Toxicity profile of lapatinib plus capecitabine in advanced breast cancer – a single-centre follow-up study

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ABSTRACT

Breast cancer is the most prevalent female neoplasm in Poland as well as in the rest of the world, accounting for 25% of all cancers. Lapatinib is a reversible inhibitor of the HER-1 and HER-2 tyrosine kinase receptors. Combined with capecitabine, it is administered in patients suffering from advanced breast cancer with HER-2 receptor overexpression.

The present article analyses data obtained from medical records of 24 breast cancer patients treated with lapatinib and capecitabine in the years 2010–2015, in order to examine the treatment-related toxicity. The major adverse effects observed under treatment included diarrhoea, nausea, emesis, skin toxicity, and elevated transaminases. In 3 patients, grade 3 adverse events were reported, as assessed in accordance with CTCAE. The most frequent cause behind the cessation of treatment was disease progression. The analysis has indicated that lapatinib plus capecitabine is a well-tolerated treatment regimen.

KEY WORDS: lapatinib, capecitabine, breast cancer, adverse reactions

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INTRODUCTION

Breast cancer is the most prevalent female neoplasm in Poland and in the rest of the world, accounting for 25% of all cancers. In 2010, in Poland, 15 784 new cases of breast cancer were diagnosed, and 5226 breast cancer-related deaths were registered [1]. Around 5–10% of all breast cancers are diagnosed at the stage of metastatic disease, and in around 20% of patients who undergo radical treatment, the disease relapses (be it local recurrence or distant metastases) [2].

Treatment plan should be elaborated on the basis of the tumour molecular profile, the degree of disease advancement, and the patient's general condition. Presently, it is of great clinical significance to be able to differentiate between 3 major breast cancer types, different in terms of their biological features, clinical course of the disease, and susceptibility to treatment. The 3 types include the hormone receptor-positive cancer, whose cells express the oestrogen receptor, the HER-2-positive breast cancer, and the triple-negative cancer, whose cells have neither the oestrogen nor the progesterone receptors, and whose HER-2 receptor expression is not elevated [3].

Discovery of molecular mechanisms in breast cancer was a turning point in the treatment, and made it possible to apply a therapy targeted at specified molecules involved in the process of cancer formation and progression.

The HER-2 receptor is normally present on the surface of many cells, while in around 20% of breast cancer patients it is overexpressed, which contributes to an unfavourable prognosis in that group of patients [4]. The HER receptors, including 4 structurally related receptors, consist of the extracellular, transmembrane and intracellular domain that exhibits tyrosine kinase activity. Once the ligand binds with the extracellular domain of the receptor, the signalling pathway is activated [5]. In breast cancer pathogenesis, a special role is played by abnormalities in the transmission of signals related to the HER-2 receptor activity. Lapatinib is a small molecular tyrosine kinase inhibitor that blocks the HER-1 and HER-2 receptors, causing reversible inhibition of the tyrosine kinase that is linked to the human epithelial growth factor receptor (HER-1 and HER-2) [3]. Moreover, it inhibits the intracellular domain of the HER-2 kinase whereas for instance trastuzumab targets the extracellular domain. Lapatinib prevents transmission of the signal released by a part of the HER-2 receptor, once it has lost its extracellular domain.

It has been demonstrated that combining lapatinib with capecitabine in the treatment of breast cancer prolongs progression-free survival [6]. Due to the relatively small molecular size, lapatinib penetrates the blood–brain barrier, which may be particularly efficacious in the treatment of breast cancer metastases to the brain [3].

Small-molecule tyrosine kinase inhibitors selectively impact neoplastic cells, which is why the treatment is well-tolerated. In particular, it is free of the typical myelotoxic symptoms associated with chemotherapy.

The most frequently reported adverse reactions related to the treatment with lapatinib and capecitabine include diarrhoea, skin and nail lesions, nausea, and fatigue. The aim of the analysis below was to assess the incidence of adverse events in the course of the lapatinib plus capecitabine treatment.

STUDY GROUP AND METHODS

We have analysed data taken from the medical records of breast cancer patients treated with lapatinib plus capecitabine. The analysis included patients treated at the Oncology Department in Elbląg from April 2010 through October 2015. All of the patients were histopathologically diagnosed with metastatic breast cancer, and had documented overexpression of the HER-2 receptor (IHC 3+ score) or *HER-2* gene amplification (FISH score of 1+). At least 2 treatment regimens, including anthracyclines and taxanes, had been offered to all the patients, with confirmed treatment failure or contraindications to further use. Additionally, disease progression had been reported in them following treatment with trastuzumab.

The database identified 24 metastatic breast cancer patients treated with lapatinib plus capecitabine. The patients who initiated the above-mentioned treatment were aged 29–76. Most of them (70%) had stage III and IV of the primary disease. In 12 patients, progression within the central nervous system was the reason behind initiating the treatment with lapatinib plus capecitabine.

The patients received lapatinib dosed at 1250 mg daily, combined with capecitabine dosed at 2000 mg/m^2 daily for the first 14 days, using the 21-day treatment cycle. Depending on the intensity of adverse reactions, the drug dose could be reduced to 50–80% of the baseline dose. Treatment was continued until disease progression or unacceptable toxicity. Efficacy of the lapatinib plus capecitabine treatment regimen was not assessed, i.e. parameters such as the rate of response to chemotherapy, progression-free survival, and overall survival were not examined.

TOXICITY ASSESSMENT

Adverse reactions were assessed for patients who had received at least 1 treatment cycle. Complications under treatment were analysed on the basis of the patients' medical histories. The intensity of adverse events was determined in accordance with the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0, elaborated by the National Cancer Institute [7].

RESULTS

Gastrointestinal complications

The most frequently observed adverse effect under the treatment was diarrhoea, reported in 14 patients (58%). CTCAE grade 3 diarrhoea affected 1 patient. In 5 patients, diarrhoea was the reason behind capecitabine dose reduction, and in 3 of them it resulted in the reduction of the lapatinib dose. Apart from dose reduction, symptomatic treatment was administered in accordance with the management algorithm presented in table 1. Nausea and emesis occurred in 70% of patients, but its intensity was limited to grade 1 and 2.

Skin and mucosa toxicity

Amongst the most frequently reported skin-related complications, there were the following: the hand-foot syndrome, exanthema, pruritus and skin dryness, lesions around the nails, and inflammatory lesions of the oral cavity mucosa. In total, skin toxicity affected 13 patients. In 9 of them, the hand-foot syndrome was observed, including one grade 3 case. The syndrome resulted in the capecitabine dose reduction in 5 patients, and in the reduced dose of lapatinib in 1 patient while 1 patient had to cease the combined treatment altogether due to that complication, and switch over to lapatinib monotherapy. Thus prevention plays an important role. Before the initiation of the treatment, patients were duly informed about the possibility of skin lesions, and were instructed on how to prevent them. Externally applied emollients as well as combination preparations, including glucocorticosteroids and antibiotics, e.g. betamethasone dipropionate and gentamicin, were effective against skin toxicity, followed by creams or emulsions containing metronidazole or (less frequently) antibiotics, such as erythromycin and clindamycin.

Liver function abnormalities

In 3 patients the values of liver transaminases were elevated. The liver enzymes went back to normal after a 3-week-long break in treatment. In 1 patient there was CTCAE grade 3 toxicity following the 4th treatment cycle, which resulted in treatment termination.

DISCUSSION

Our analysis has indicated that combined treatment with lapatinib plus capecitabine is a well-tolerated regimen. Grade 3 toxicity was reported in 3 patients, and included events such as diarrhoea, the hand-foot syndrome, and elevated liver transaminases. The longest treated patient, who has received 39 cycles so far, required lapatinib dose reduction, starting from the 3rd treatment cycle, due the grade 2 hand-foot syndrome. In the majority of patients, adverse events occurred after the first treatment cycles (2nd–3rd cycle). The major cause of the treatment termination was disease progression, and 2 patients decided to discontinue treatment due to unacceptable toxicity.

TABLE 1.

Management algorithm for diarrhoea in the course of treatment with lapatinib plus capecitabine.

CTCAE toxicity grade	Therapeutic action	Dosage of lapatinib plus capecitabine	To be done before the initiation of treatment
1–2	• lactose-free and fibre-free diet • orally administered fluids (isotonic fluids 1 l/24 h) • small meal portions • loperamide – initial dose of 4 mg, followed by 2 mg every 4 hours or 2 mg after each loose stool (continuation of treatment for at least 12 hours without diarrhoea)	Continuation of treatment	• take patient's gastrointestinal history (including the frequency and consistency of the stools passed) • rule out gastrointestinal tract infection • assess the patient's diet and offer dietary counselling
≥ 3	• oral isotonic fluids (1–1,5 l/24 h), consider intravenous fluids • consider hospitalisation of the patient • continue treatment with loperamide (maximum dose of 16 mg/24 h)	Discontinuation of treatment until the adverse events are reduced to grade ≤ 1	• complete patient's history with additional symptoms (e.g. contractile pain, nausea, emesis, fever) • collect faecal specimen for stool culture

TABLE 2.

Adverse events observed in the course of treatment with lapatinib plus capecitabine (n = 24).

Adverse event	Complication incidence n (%)
diarrhoea	14 (58%)
hand-foot syndrome	9 (38%)
skin lesions	7 (29%)
lesions around the nails	4 (17%)
liver toxicity	3 (13%)

A randomized phase 3 trial assessing the efficacy and toxicity of combined treatment with lapatinib plus capecitabine reported the following most frequently observed adverse events: diarrhoea, the hand-foot syndrome, nausea, emesis, and rash. Diarrhoea affected 60% of the patients treated with the combined regimen, and 39% of the patients on capecitabine only. Grade 3 or 4 diarrhoea affected 13% and 11% of patients respectively. In both groups, the hand-foot syndrome was observed in 49% of subjects. Rash occurred in 27% of patients subject to combined therapy, as compared to 15% of patients in the course of monotherapy with capecitabine. In 4 patients under combined treatment, and in 3 patients treated with capecitabine, serious liver and bile ducts complications were reported [8].

The management of diarrhoea remains empirical, and is generally based on expert opinions. Early diagnosis and treatment as well as modification of the lapatinib dose helps prevent serious complications. The analysis published by Crown et al., involving 2093 patients treated with lapatinib, indicated that in 40% of the diarrhoea cases reported, the symptoms occurred within the first 6 days of a cycle, and lasted 7–9 days on average [9].

The American Society of Clinical Oncology determined the standards of dietary management in diarrhoea. The recommendations include withdrawal of products containing lactose and fibre, increased intake of fluids (8–10 cups a day), and frequent ingestion of small meal portions [10].

In turn, the neoALLTO trial analysing the efficacy of lapatinib and trastuzumab monotherapies as well as that of their combination in neoadjuvant treatment of patients with HER-2-positive breast cancer, indicated a statistically significantly more frequent occurrence of rash, diarrhoea, and liver toxicity (defined as elevated transaminases, alkaline phosphatase and/or bilirubin) in the study arms involving lapatinib. It was observed that the occurrence of rash at the beginning of treatment was associated with a higher rate of pathological complete response, mainly in females over the age of 50. A similar association was not observed for diarrhoea or hepatotoxicity [11].

Drugs targeting the epidermal growth factor receptor (EGFR), such as lapatinib, have a similar spectrum of dermal adverse effects. The mechanism behind the occurrence of rash is linked with the role that EGFR plays in maintaining the homeostasis of the epidermis, hair follicles and sebaceous glands [12, 13]. Results of different studies indicate that EGFR inhibition has a considerable impact on the proliferation and differentiation of the hair follicle and epidermal cells, involving the basic cytokines – interleukin 1 and tumour necrosis factor α [14]. Intensified eruptions (CTCAE grade 3) occur rarely, in < 10% of the patients [15, 16]. In those patients, both topical and systemic treatment is required, sometimes combined with dose reduction or even temporary discontinuation of the EGFR inhibitor treatment. Folliculitis is usually reported to last for up to 6 months from the initiation of treatment, while later complications chiefly include hair and nail lesions as well as skin dryness [17].

CONCLUSIONS

Information about prevention, early diagnosis, and adequate management of adverse events are all important factors determining the success of combined treatment with lapatinib and capecitabine.

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Authors' contributions:
Zuzanna Borysiewicz: 80%
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