Everolimus with exemestane in elderly breast cancer patients – case report

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ABSTRACT

Treating elderly patients suffering from metastatic breast cancer still constitutes a significant therapeutic problem. The possibility of administering everolimus in combination with exemestane appears to be a promising therapeutic option in the case of hormone-dependent cancers, without HER2 receptor overexpression.

KEY WORDS: breast cancer, everolimus, exemestan, elderly

INTRODUCTION

Breast cancer is the most common neoplasm in women. In 2011, nearly 17,000 breast cancer cases were reported in Poland [1]. Postmenopausal women are the ones affected by the disease significantly more often than the general population. In the 19–54 age bracket, slightly over 5,300 new breast cancer cases were observed in Poland in 2011, whereas in the 55–69 age group, there were as many as over 7,500 new cases. In the group aged 70 and more, on the other hand, the number of breast cancer cases reported was over 3,600. Thus, breast cancer develops more than twice as often in postmenopausal women as compared with the premenopausal ones.

In 2011 in Poland, nearly 5,500 deaths were reported due to breast cancer [1].

Around 60–70% of all breast cancer cases are cancers with confirmed presence of steroid receptors (estrogen and/or progesterone ones).

The gold standard still binding in the treatment of hormone-responsive breast cancer, is tamoxifen, a selective estrogen receptor modulator, known for over 40 years now.

Aromatase inhibitors (steroid and non-steroid) are universally accepted as a standard therapeutic option for postmenopausal women suffering from hormone receptor-positive (HR+) metastatic breast cancer. Another hormonal treatment option is fulvestrant (SERD, selective estrogen receptor down-regulator), as well as megestrol acetate, and medroxyprogesterone.

Even though the available hormonal therapeutic options are ever greater, the problem lies in the relatively limited clinical benefits stemming from the consecutive lines of hormonal treatment, and the relatively short median time to progression.

An interesting treatment option for hormone-dependent metastatic breast cancer appears to be the combination of an mTOR inhibitor, such as everolimus, with a steroid aromatase inhibitor like exemestane. The treatment is quite safe, and its efficacy has

been proven in a randomised phase III clinical trial comparing it to exemestane alone [2].

A safe and possibly low-toxic therapy is particularly significant in the case of the therapeutically difficult group of elderly patients. Below you will find treatment cases pertaining to that very group of metastatic breast cancer patients.

CASE 1 (K.S. BORN 1938)

The patient was diagnosed with left breast cancer in 2003 (she was 65 years old at the time). Mastectomy and axillary lymphadenectomy was performed, confirming ductal carcinoma, pT2N0, G2, ER – pos, PgR – pos, HER2 – neg (0). As adjuvant treatment, tamoxifene was administered for 5 years at the dose of 20 mg/day.

In 2010, bone metastases were detected. The patient received palliative radiotherapy in the region of the right hip joint and right ribs. Aromatase inhibitor treatment (anastrozole) was initiated. Additionally, bisphosphonates were included in the treatment regime (disodium pamidronate). No significant treatment-related complications were observed, even though the patient suffers from concomitant diseases: for over 10 years, she has been treated for type 2 diabetes, arterial hypertension, and hypercholesterolemia. She has been taking the following medications: metformin 3 × 500 mg, enalapril 2 × 20 mg, simvastatin 1 × 20 mg.

In January 2013, the 75-year-old patient was diagnosed with disease progression in the form of lung metastases (with the lesions detected by accident during a chest X-ray examination). The number of bone metastatic lesions also increased, and the pain intensified (in the area of the left thigh and pelvis). The patient received palliative radiation (800 cGy) targeting the femoral bone. Her general condition was very good (ECOG 0).

The decision was made for the treatment to include an mTOR inhibitor (everolimus) and exemestane. The patient began the therapy on 6 February 2013, with the dosing schedule as recommended in breast cancer, i.e. everolimus at 10 mg/day orally, and exemestane at 25 mg/day orally.

In week 3 of the treatment, oral cavity mucositis was detected and assessed as grade 4 lesions (version 4.0 in accordance with CTCAE), with the accompanying grade 2 xerostomia, and grade 1 skin pruritus. The patient was instructed to stop the everolimus therapy. It was recommended that the patient rinses her mouth with a mixture containing vitamins A and E, and that she modifies her diet (to consist of ground soft foods). The patient continued with the exemestane treatment. In week 4 of combined therapy, the symptoms of mucosal damage receded completely. Grade 1 xerostomia continued. The decision was taken to return to the original therapeutic regime. There was no recurrence of oral cavity mucosal damage. In week 8, elevated blood glucose levels were reported (220–250 mg%), requiring a modification of the diabetes treatment pattern. The dose of metformin was increased to 3 × 850 mg. There were no other adverse events pertaining to the mTOR inhibitor treatment.

Chest CT, performed in week 11 of treatment, reported a reduction in the metastatic lesions, due to RECIST stabilization disease, while in the examination from week 24, partial remission of the lung metastases was observed. At the moment, the patient continues the combined treatment involving both everolimus and exemestane.

CASE 2 (K.SZ. BORN 1941)

The 68-year-old patient reported to an oncologist in 2009 because of the primary left breast cancer with skin, subcutaneous tissue, and bone metastases. Histopathology of the breast specimen confirmed an ER and PgR receptor-positive, HER2 negative (1+) lobular carcinoma. The treatment was started with tamoxifen at 20 mg/day. Palliative radiotherapy was also administered in the region of lumbar spine, and the patient received bisphosphonates (disodium pamidronate). As regards internal medicine history, the patient reported long-standing history of COPD and arterial hypertension. She was taking inhalatory bronchodilators, as well as perindopril at the dose of 10 mg.

Stable disease was achieved, with no significant adverse events.

In July 2011, disease progression was observed, involving lung metastases causing cough of varying intensity. Letrozole at 2.5 mg/day was applied, leading to a slight reduction in the size of the metastatic lesions (within the definition of stable disease, in accordance with the RECIST criteria). Treatment tolerance was very well.

In August 2012, yet again disease progression was observed in the patient's lungs. Bisphosphonates were continued, and fulvestrant was additionally included at the dose of 500 mg i.m., on day 1 and 15, and later on every 28 days. Treatment tolerance was very high, and stable disease was achieved for around 6 months.

In January 2013, another manifestation of disease progression was detected in the form of new metastatic lesions in the patient's lungs and bones. The patient received palliative irradiation of the thoracic spine segment. The patient's general condition (72 years old at the time) was good (ECOG 1). It was decided that she can be qualified for the treatment involving everolimus and exemestane.

The patient continued the therapy for 11 months, achieving partial remission. Throughout the treatment, the only adverse events observed included grade 1 skin dryness (since week 4 of the treatment), grade 2 lack of appetite (since week 8), grade 1 weight loss, and periodical constipation of varying intensity (maximum grade 2).

Once disease progression had been confirmed (increased volume of metastatic lesions within the lungs), the patient was qualified for chemotherapy (ADM in monotherapy).

DISCUSSION

Over the recent years, everolimus, an mTOR inhibitor, in combination with exemestane, has been proven as an efficacious treatment option for postmenopausal women with metastatic, hormone receptor-positive breast cancer without HER2 receptor overexpression, who progressed on non-steroid aromatase inhibitors. The BOLERO-2 study results, published two years ago, demonstrate a high efficacy of combined treatment involving everolimus and exemestane, in comparison with exemestane alone [3]. The study pointed to an over two-fold increase in the mean time to progression in the group of patients subject to combined treatment (6.9 vs 2.8 months; HR = 0.43, $p < 0.001$). The significantly higher efficacy of combined treatment was confirmed in all of the selected subgroups (e.g. patients below and over the age of 65, patients with visceral metastases, patients previously treated with a single line of palliative chemotherapy, patients previously treated with fulvestrant, etc.). The observed toxicities related to combined treatment were not serious. They mostly involved mucositis, rush, fatigue, loss of appetite, diarrhoea, and less frequently cough, taste and smell disturbances, non-infectious pneumonia, hyperglycaemia, elevated liver enzymes, loss of body mass. In the majority of cases, the intensity of the observed treatment-related side effects never exceed the grade 2 [4].

It goes without saying that a fundamental benefit stemming from the combined treatment involving everolimus and exemestane is the possibility of delaying the need for palliative chemotherapy. Such an option cannot be overestimated in the group of elderly patients. Based on numerous publications, we know that post-chemotherapy complications in the group of over 75-year-olds are much more frequent than in the younger age groups. In many cases, the patients' general condition and concomitant diseases to a large extent restrict the possibility of applying chemotherapy at all. Thus, as it frequently happens, hormonal treatment remains the only real therapeutic option in the group of elderly breast cancer patients. Hence, the relatively safe and at the same time efficacious treatment involving everolimus, an mTOR inhibitor, in combination with exemestane, might become the only sensible therapeutic choice for that particular group of cancer patients [5].

The paper published by Kathleen I. Pritchard in Clinical Breast Cancer in December 2013 [6] is very interesting in the context of the discussed problem. It presents a detailed analysis of the safety and treatment results achieved in the above mentioned BOLERO-2 study in the 70 plus age group. 164 study subjects were aged 70 or over (121 in the group treated with everolimus and exemestane, and 43 of them in the exemestane arm). As compared with the younger population, more patients were qualified for treatment in a significantly poorer general condition (ECOG 2). The results were 3.3% vs 1.4% in the combined treatment group, and 9.3% vs 1.5% in the group treated solely with exemestane.

Significant concomitant diseases were diagnosed in a larger number of patients treated with the combined therapy – 95% vs 92.9%, whereas for the exemestane group the figures were 88.4% vs 93.4%. Patients over the age of 70 were more likely to take internal medications, including chiefly convertase inhibitors, angiotensin II antagonists, benzodiazepines, platelet aggregation inhibitors, proton pump inhibitors, and thyroid hormones. On the other hand, it was less frequent for the elderly patients to be taking bisphosphonates.

Treatment efficacy was significantly higher in the group of patients treated with everolimus and exemestane, with the mean time to progression amounting to 6.7 months as compared with 1.51 months in the exemestane arm (HR = 0.44; 95% CI: 0.36–0.54).

Similarly to the group of younger women, 67% of patients receiving combined therapy required dose modification at some point. The treatment was interrupted at least once in 62.7% of the elderly patients as compared with 60.7% of the younger ones. Dose reduction was required in 39.0% of patients aged 70 and over, and in 39.6% of patients below the age of 70.

Toxicity profile was very similar in both age groups. Somewhat more frequently anaemia, fatigue, loss of appetite, elevated creatinine level, and urinary tract infections were reported for the elderly patients.

To sum up, both the toxicity profile and treatment efficacy of everolimus in combination with exemestane appear to be comparable in the groups of elderly and younger patients, which undoubtedly encourages one to apply that therapeutic option in the group of patients aged over 70, especially in the context of a significantly higher risk of serious adverse events related to chemotherapy in that very age group. The author's own experience confirms the fact beyond any doubt.

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