Everolimus – effectively reverses acquired resistance on endocrine therapy of patients with advanced breast cancer. A case report

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ABSTRACT

Breast cancer is the most common malignancy among women in Poland. Endocrine therapy is the first line of treatment in hormone--receptor-positive advanced breast cancer. Progression during endocrine therapy is unavoidable. Administration of mTOR inhibitor gives a chance of reversing the acquired resistance. This paper presents a case report of a patient with metastatic breast cancer successfully treated with everolimus added to endocrine therapy.

KEY WORDS: breast cancer, everolimus, endocrine therapy

INTRODUCTION

Breast cancer is the most common malignancy among women worldwide. Poland is a country with medium morbidity rate, however it is the most common malignancy among Polish women (22%). Since the 80's of the XXth century morbidity rate is increasing, with stable mortality rate [1]. It seems to be the result of better diagnostic and treatment individualization. In the years 2010–2025 an increasing tendency in morbidity rate is predicted. The highest risk occurs in women aged 50–69 years old, and in that group screening is recommended [2]. Invasive carcinoma – no special type (NST) (former *ductal carcinoma*) accounts for 70–80% of all malignancies. In diagnostic, beside physical examination, breast imaging, abdominal ultrasonography and chest X--ray are obligatory. In higher stages also bone scintigraphy should be performed. Before starting the treatment, it is necessary to asses stage of the disease, receptor status (ER, PR, HER-2) and the Ki-67 labeling index. Treatment of the breast cancer is multidisciplinary and according to the European Society of Breast Cancer Specialists (EUSOMA) guidelines should take place in fully equipped multidisciplinary and multiprofessional breast clinics – *breast units*, which are diagnosing and treating breast cancer – at least 150 newly diagnosed cases a year [3]. This paper presents a case of a breast cancer patient effectively treated with everolimus with exemestane.

CASE REPORT

In June 2000, 48-years old female patient with lump in the left breast was admitted to Maria Sklodowska-Curie Memorial Institute of Oncology in Cracow. Physical examination revealed mobile tumor sized 3 x 3 cm, localized on the border of upper quadrants in the left breast. Physical examination did not show any other abnormalities. There was no cancer history in the patient's family. Performed mammography revealed tumor with maximal diameter of 2,5 cm. Fine needle aspiration biopsy (FNA) detected cancer cells. Imaging tests confirmed that the disease was localized (T2N0M0). On the 20th of June 2000 Patey's mastectomy was performed. Postoperative histological examination reported: *carcinoma ductale infiltrans Bloom I*, ER and PR positive, HER-2 negative. Tumor cells were found close to the edge on the side of chest wall. Cancer metastases were found in 1/12 removed axillary lymph nodes. Patient was qualified to adjuvant chemotherapy. From July to December 2000 six courses of CMF (cyclophosphamide, methotrexate, 5-fluorouracil) chemotherapy were administered, with acceptable treatment tolerance. Chemotherapy was followed by endocrine therapy with tamoxifen. During tamoxifen treatment anxiety and depression symptoms occurred. Patient was treated in mental health outpatient clinic, were depression medications were prescribed. In March 2006 five years period of endocrine therapy was finished. Patient stayed under oncologists control, without any signs of the disease. In January 2010 patient was admitted to the Institute with severe pain in sternum and ribs. Performed bone scintigraphy revealed isolated osteosclerotic focus in sternum. Visceral metastases were not found, anastrozole endocrine therapy was administered. Bisphosphonates (clodronate) therapy was started. Patient was qualified to radiotherapy. Considering solitary metastatic focus and good general condition, patient received 50 Gy dose in 25 fractions (from March to May 2010). As a result of the therapy, bone pains relieved and regression of sternum metastasis was achieved. In April 2011 bone scintigraphy revealed a progression of sternum metastasis and new lesions all over the skeleton. Intravenous bisphosphonate (pamironate) was administered, patient was qualified to next--line endocrine therapy (fulvestrant). Treatment lasted from May to August 2011, when bone scintigraphy revealed progression of the lesions. Patient was qualified to palliative chemotherapy. From October 2011 to March 2012 six courses of FAC (5-fluorouracil, adriamycin, cyclophosphamide) chemotherapy were administered, with acceptable tolerance and stabilization of disease symptoms. Further progression of lesions was confirmed in bone scintigraphy made in April 2012. Two lumps sized about 1 cm each appeared on the skin surface around mastectomy scar. Cancer cells with the same phenotype as original tumor were found in fine needle aspiration (FNA) biopsy. Additional imaging (abdominal ultrasonography, chest X-ray) did not reveal visceral metastases. Pamidronate and analgesic treatment were continued. The application to the Lesser Poland region branch of National Health Fund for everolimus with exemestane treatment was sent. Patient started the treatment in October 2012. After a month patient did not need any analgesics, regression of the skin lumps was achieved. In November 2012 bisphosphonate therapy was ended. Actually (February 2014) patient is still being treated with everolimus and exemestane. Treatment tolerance is very good. Patient is not complaining of any symptoms related to drugs toxicity or the disease. Remaining long-lasting effect of the treatment suggests that the acquired resistance on endocrine therapy has been reversed.

DISCUSSION

Metastatic breast cancer (MBC) treatment remains challenging for oncologists. Treatment individualization is necessary. In this paper, a case of patient with long-lasting history of the disease

was presented. At the early stage surgery, adjuvant chemotherapy and endocrine therapy were administered, resulting in a 10-years disease free period of time. At the time bone metastases were found, endocrine therapy with non-steroidal aromatase inhibitor was started. Patient was qualified to bisphosphonates and radiotherapy. The disease was asymptomatic for nearly a year, followed by a rapid progression. Next line endocrine therapy (fulvestrant) was started however, the disease was progressing. Considering the acquired resistance on endocrine therapy, chemotherapy was started however, the effect was poor. Finally everolimus and exemestane were used, which effected in reversing the acquired resistance. Fast symptoms relief with response lasting until today, after 17 months of therapy were achieved.

Endocrine therapy should be the first line of treatment of a hormone-receptor-positive metastatic breast cancer (MBC) – luminal A type [4]. International guidelines recommends bisphosphonates in treatment of breast cancer bone metastases [5, 6]. It was also approved by the ABC-1 consensus conference experts [7]. Chemotherapy should be considered in case of proven acquired resistance on endocrine therapy, rapid disease progression or massive visceral metastases. Despite of good response at the beginning of the endocrine therapy, development of acquired resistance is unavoidable. One of its known mechanisms is phosphatidylinositol 3-kinase (PI3K) pathway activation [8]. Everolimus is an analog of rapamycin, acts as an inhibitor of mTOR kinase [9], which may lead to the reversal of tumor cells acquired resistance on endocrine therapy. BOLERO-2 study compared exemestane monotherapy versus exemestane combined with everolimus. A total of 724 patients with estrogen receptor-positive, HER-2/neu negative advanced breast cancer with recurrence or progression following prior therapy with letrozole or anastrozole were randomized. Improvement in median PFS (additional 4 months), ORR and clinical benefit (12% vs 1% and 51% vs 26%; $p < 0,0001$) respectively, for the arm with everolimus were achieved [10]. Based on recent two prospective trials, it was proven that there are differences in the expression of steroid and HER-2 receptors between the primary tumor and the metastases. More often it is related to steroid receptors (16–40%) rather then HER-2 receptor (10%) [11, 12]. According to European Society for Medical Oncology (ESMO) guidelines in case of recurrent breast cancer, re-evaluation of immunohistological cancer subtype from metastatic focus should be performed. Re-evaluation may be skipped when metastases occurs in the period of 1–2 years from primary tumor, biopsy is burden with high risk or it will not affect on further treatment. Such proceedings may open the way for targeted therapy for a certain part of patients [13]. In presented case there was no change in hormone receptors expression after immunohistological assessment of the matstasic cells. Metastases to bones and local recurrence without visceral metastases, with confirmed luminal A subtype, indicated endocrine therapy as the best option. When the acquired resistance occurred, cytostatic chemotherapy was started, unfortunately with further disease progression. Finally, everolimus with exemestane treatment allowed to reverse the acquired resistance and to achieve disease regression. Presented case reveals that among luminal A subtype patients with acquired resistance, everolimus with exemestane treatment may result in long term response in MBC, after using of almost all available therapeutic options.

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