Liposomal doxorubicin in first line metastatic HER-2-positive breast cancer for prevention the cardiotoxicity

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ABSTRACT

We describe a 62 year old female with metastatic HER-2-positive breast cancer, and with independent cardiovascular comorbidities. She was earlier treated with J131 therapy due to thyroid toxicity. She developed grade 2 mitral and tricuspid valvular insufficiency as a result of uncontrolled hypertension. In 2013, the patient was diagnosed with luminal B2 breast cancer with liver and bone metastases, and a large infiltration of the left breast together with the surrounding soft tissue. She was treated with liposomal doxorubicin and cyclophosphamide, with the dose of anthracycline slightly reduced to 50 mg/m^2 because of the elevated liver enzymes. She was in complete remission during treatment, without any cardiac or hematologic toxicity. The treatment was prolonged to eight cycles until the liver tests returned to normal. The cumulative dose of liposomal doxorubicin amounted to 400 mg/m^2 (with the maximum recommended dose of 600 mg/m^2). We decided to administer the liposomal form of doxorubicin, which is less cardiotoxic than conventional doxorubicin, as first-line treatment in order to prevent cardiotoxicity in a patient who is a candidate for another cardiotoxic therapy involving trastuzumab in the future. The patient's disease progressed 10 months following the completion of first-line therapy.

There are no cardiologic contraindications to trastuzumab and there are no signs of liposomal doxorubicin-related cardiotoxicity or deterioration of the valvular insufficiency.

KEY WORDS: liposomal doxorubicin, cardiotoxicity, HER-2 overexpression

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INTRODUCTION

The tremendous progress made in the field of breast cancer treatment, including the treatment of metastatic and HER-2-positive disease, prompts us to consider different strategies enabling the accomplishment of maximum therapeutic efficacy, while adhering to the principle of therapeutic safety [1]. Such strategies should take into account the fact that most of the patients are candidates for several lines of treatment, and that the toxicity induced in the course of treatment may limit further therapeutic options [1–3]. It goes without saying that many oncological drugs are cardiotoxic. This affects the qualification for a particular type of systemic treatment in patients suffering from cardiovascular diseases, as their risk of severe treatment-related complications is significantly higher [2]. Cardiotoxicity may also develop in the course of chemotherapy in patients whose risk of cardiovascular complications is not higher than normal, especially if they undergo several chemotherapy lines (breast cancer patients may be subject to as many as 5–6 treatment lines) [1, 4]. Contemporary oncological treatment involves an extended set of indications for cardiac monitoring. It is not only recommended for patients treated with doxorubicin or trastuzumab, but also those who take medications used in the treatment of neoplasms other than breast cancer, including capecitabine and sunitinib. An important aspect of the problem is also the accumulation of subclinical damages in the course of a long-standing therapy involving several treatment lines [2, 4, 5].

CASE PRESENTATION

The patient (born in 1951) reported at the Oncology Centre in Bydgoszcz in August 2013, diagnosed with metastatic adenocarcinoma on the basis of prior examinations, including imaging tests and fine-needle biopsy. The primary focus had been determined as unknown, with disease dissemination to the liver, ovaries, peritoneum and omentum, and with enlarged peripheral lymph nodes resulting in an oedema of the left upper limb. The physical examination of 19 August 2013 revealed cervical and supraclavicular lymph node packages on the left side, oedema of the left upper limb, left breast tumour with orange-peel appearance and retracted mamilla, palpable intraabdominal mass 7 cm in diameter, and an enlarged liver. Based on that, breast cancer was diagnosed as the primary focus, which was later confirmed by fine-needle and core biopsy of the breast lesion. Further examinations also revealed bone metastases, and a five-fold elevation of the liver function tests, including ALT, AST and alkaline phosphatase.

The stage of clinical advancement was determined as T4b-N3cM1, with the patient's performance status evaluated as WHO 2. The patient's general condition reflected the advancement of the neoplastic process, as the previously diagnosed cardiovascular conditions did not seem to affect her physical performance. As regards concomitant diseases, she reported hypertension, hyperlipidaemia, and grade 2 mitral and tricuspid valve insufficiency. She had also been treated with radioactive iodine for hyperthyroidism in the course of hyperactive nodular goitre. Cardiovascular assessment had initially been performed in the patient's dwelling place, as it has only been possible to offer cardiovascular diagnostics directly at the Oncology Centre since the beginning of 2014. Due to the diagnosed cardiovascular conditions the patient received low-molecular-weight heparin as well as amlodipine and ramipril. Her ECG revealed a levogram, semi-horizontal heart position, non-specific ST segments, heart rate 76/min; ejection fraction of 70%, and no cardiac contractility abnormalities. Chest X-ray revealed a slightly enlarged cardiac silhouette.

Due to urgent indications for chemotherapy (elevated liver function tests, and the patient's general condition), we could not wait for the results of core biopsy, and the dynamics of the process as well as the location of metastases weighed against potential hormone-dependency of the disease. It was decided to initiate chemotherapy based on the result of fine-needle biopsy, with just the diagnosis of adenocarcinoma in hand. Taking into account the patient's overall condition and concomitant diseases, the MC regimen was administered, i.e. non-pegylated liposomal doxorubicin and cyclophosphamide, as first-line treatment. Liposomal doxorubicin was dosed at 50 mg/m^2, and the dose of cyclophosphamide was 600 mg/m^2. The patient tolerated the treatment very well, with no hematologic, dermal or cardiovascular toxicities, as confirmed in physical examination, blood count, ECG, and clinical assessment of the patient's general condition and performance. As a result of the first chemotherapy cycle, her general condition significantly improved, with the liver function tests back to normal.

In the meantime, core biopsy revealed the luminal B2 breast cancer type, positive for oestrogen receptors, negative for progesterone receptors, HER-2(+++) and Ki-67 of 40% [11]. There were indications for trastuzumab therapy. However, trastuzumab reimbursement rules adopted in Poland stipulate that in the course of metastatic disease treatment, patients are entitled to it provided that first-line anthracycline

treatment has failed or there are documented contraindications for the use of anthracyclines. The patient did not meet any of the criteria, and could not be a candidate for first-line trastuzumab treatment. There were fears that following doxorubicin therapy, her cardiac contractility might be compromised, which would make the anti-HER-2 treatment impossible in the future. Eventually, it was decided to continue with the treatment as it was, with early response assessment, and under close cardiovascular follow-up.

Following the second cycle, complete regression of the breast lesions and cervical-supraclavicular lymph nodes was observed. Additionally, the left upper limp oedema receded, and the liver, ovarian and intraperitoneal foci were significantly smaller. Adenocarcinoma markers went back to normal. The patient's general condition improved as well, with her performance status assessed as WHO 1. The decision was taken to continue treatment. A follow-up cardiac examination performed after the third treatment cycle, revealed a slight reduction in the ejection fraction, from 70% to 64%, without any significant changes.

Following the sixth treatment cycle, complete remission of the above mentioned lesions was revealed under physical examination as well as in the imaging tests of the abdominal cavity. Bone lesions were stable. Cardiac monitoring did not reveal any worsening in terms of the examined parameters of the cardiovascular system, with the ejection fraction back to 70%. Taking into account the patient's considerable improvement and lack of complications, it was decided to administer 2 more treatment cycles, leading up to a total of 8 cycles, as the liver enzyme tests (AST and ALT) went back to normal only in the course of the 6th cycle. The patient tolerated the treatment very well at all times, with no hematologic, dermal or cardiovascular complications reported. Chemotherapy was administered from August 2013 to February 2014.

Once cytostatic treatment had been completed, aromatase inhibitor hormone therapy was initiated, starting the patient on letrozole. In December 2014 (10 months after the completion of chemotherapy), the patient reported that her condition had deteriorated, and the tests performed indicated a significant disease progression within the osseous system and the liver, with liver function tests elevated yet again. The patient's performance status went back to WHO 2. Her condition deteriorated quite suddenly, as until November 2014 she was fine, remaining under the supervision of a cardiologist, and taking letrozole. Once hormone therapy had been deemed unsuccessful, it was decided to switch to second-line chemotherapy. Paclitaxel treatment was initiated, with a view to adding trastuzumab as soon as there was improvement in blood chemistry results. From the cardiovascular perspective, there were no contraindications for trastuzumab. In current tests, the patient's EF is 70%, she suffers from grade 2 tricuspid valve insufficiency, and grade 1 mitral valve dysfunction. Her cardiac contractility is normal, there are no lesions within the pericardium, LA is 3.2 cm, RV 2.9 cm, LV 4.6 cm, Ao 2.7 cm, and IVSd 0.9 cm. Presently, the patient receives ramipril (10 mg), amlodipine (10 mg), hydrochlorothiazide (12.5 mg), losartan potassium (25 mg), and atorvastatin (20 mg). RR is 138/84, HR 80/min, heart rate is regular, and ECG still reveals a levogram, semi-horizontal cardiac position, and non-specific ST segments.

The patient has remained responsive to chemotherapy. Already following the first cycle of paclitaxel, her general condition improved considerably, with her performance status once again assessed as WHO 1. Liver function test levels have been reduced by half.

DISCUSSION

First-line treatment in breast cancer is doxorubicin, most frequently combined with cyclophosphamide. The treatment needs to be administered with due caution, especially in patients with increased risk of cardiotoxicity [1, 6–8]. There is data suggesting that the use of liposomal doxorubicin in combination with cyclophosphamide as first-line treatment of metastatic disease not only reduces the risk of cardiotoxicity, but also improves the long-term treatment outcomes, especially by reducing the number of complications, including grade 4 neutropenia, and thanks to better treatment tolerance by the patients. It rarely results in a deterioration of the patients' quality of life [9, 10].

The commonly recognized cardiotoxicity risk factors in the course of anthracycline treatment include: age over 70, uncontrolled arterial hypertension, diabetes, thromboembolic incidents, prior anthracycline use, mediastinal radiotherapy, and exceeding the cumulative dose of 450–500 mg/m^2 [2]. In accordance with the product's description, the drug is contraindicated in patients with acute or past myocardial infarction, several arrhythmia, myocarditis and heart rate abnormalities. Producers recommend a prolonged (even up to 24 hours) doxorubicin infusion as cardioprotective in high-risk patients. Other recommendations mention

the fact that the cumulative dose should not be exceeded, and inform about pegylated and non-pegylated liposomal doxorubicin playing a role in preventing anthracycline-induced cardiomyopathy [4, 5]. Reduction in cardiotoxicity results from a change in the distribution of liposomal doxorubicin in human tissues, and the fact that it remains enclosed in liposomes until it comes into contact with a neoplastic focus, as well as from a lower concentration of the drug in blood serum thanks to a slower release of the drug into the bloodstream. Thanks to all that, the myocardium is less exposed to its direct toxic effect, which is oxidative stress [1].

The patient's hypertension is presently controlled. Several years earlier (before the initiation of anti-hypertensive treatment), she developed mitral and tricuspid valve insufficiency and hyperthyroidism. In our opinion, those were cardiotoxicity risk factors. Additionally, the effect of combined administration of doxorubicin and trastuzumab on cardiotoxicity is well known, leading to recommendations not to administer the two drugs simultaneously, and not to increase the volume of doxorubicin to the level of maximum cumulative dose, if trastuzumab therapy is planned as well [4, 7, 12]. In such patients, the risk of cardiovascular complications can be as high as 28% [1, 7]. In the discussed case, throughout the treatment with the use of non-pegylated liposomal doxorubicin, there was no drop in LVEF, apart from a transient one from 70% to 64% (not a significant change), following the third cycle, with the EF back to 70% during further treatment cycles. Presently, LVEF is stable. Our decision on the choice of treatment was both therapeutic and preventive in character, as we wished to enable the patient further anti-HER-2 treatment with trastuzumab, which is a standard second-line treatment.

CONCLUSION

Liposomal doxorubicin seems to be effective and safe in metastatic HER-2-positive breast cancer coexisting with arterial hypertension, valvular insufficiency and other internal medical problems.

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