimated that around 20 million people worldwide are diagnosed with cancer each year, while in Poland alone, approximately 170,000 people develop cancer each year. Breast cancer is one of the most common cancers around the world, ranking first among women. According to the WHO, 2.3 million women were diagnosed with breast cancer in 2022, and 670,000 died because of it. Stomach cancer is one of the most common cancers too with a higher incidence in men including approximately 970 000 new cases around the globe in 2022. The increasing incidence of the disease compels the search for new treatment options. Advances in molecular science allow for more specific diagnosis and classification of cancers based on their genetic abnormalities, which enables use of targeted treatment. One treatment option is to block the proliferation of cancer cells with the HER2 receptor present on their cell membrane. It is a proto-oncogene which is a member of the human epidermal growth factor receptor (HER/EGFR/ERBB) family. In healthy cells its function is regulation of signals responsible for cell growth and division, which fails when mutation occurs. First reports of his oncogenic potential were presented in the 1980's [1]. Using transgenic mice that had the HER2 proto-oncogene, scientists proved that it can cause cancer in the mammary gland [2].

Further research showed that HER2 gene overexpression occurs in different forms of cancers including: breast cancer, stomach cancer, esophagus cancer, ovary cancer, colon cancer, bladder cancer, lung cancer, endometrial cancer, uterine and cervical cancer [3]. The presence of overexpression of the HER2 receptor or amplification of its gene is an unfavorable prognostic factor for the patient [4]. Patients with HER2-overexpressing breast cancer have a shorter disease-free survival compared to patients with HER2-negative breast cancer [5].

The presence of this receptor in gastric tumors increases the relative risk of death 5-fold compared to tumors without its expression [6]. Which is why the HER2 receptor became a target for scientists to search for molecular drugs that are capable of interacting with it. The goal was to find medicaments that could inhibit further growth of cancer cells by binding to the HER2 receptor. The breakthrough was the discovery of trastuzumab.

Trastuzumab is a humanized IgG1 kappa monoclonal antybody that selectively binds with high affinity to the extracellular domain of the HER2 (human epidermal growth factor receptor 2 protein) [7]. One of its mechanisms of action is immune mediated response which include the activation of antibody-dependent cellular cytotoxicity (ADCC). Activating natural killer cells (NK) by the Fc domain of trastuzumab activates the lysis of cancer cells [8].

In studies conducted on mice, it was observed that trastuzumab inhibited the angiogenesis process in experimental human breast cancer cells which prevented the cancer from growing [9]. Trastuzumab stops cell cycle at G1 by inducing the formation of p27/Cdk2 complex and acts as an inhibitor at critical signalling pathways: PI3K/Akt and ras-Raf-MAPK and also induces receptor HER2 downmodulation [10]. This article summarizes and presents the results regarding the efficacy and safety of trastuzumab therapy based on information collected from completed and ongoing clinical trials.

Methodology

This article is based on existing studies describing clinical application of trastuzumab in treatment of neoplasm types including HER2-positive breast cancer and stomach cancer. The references included in the bibliography were sourced from the PubMed database. The purpose of this paper is to gather available information regarding the efficiency and safety of trastuzumab and potential benefits from including it in therapy of breast and stomach cancers.

Results

As mentioned before trastuzumab is currently used in treatment of breast cancer and stomach cancer. Over the last few years this monoclonal antibody has been successfully tested for both safety and treatment effectiveness. The indications and results of its inclusion in treatment are described below.

Breast cancer

One of the largest and first clinical trials conducted with usage of trastuzumab is the HERA study, which enrolled over 5,000 women from various countries. After receiving primary treatment, these patients were randomly assigned to an observation group or to a group which received trastuzumab for one year or two years. The results were as follows: 10-years disease-free survival was 63% in the observation group, 69% in the group receiving trastuzumab for one year and 69% in the group receiving trastuzumab for two years. It corresponded with an absolute benefit of 6–8% in disease-free survival at 10 years for those receiving trastuzumab therapy for one year and 6.0% for those receiving trastuzumab therapy for two years compared with the observation group [11].

The National Surgical Adjuvant Breast and Bowel Project trial B-31 and The North Central Cancer Treatment Group trial N9831 investigated the addition of trastuzumab to chemotherapy for breast cancer patients. These trials included women who had undergone surgical removal of HER2-positive breast cancer. NSABP-B31 trial included two groups: the study group in which trastuzumab was added to doxorubicin, cyclophosphamide and paclitaxel and group control without trastuzumab. N9831 trials had 3 groups: group A: cyclophosphamide, doxorubicin and paclitaxel, group B: the same drugs and 52 weeks of trastuzumab after paclitaxel and group C: 52 weeks of trastuzumab with paclitaxel. The results showed that patients alive and disease-free at three years were 75.4% in the control group and 87.1% in the trastuzumab group. After 4 years it was 67.1% and 85.%, respectively. The absolute survival rate at 3 years was 94.3%in the trastuzumab group and 91.7% in the control group [12].

Results from the BCIRG 006 study also confirm the value of trastuzumab. The first group of patients received doxorubicin and cyclophosphamide followed by docetaxel. The second group received additionally trastuzumab to docetaxel. The third group received docetaxel plus carboplatin with trastuzumab. For the first group of patients: doxorubicin, cyclophosphamide and docetaxel, the 5-years rate of disease-free survival was 75% and a rate of overall survival was 87%. Patients who received doxorubicin, cyclophosphamide and docetaxel with trastuzumab (second group) had the 5-year rate of disease-free survival at 84% and the rate of overall survival at 92%. For patients receiving docetaxel plus carboplatin with trastuzumab the 5-year rate of disease-free survival was 81% and the rate of overall survival was 91%. Results according to nodal status and tumor size showed that node-negative patients' 5-years disease-free survivals were 93% in the second group, 90% in the third group compared to 85% in the first group. Also health-related quality of life questionnaires indicated the benefits of therapy with trastuzumab [13,14].

Gastric cancer

ToGA trial conducted with participation of 594 patients who were randomly assigned to a group where they received chemotherapy alone (cisplatin plus capecitabine or cisplatin plus fluorouracil) or a group where apart from chemotherapy they also received trastuzumab. Results showed that median overall survival was higher in the group receiving chemotherapy plus trastuzumab and amounted to 13.8 months vs 11.1 months in the chemotherapy alone group. Progression-free survival was also higher in the trastuzumab plus chemotherapy group at 6.7 months vs 5.5 months in the chemotherapy alone group. The duration of response was also significantly longer in the trastuzumab plus chemotherapy group at 6.9 months vs 4.8 months in the chemotherapy alone group. Patients with higher HER2 expression had longer overall survival than patients with lower HER2 expression. Patients with high HER2 expression who received trastuzumab plus chemotherapy had a longer survival compared to patients who received chemotherapy alone: 16.0 vs. 11.8 months. Added trastuzumab extended the Quality-adjusted Time Without Symptoms of Disease or Toxicity (Q-TWiST) by 2.42 months compared to receiving chemotherapy alone [15,16].

Colon cancer

An open-label, phase II trial concerned 21 patients. In the first weeks of the study, trastuzumab was administered along with chemotherapy, then after several cycles, trastuzumab was administered as maintenance therapy. Two patients reached the study endpoint, the rest discontinued the study due to disease progression. Results showed that median progression-free survival (PFS) was 4.3 months. Objective response during treatment was observed in 7 patients while disease stabilization was observed in 11 patients.

The presence of more HER2 receptors on cancer cells was characterized by a better response to treatment and PFS [17].

Discussion

The collected information allows us to confirm the clinical usefulness of trastuzumab in the treatment of breast and gastric cancer. Disease-free survival, absolute survival rate, median overall survival, progression-free survival and the duration of response were significantly higher in groups of patients who received trastuzumab as a treatment. It is also worth noting that trastuzumab therapy has significantly improved the quality of life of patients.

Trastuzumab is currently used in breast cancer as both neoadjuvant and adjuvant therapy, along with other chemotherapeutic agents or as monotherapy. However, better results are achieved when it is used in combination with other drugs. In gastric cancer, it is administered in conjunction with other pharmaceuticals for metastatic disease.

Studies have shown that patients with overexpression of the HER2 receptor on cell membrane responded better to treatment compared to those with reduced expression. Therefore, when qualifying for treatment, HER2 receptor levels should be considered by performing tests at specialized centers using immunohistochemical methods, FISH, and CISH.

It is also worth mentioning the side effects of the drug, which may influence patient selection for treatment. Among the more serious side effects are the occurrence of heart failure and reduced ejection fraction. Before starting treatment, patients should be examined for cardiac diseases and perform tests such as an ECG or ultrasound, which should also be performed during trastuzumab treatment to assess the effect of this drug on the patient's heart.

Special attention should be paid to patients with heart failure and those previously treated with anthracyclines or cyclophosphamide due to their cardiotoxic effect..

There is also widespread discussion about the possible mechanisms of resistance occurring during trastuzumab therapy. This mechanism may be caused by changes in the structure of the HER2 receptor or the activation of alternative signaling pathways in cells. In this case other targeted treatment is used.

Despite various concerns, trastuzumab remains a drug that has had a documented effective position in cancer treatment for many years.

Conclusions

Trastuzumab is effective in the treatment of breast cancer and gastric cancer. The drug's safety profile is known, so it can be effectively and safely included in the therapy. Added trastuzumab to treatment shows advantages over other standard therapies in key indicators considered in clinical trials like disease-free survival or median overall survival. Due to the presence of HER2 receptors not only on breast or stomach cancer cells but also on colon cancer, esophagus cancer, ovary cancer, bladder cancer, lung cancer, endometrial cancer, uterine cervix, the possibility of using trastuzumab in other HER2-positive cancers should be further explored with purpose of including trastuzumab in those neoplasm treatment. It is also worth paying attention to the HER2 receptor and its structure in order to discover other possible capture points that can inhibit the growth and induce the death of cancer cells. Recently the U.S. Food and Drug Administration (FDA) granted accelerated approval for using trastuzumab with other HER2 inhibitor tucatinib in HER2-positive colorectal cancer which shows that research in this direction may bring benefits in the treatment of many other cancers and enable patients to access advanced personalized therapies using HER2 inhibitors acting on multiple endpoints which could save many patients suffering from neoplasm around the world.

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