Case report

Lapatinib in the treatment of advanced HER2-positive breast cancer

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ABSTRACT

The overexpression of the HER2 receptor and its gene amplification are observed in c. 20% of newly diagnosed cases of breast cancer and associated with a more aggressive clinical course and poorer prognosis. New HER2-targeted drugs, such as lapatinib, pertuzumab and trastuzumab emtansine, significantly improve patient outcomes. The article reviews the role of lapatinib in HER-targeted therapy and describes the treatment sequence of two women with HER2-positive advanced breast cancer.

Key words: advanced breast cancer, human epidermal growth factor receptor 2, HER2, lapatinib, capecitabine

INTRODUCTION

The overexpression of the human epidermal growth factor receptor 2 (HER2) is an aggressive biological feature associated with c. 20% of all diagnosed cases of early breast cancer. Despite increasingly better treatment methods and combined therapies, the HER2-positive type continues to pose a serious clinical problem.

Its treatment relies on the blocking of signal transmission along the HER2 receptor pathway, which is responsible for the proliferation and survival of cancer cells. The first molecule ever used for that purpose was trastuzumab, a monoclonal antibody that inhibits the extracellular domain of the HER2 receptor. First approved for the palliative treatment of HER2-positive breast cancer in Europe in 2000, six years later trastuzumab was also registered for use in adjuvant therapies [1, 2].

Another drug, lapatinib, was registered in Europe in 2008. The substance serves as an intracellular tyrosine-kinase inhibitor of two receptors:

- the endothelial growth factor receptor (EGFR), and
- the HER2.

Even more drugs targeted at blocking the HER2 receptor are available today, such as, for instance, pertuzumab, trastuzumab emtansine (TDM1, a conjugate of trastuzumab and a microtubule inhibitor), and neratinib, which is still approved only in the United States. The appropriate treatment sequence needs to be established in later course.

CASE STUDY 1

In 2004, a 48-year-old patient was diagnosed with locally advanced breast cancer (labeled cT3 N1 according to the TNM classification). During pre-operative treatment, she was administered 8 courses of chemotherapy with doxorubicin and cyclophosphamide; due to an increased risk of cardiotoxicity, current guidelines recommend no more than four. Since the patient was treated in another center, the rationale for such prolonged pre-operative therapy is not known. The woman then underwent radical right-sided mastectomy and lymphadenectomy. Post-operative histopathological examination showed an invasive ductal carcinoma with partial response to treatment: type T2 N1 according to the TNM system, and immunohistochemical assays allowed to further diagnose it as the luminal B type with the overexpression of the HER2 receptor. Due to the advanced stage of the disease, the patient underwent radiotherapy targeted at the scar area, as well as the right-side supraclavicular and axillary lymph nodes. Adjuvant treatment was based on an aromatase inhibitor, anastrozole, because the medical interview revealed that she had previously undergone total hysterectomy. Hormonal treatment was terminated in March 2009.

Fourteen months later, in May 2010, the patient suffered a relapse. CT scans revealed numerous secondary lesions in the lungs; two were surgically removed in order to determine the status of ER, PgR, and HER2 receptors. Microscopic analysis revealed that the breast cancer had already infiltrated lymphatic vessels and the pleural cavity, while immunohistochemical assays revealed the presence of estrogen and progesterone receptors and the overexpression of the HER2. Additional tests, such as the echocardiogram, confirmed that the ejection fraction (EF) had dropped to 43%, even though no clinical symptoms of circulatory failure were observed. The patient was referred to the Otwock European Health Center for consultation and further cardio-oncological treatment.

Because of reduced heart function parameters, she could not be put on combined treatment with a HER2-targeted drug. Appropriate cardiac treatment was thus introduced, along with capecitabine-based monotherapy. A total of 8 courses were administered before May 2011. The patient tolerated the treatment very well and no further deterioration in heart function was observed. Side effects included the palmar-plantar erythrodysesthesia syndrome (grade 1). A follow-up CT scan performed after treatment confirmed that the disease had stabilized. Supporting hormonal therapy was then introduced, with tamoxifen at a single daily dose of 20 mg.

After 20 months, in February 2013, the patient began to report intense headaches, dizziness, and vomiting. An MRI scan of the central nervous system revealed a focal metastasis (33 mm in diameter) in the left hemisphere of the cerebellum, accompanied by a large edema. The latter was surgically removed. Histopathological examination confirmed the presence of breast cancer invasion with biological parameters as described above and the patient underwent radiotherapy (30 Gy in total) targeted at the total cerebral area. Additional imaging tests showed the progression of pulmonary lesions, as well as new metastases in the liver. The EF, as determined by the echocardiogram, equaled 45%.

In June 2013, the patient was put on docetaxel-based therapy. A total of 8 courses were administered before December 2013

and she was under observation throughout the duration of treatment. In June 2014, a massive progression of the disease occurred. The EF stood at 50%. Following cardiac evaluation, in July 2014, the patient was qualified for therapy with trastuzumab under the National Health Fund drug program, accompanied by hormonal treatment with letrozole. After three courses, imaging tests confirmed partial response to treatment, which persisted over the next several months. A total of 16 courses of trastuzumab were administered. In July 2015, a check-up CT scan showed a further progression of the disease, with new lesions in the pleural cavity. The patient was enrolled in the National Health Fund drug program and put on treatment with lapatinib (1250 mg/24 h on a continuous basis) and capecitabine (2000 mg/m^2 of BSA/24 h for 14 days with a 7-day break administered in 21-day cycles). After 8 courses, the woman reported dermatological complications, including grade 3 palmar-plantar erythrodysesthesia, as evaluated on the basis of the CTC (*Common Toxicity Criteria*). The dosage of cabecitabine was first reduced and then the drug was withdrawn altogether. When the symptoms subsided to grade 1, the patient continued on her treatment with the previously prescribed dose of lapatanib. The therapy was only suspended after the 14th course of the drug when the EF dropped to 35%. Three weeks later, however, echocardiographic parameters considerably improved (EF = 45%), which allowed the patient to resume treatment, which included a total of 17 administrations of lapatinib and capecitabine, and the disease was stabilized throughout the period.

In 2016, the patient suffered an ischaemic brain stroke and was admitted to a rehabilitation facility for several months. Her health, however, continued to deteriorate. According to the last piece of information obtained from her family in January 2017, the woman already required home hospice care.

DISCUSSION

In the case described above, lapatinib was used in accordance with the registration guidelines based on the EGF100151 trial. The trial group included patients with advanced or metastatic HER2-positive breast cancer, all after ineffective treatment with anthracyclines, taxanes, and trastuzumab. Lapatinib at a continual dose of 1250 mg/24 h was combined with capecitabine, at 2000 mg/m^2 of BSA/24 h administered in 2 doses over 14 days of a 21-day cycle. As compared with capecitabine-based monotherapy, the treatment significantly increased the time to progression (8.4 vs. 4.4 months; HR = 0.49; 95% CI: 0.34–0.71; $p < 0.001$) [3]. Time to progression was also shown to have no correlation with the location of metastases, the number of neoplastic foci, the concentration of estrogen and progestagen receptors, or with the length of previous trastuzumab-based therapy [4].

No cross-resistance was observed between lapatinib and trastuzumab. The treatment is also effective in patients previously treated with capecitabine; the outcomes, however, are little worse than those observed in patients who have not received the drug [5].

The most frequent adverse effects included:

- diarrhea
- the hand-foot syndrome
- nausea
- vomiting
- skin rash.

Only 13% of patients discontinued the treatment on account of these adverse effects [3]. The two-drug program did not cause any deterioration in quality of life (QoL) parameters [6].

Treatment with lapatinib rarely caused cardiac complications, the most frequent of which involved a reversible, asymptomatic decrease in the ejection fraction. Asymptomatic cardiac events affected only 1.4–1.6% of patients; as few as 0.2% suffered asymptomatic heart failure. The EF decreased to a mean value of 43% and the event, on average, occurred in the 13th week of treatment and continued for a mean of 7.3 weeks. The parameter improved in 88% of patients. Neither combined therapy with several HER2-targeted drugs, nor previous treatment with trastuzumab and anthracycline increased the risk of heart complications [7, 8].

The patient in question received lapatinib and capecitabine for a total of 14 months. The treatment was well-tolerated and the disease was brought under control; no progression was observed in the CNS or the lungs. Despite the presence of echocardiographic markers of heart failure, the patient underwent treatment with two drugs, one targeted and the other cytostatic, which could further affect heart function. Trastuzumab and lapatinib were both administered under strict cardio-oncological supervision and no major, irreversible complications were observed. The treatment allowed the patient to enjoy a good quality of life, maintain daily activity, and continue professional work in the long run. Thanks to the optimal sequence of combined treatment, the patient survived for more than 6 years after the initial diagnosis of the metastatic lesions in the lungs.

CASE STUDY 2

In 2013, a 56-year-old woman was diagnosed with early breast cancer. The patient did not agree to conservative treatment and, in December 2013, underwent left-sided mastectomy with the sentinel lymph node procedure. Histopathological examination allowed to diagnose an invasive ductal carcinoma (G2/3 pT1c N0), with the expression of steroid receptors and the overexpression of HER2 (3+). The patient was first treated in another center. In January 2014, the head physician ordered a CT scan, which revealed metastases in the lungs and bones. The patient was referred for treatment at the Otwock European Health Center, in the framework of a clinical trial of docetaxel, pertuzumab, and trastuzumab. In October 2014, following 10 courses, a follow-up CT scan showed that the disease had progressed. The patient was enrolled in the National Health Fund drug program and prescribed treatment with lapatinib (1250 mg/24 h, continual) and capecitabine (2000 mg/m^2 of BSA/24 h for 14 days with a 7-day break in 21-day cycles). After 1 course, the patient reported symptoms of grade 3 toxicity according to the CTCAE (*Common Terminology Criteria for Adverse Events*):

- diarrhea that lasted 2 weeks
- dehydration
- electrolyte imbalance.

Accordingly, during the second course of lapatinib, capecitabine was replaced with an aromatase inhibitor, letrozole. In December 2014, the patient suffered a seizure attack with a loss of consciousness. An MRI scan of the central nervous system revealed numerous metastases in both brain hemispheres and the patient underwent radiotherapy (20 Gy) targeted at the entire cerebral area. The follow-up CT chest scan showed the partial regression of lung metastases. In accordance with the criteria of the National Health Fund drug program, treatment with lapatinib had to be terminated on account of the new lesions in the brain. However, clear indications for further targeted therapy existed, especially because of secondary lesions in the CNS and the lungs, and the treatment was continued on commercial terms. Over the next year, imaging tests continued to show the partial regression of lesions in the CNS and the lungs. Two episodes of tonic-clonic seizures followed, but the results of imaging tests did not change. Treatment with lapatinib and letrozole was continued. After 4 more months, in March 2016, another seizure attack occurred. Imaging tests showed hemorrhagic foci in metastatic lesions. The dose of antiepileptic drugs was increased and the patient's general condition improved. Targeted treatment continued as before. No disease progression was observed in imaging tests but the patient's neurological condition soon deteriorated to the point that further treatment was impossible.

DISCUSSION

In the case described above, lapatinib was used in accordance with the guidelines of the EGF30008 trial, i.e. in combination with hormonal therapy based on an aromatase inhibitor, letrozole. The plan prescribes a higher dose of lapatinib (1500 mg/24 h) than that administered in combined treatment with capecitabine. As compared with letrozole-based monotherapy, the treatment significantly increased the time to progression (HR = 0.71; 95% CI: 0.53–0,96; p = 0.019; 8.2 vs. 3 months), and clinical advantage, defined as a response that persists for at least 6 months, was more frequently observed (48% vs. 29%; p = 0.003) [9].

Patients with HER2-positive breast cancer are at a particularly high risk of metastases. During trastuzumab-based treatment, 10–48% develop symptomatic lesions in the brain [10–14].

Because of its high molecular mass and physicochemical properties, trastuzumab largely fails to cross the blood-brain barrier, and thus shows little effectiveness in the prevention of cerebral metastases. These often occur even when the extracranial foci are under control.

Lapatinib is a smaller molecule with a greater ability to cross the blood-brain barrier. Interestingly, the registration trial EGF100151 showed that CNS metastases were significantly less frequent in patients treated with lapatinib and capecitabine than those who received capecitabine-based monotherapy (2% vs. 6%) [3]. This warranted the conclusion that lapatinib penetrates into the central nervous system and may prevent CNS metastases, as well as treat secondary CNS lesions already present, which was supported by further research. When treated with lapatinib and capecitabine after prior radiotherapy, approximately 20% of patients with symptomatic brain metastases show objective response to treatment and a general improvement in neurological condition [16, 17].

Combined treatment with lapatinib and capecitabine was tested on a very large group of patients with CNS metastases in the framework of an expanded access program. Objective response to treatment was observed in 10–38% of patients [5, 17, 18].

Lapatinib is also active in CNS metastases not previously treated with radiotherapy, as confirmed by a phase II clinical trial (LANDSCAPE) [19]. 65.9% of patients showed objective response to treatment, even though total regression was not observed. The mean time to progression equaled 5.5 months and time to radiotherapy – 8.3 months. The patient discussed above received lapatinib and letrozole for nearly 2 years. Despite its advanced

stage and the presence of brain metastases, which considerably worsened the prognosis, the disease was put under control and did not progress in the central nervous system. The treatment was well-tolerated.

SUMMARY

Both case studies attest to the significant long-term clinical advantage of lapatinib combined with capecitabine and letrozole in the treatment of HER2-positive metastatic breast cancer after the failure of trastuzumab-based targeted therapy. Patients with brain metastases may particularly benefit from the treatment. Lapatinib is well-tolerated and has a well-studied toxicity profile. If necessary, protocols for therapy modification are available.

Blocking the HER2 receptor may lead to cardiac complications, but the latter are more frequent during treatment with trastuzumab. Follow-up protocols, including heart function tests, allow to detect potential cardiotoxic effects at an early stage. The introduction of appropriate procedures, the treatment of heart dysfunctions, and further strict cardio-oncological supervision ensure the safety of the treatment.

CONCLUSIONS

New drugs that focus on blocking signal transmission along the HER receptor pathway lead to a significant change of prognosis in HER2-positive breast cancer. The choice of the optimal treatment sequence depends on:

- earlier adjuvant treatment
- time to relapse
- previous anti-HER2 therapies
- drug availability.

Lapatinib is a drug with confirmed effectiveness, a good safety profile, and a well-defined role in the treatment of advanced breast cancer.

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