CASE REPORT

Successful ethinylestradiol therapy for a metastatic breast cancer patient with heavily pre-treated with endocrine therapies

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Received: 8 September 2015 / Accepted: 18 December 2015 / Published online: 7 January 2016
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Abstract The critical strategy leading to the success of endocrine therapy in metastatic breast cancer is extended duration of treatment. Here, we report a case with late-stage metastatic breast cancer who dramatically responded to high-dose estrogen treatment with a long-term stable disease. A 52-year-old female with metastatic breast cancer was referred to our hospital. She had already received several courses of systemic therapy: LH-RH agonist and tamoxifen and docetaxel. At first visit to us, she had a multiple liver tumor and an irregular mass in the left breast. We started endocrine therapy of LH-RH agonist and anastrozole with a stable disease for 12 months. After the disease progression, LH-RH agonist and letrozole, TS-1, vinorelbine, and nab-paclitaxel were administered. Further, she received the exemestane therapy as the fifth line, but the disease progressed after 4 months. We then started ethinylestradiol (EE2) therapy. Two months later, the tumor in liver rapidly decreased from 15.8 to 10.6 cm, of which the tumor shrinkage rate was 33 %. Subsequently, the patient had stable disease for 12 months. After 14-month EE2 therapy, the patient had a regrowth of the liver tumors, and was then treated with letrozole again. This therapy had continued for 5 months. Estrogen therapy

is beneficial for postmenopausal patients with heavily pre-treated who could have acquired resistance to aromatase inhibitor.

Keywords Metastatic breast cancer · Ethinylestradiol therapy · Endocrine therapy

Introduction

Metastatic breast cancer (MBC) is an incurable disease for which the goal of treatment is to achieve prolonged disease stabilization while maintaining quality of life. A number of endocrine therapy for estrogen receptor (ER)-positive breast cancer in a metastatic setting have been developed so far, including luteinizing hormone-releasing hormone (LHRH) agonists, selective estrogen receptor modulator (SERM), selective estrogen receptor downregulator (SERD), aromatase inhibitor (AI), and additive sex-hormone treatment such as androgen, progesterone, and estrogen.

In postmenopausal metastatic breast cancer, several phase-III trials showed that AIs were superior to tamoxifen (TAM) in time to progression as a first-line endocrine therapy [1, 2]. If the cancer re-progresses without life-threatening visceral disease, we can recommend the subsequent endocrine therapy with a different mechanism of action to the prior therapy. Several comparative trials of second-line or third-line endocrine therapy in cases refractory to AIs showed the efficacy of sequential use of endocrine therapy [3–5]. After third-line therapy, additive sex-hormone treatment especially for estrogen should be considered as one of the treatment options. Estrogen therapy using a high dose of diethylstilbestrol (DES) for advanced breast cancer was first reported in 1944 [6].

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Although the paradoxical mechanism of action has not been completely elucidated, recent reports showed the efficacy of estrogen, DES, and ethinylestradiol (EE2) therapy [7, 8]. According to them, the clinical benefit rate (CBR) ranged from 29 to 56 %. Our prospective observational study also showed that EE2 therapy (3 mg/day) is beneficial for postmenopausal breast cancer patients with heavily pre-treated with endocrine therapies who are refractory to AIs [8]. Here, we describe a case with late-stage metastatic breast cancer who dramatically responded to high-dose estrogen treatment and had a long stable disease (SD).

Case report

A 52-year-old female with metastatic breast cancer was referred to our hospital. Ten years ago, she underwent breast-conserving surgery and axillary-lymph-node dissection with left breast cancer. A histopathological examination of the tumor specimen at surgery revealed invasive ductal carcinoma, and positive for estrogen (ER) and

progesterone receptor (PgR). Human epidermal growth factor receptor (HER2) status was not evaluated at this point. Pathological staging was T1N0M0 stage I. The patient had received no adjuvant systemic therapy. Four years and 7 months after surgery, she had a diagnosis of the metastatic liver tumor of the breast cancer. Until visiting our hospital, she had received several courses of systemic therapy: LH-RH agonist and tamoxifen (TAM) for 3 years, unknown cycles of docetaxel (75 mg/m^2), LH-RH agonist and TAM for 8 months. Because of the disease progression, the patient was referred to our hospital.

The physical examination at first visit to us revealed an irregular hard mass measuring $2.3 \times 1.4 \text{ cm}$ in diameter on the left breast and multiple liver tumor. Laboratory data showed increased levels of tumor markers; CEA was 3.5 ng/ml and CA15-3 was 1472 U/ml . Computed tomography (CT) revealed multiple liver tumors, the biggest size of which was $10.4 \times 8.1 \text{ cm}$ and an irregular mass in the left breast. No other distant metastasis was found. Pathological examination of the core-biopsy specimen obtained from the left breast tumor indicated the recurrence of invasive breast cancer. The breast tumor was positive for

Fig. 1 Pathological examination of the core-biopsy specimen from increasing tumor in the liver. H&E stain, $\times 40$ magnification (a), $\times 100$ magnification (b). ER staining was high (c) and PgR staining was low (d) before EE2 treatment ($\times 100$ magnification)

Fig. 2 Clinical course during EE2 and the subsequently AI treatment. CEA and CA15-3 reduced promptly after the therapy. Two months later, the liver mass decreased from 15.8 to 10.6 cm, which reached a partial response

ER (100 %), negative for PgR (0 %), and HER2 (score1+), which was similar to the biology of the patient's primary breast carcinoma.

As the third-line endocrine therapy, LH-RH agonist and anastrozole were administered for 12 months (clinical response; PR) and subsequently LH-RH agonist and letrozole were administered for 3 months (PD). After the disease progression of liver metastasis, she received chemotherapy: TS-1 (60 mg/day) for 12 months, vinorelbine (25 mg/m²) for 21 months with long SD, and nab-paclitaxel (260 mg/m²) for 3 months. Since she had refused to receive chemotherapy which had strong side effect at the first visit to our hospitals, we selected the above regimens that were considered to be well tolerated with fewer adverse effects. We performed CNB from increasing tumor in the liver to confirm the hormonal receptor status. Histological findings showed that the positive staining of ER was retained (Fig. 1). We, therefore, re-administered the endocrine therapy as the fifth line. However, the disease progressed after 4 months under the exemestane therapy. As the patient was considered to have an acquired resistance to the endocrine therapy, we started EE2 therapy (3 mg/day, 1 mg, *ter in die*). The clinical course during EE2 treatment is shown in Fig. 2. Two months later, the tumor in liver decreased from 15.8 cm to

10.6 cm, of which the tumor shrinkage rate was 33 %. Subsequently, the patient had stable disease for 12 months.

As adverse events due to ethynylestradiol such as headache, general fatigue, fever, flash, and nipple pain were seen at the beginning of the therapy, we reduced the dose of EE2 from 3 to 2 mg/day. Thereafter she had chronic toxicity in relation to EE2 such as nipple/areola pigmentation, endometrial thickening, irregular vaginal bleeding, and weight gain, but she maintained quality of life without withdrawing the treatment.

After 14-month EE2 therapy, the patient had a regrowth of the liver tumors, and was then treated with AI again. This therapy had continued for 5 months and the disease of liver metastasis was also stable during the therapy. Eight months after the end of letrozole therapy, she eventually died due to breast cancer.

Discussion

We showed a case of late-stage metastatic breast cancer who responded well to the EE2 therapy. Sequential use of endocrine therapies is fundamental of ER-positive advanced breast cancer to extend the duration of disease stabilization without severe adverse events.

In the present case, long SD was found while the patients were treated with LH-RHa and anastrozole as the third-line therapy, but the following endocrine therapy meaning LH-RHa and letrozole or exemestane therapy suppressed disease progression only for the short period. At this point, she was considered to have acquired resistance to AI therapy. It is postulated that extremely low estrogen environment encountered in the presence of AI has enhanced the sensitivity of breast cancer cells to estrogen, leading to proapoptotic effects and beneficial tumor regression [9]. Indeed, the response of large liver tumors was prompt and evident after initiation of EE2 therapy, and has been sustained for 14 months in the present case. Our previous observational study about EE2 therapy determined the efficacy and safety of EE2 in 18 breast cancer patients [8]; the response rate was 50 % and the clinical benefit was 56 %. These results compare well with those from the phase 3 randomized clinical trial by comparing flutestran and exemestane in patients with disease progression after aromatase inhibitor (clinical benefit rates are 32.2 and 31.5 %, respectively) [3].

The mechanism about how EE2 suppresses tumor growth has been poorly understood. Some previous studies have suggested the involvement of the extrinsic (Fas/FasL) pathway or NF-kappaB-mediated pathway in estrogen-induced apoptosis process [10, 11]. In addition, our recent study showed that EE2 treatment activated ER downstream genes, especially for PgR, but it did not stimulate tumor growth [12]. Stimulation of non-genomic pathway of ER signaling or imbalance of activation may affect the response to EE2 therapy. We need further investigation to examine its function.

There is no consensus about the optimal point to start EE2 treatment. In several clinical trials [7, 8], EE2 treatment was adopted for the postmenopausal women with AI resistance. Further, all the patients had been heavily treated before EE2 therapy in advanced setting. According to these studies, the patients who had experienced long clinical benefit to previous endocrine therapy tended to respond well to the EE2 therapy. The positivity of ER staining prior the EE2 therapy was also considered to be critical. We confirmed the staining of ER expression in the liver tumor by core-needle biopsy. Repeating core biopsy during the treatment course is recommended to obtain some additional information on the choice of targeted therapy [13].

The other remarkable point is the post-treatment efficacy of the EE2 therapy. After the failure of EE2 therapy, we performed AI therapy again for 5 months. The same medication can become effective again after EE2 therapy even if it failed before. This underlying mechanism is unclear, but EE2 therapy may change or modify the hormonal environment surrounding the tumor cells, which lead to re-sensitize to antihormonal therapy.

Regarding the adverse events, acute symptoms of EE2 toxicity, such as nausea, general fatigue, muscle-skeletal pain, fever, and vaginal bleeding, are seen in most patients. However, these are mostly manageable and tolerable and no severe adverse events such as stroke, myocardial infarction, and deep venous thrombosis were not found in our previous study [8]. The safety of EE2 treatment was demonstrated as above, but we have to determine to reduce the daily dosage of EE2 if the patients feel any intolerable adverse effects.

In conclusion, EE2 treatment is beneficial for the postmenopausal patients who were heavily pre-treated with endocrine therapies and even had heavy visceral metastases. Sequential endocrine therapy including EE2 might prolong the duration of treatment response in MBC.

Compliance with ethical standards

The authors have declared no conflicts of interest. No external sources of funding were used for this study. Approval for the analyses conducted in the study was received from the ethics committee of Kumamoto University Graduate School of Medical Sciences. Informed consent was obtained from all patients.

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