Recurrent Male Breast Cancer Accompanied by Carcinomatous Pleuritis That Responded to Combination Therapy with High-Dose Toremifene and Docetaxel

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Key Words

Male breast cancer · Carcinomatous pleuritis · Toremifene · Docetaxel

Summary

Background: Male breast cancer (MBC) is a rare disease with no standard treatment compared to female breast cancer. There are very few reports that go beyond second-line chemotherapy and endocrine therapy for advanced and recurrent MBC. **Case Report:** This report presents a case of recurrent MBC accompanied by carcinomatous pleuritis that responded to combination therapy with high-dose toremifene (TOR) and docetaxel (DOC). A 63-year-old male patient had previously undergone a modified radical mastectomy for left breast cancer and received several series of systemic chemotherapy and endocrine therapy. He complained of severe dyspnea, and was admitted to our hospital due to a massive left pleural effusion caused by carcinomatous pleuritis. He received combination therapy with high-dose TOR and biweekly DOC. The pleural effusion disappeared without any severe side effects after 4 cycles of the therapy. Thereafter, his disease stabilized for 1 year without re-increase of tumor markers under continuous treatment with the combination therapy. **Conclusions:** High-dose TOR and DOC might be effective even beyond second-line chemotherapy and endocrine therapy for MBC to overcome potential multiple drug resistance and diminish inevitable side effects.

Schlüsselwörter

Männlicher Brustkrebs · Karzinomatöse Pleuritis · Toremifen · Docetaxel

Zusammenfassung

Hintergrund: Männlicher Brustkrebs (male breast cancer, MBC) ist eine seltene Krankheit; anders als beim weiblichen Brustkrebs gibt es keine Standardbehandlung. Nur wenige Berichte gehen über die Zweitlinien-Chemotherapie und endokrine Therapie beim fortgeschrittenen und rezidierten MBC hinaus. **Fallbericht:** Wir berichten über einen Patienten mit rezidiertem MBC begleitet von karzinomatöser Pleuritis, der auf eine Kombinationstherapie mit hochdosiertem Toremifen (TOR) und Docetaxel (DOC) ansprach. Ein 63-jähriger MBC-Patient war nach modifizierter radikaler Mastektomie der linken Brust mit mehreren Zyklen einer systemischen Chemotherapie und endokrinen Therapie behandelt worden. Er wurde mit schwerer Dyspnoe vorstellig, und wurde mit einem linksseitigen massiven Pleuraerguss verursacht durch eine karzinomatöse Pleuritis in unser Krankenhaus aufgenommen. Eine Kombinationstherapie mit hochdosiertem TOR und zweiwöchentlichem DOC wurde begonnen. Nach 4 Therapiezyklen ohne schwere Nebenwirkungen verschwand der Pleuraerguss. Unter Fortsetzung der Kombinationstherapie stabilisierte sich die Erkrankung über den Zeitraum eines Jahres ohne erneute Zunahme der Tumormarker. **Schlussfolgerungen:** Es ist möglich, dass bei MBC hochdosiertes TOR/DOC auch über die Zweitlinien-Chemotherapie und endokrine Therapie hinaus wirksam ist und potentielle multiple Resistenzen überwinden und unvermeidliche Nebenwirkungen vermindern kann.

Introduction

Male breast cancer (MBC) is a rare disease accounting for less than 1% of all breast cancers [1]. Because of the rarity of the disease, there has been no standard treatment in comparison to female breast cancer [1, 2]. In particular, there are few reports that go beyond the second-line treatment of chemotherapy and endocrine therapy for advanced and recurrent MBC. Treatment recommendations for MBC have often been extrapolated from the data on female breast cancer. However, MBC does have some significant differences from female breast cancer, and requires different strategies for its management.

Toremifene (TOR) is a derivative of tamoxifen (TAM), developed to improve its risk-benefit profile. TOR and TAM, which belong to the selective estrogen modulators (SERMs), have similar pharmacological anti-estrogenic effects at the usual dose (20 mg/day). Both have been shown to exert anti-tumor effects independent of their anti-estrogenic action at a relatively higher dose (more than 60 mg/day) [3]. Since TOR has less genotoxicity in comparison to TAM, only TOR has been used clinically at a high-dose [4]. High-dose TOR has been occasionally used for TAM-refractory female breast cancer [5, 6]. However, the role is not fully clarified.

This paper reports a case of recurrent MBC accompanied by carcinomatous pleuritis that responded to combination therapy with high-dose TOR and docetaxel (DOC). To our knowledge, this is the first report describing a case of MBC treated with high-dose TOR. In addition, we review the literature on endocrine therapy and chemotherapy for MBC.

Case Report

A 60-year-old male patient presented to our hospital with a huge mass in his left breast in July 2003. There was an irregular-shaped and unclearly defined mass (6 × 6 × 3 cm in size) firmly fixed to the breast wall, and the

ipsilateral axillary lymph nodes were palpably enlarged. Clinical examination showed markedly elevated CA15-3 serum levels at 102 U/ml (fig. 1), and a punch biopsy showed invasive ductal carcinoma. However, no metastasis to distant organs was observed. The patient underwent a modified radical mastectomy with axillary lymph node resection (level I–III) and a partial resection of the major pectoral muscle. The pathological examination revealed a solid tubular adenocarcinoma partially invading the major pectoral muscle and the overlying skin, with tumor-free surgical margins; axillary lymph node involvement at level I (6/9); estrogen receptor (ER) (+), progesterone receptor (PgR) (–), and HER2-neu score (+1). The tumor was classified as pT4pN1M0 stage IIIB according to the UICC-TNM classification. The patient received postoperative systemic adjuvant chemotherapy with 6 cycles of CMF (cyclophosphamide 150 mg/day, orally, every 14 days; methotrexate 40 mg/m², intravenously (i.v.), days 1, 8; 5-fluorouracil 600 mg/m², i.v., days 1, 8), and simultaneously started endocrine therapy with oral TAM.

In June 2004, multiple bone metastases to a thoracic vertebra, ribs, and clavicle were recognized by bone scan. A combination therapy with 10 cycles of CAF (cyclophosphamide 150 mg/day, orally, every 14 days; adriamycin 30 mg/m², i.v., days 1, 8; 5-fluorouracil 500 mg/m², i.v., days 1, 8) was administered. However, in June 2005, he developed severe back pain, and focal radiation therapy (40 Gray) was applied to the thoracic vertebra (Th10). In addition, oral administration of the selective aromatase inhibitor (AI) anastrozole (ANA) was started instead of TAM. Although the back pain soon improved, the CA15-3 level continued to increase gradually (fig. 1).

In December 2005, the patient complained of severe dyspnea, and was admitted. Clinical examination showed a left massive pleural effusion (figs. 2, 3), and a CA15-3 serum level of 158 U/ml (fig. 1). Thoracentesis was performed immediately, and a chest tube was left in the thoracic cavity to remove and examine the pleural effusion. The cytology findings of the effusion revealed the presence of adenocarcinoma cells compatible with his previous breast cancer, and the patient was considered to be in a life-threatening state due to carcinomatous pleuritis. Since he had previously received several series of chemotherapy and endocrine therapy, combination therapy with high-dose TOR (120 mg/day, orally) and biweekly DOC (40 mg/m², i.v.) was administered to overcome the possible multiple drug resistance, after informed consent was obtained from the patient. After 4 cycles of high-dose TOR and DOC, the pleural effusion disappeared almost completely (figs. 2, 3) and the dyspnea dissolved without any severe side effects. The CA15-3 level was also reduced (fig. 1). This was regarded as a partial response. His disease stabilized for near 1 year without re-increase of

Fig. 1. Clinical course and CA15-3 serum level which decreased after surgery and treatment with high-dose TOR and DOC.

Fig. 2. Chest radiography: **a** Before administration of high-dose TOR and DOC, massive pleural effusion in the left thoracic cavity. **b** After 4 cycles of high-dose TOR and DOC, pleural effusion disappeared from the left thoracic cavity.

Fig. 3. Chest computed tomography: **a, b** Before administration of high-dose TOR and DOC, massive pleural effusion in the left thoracic cavity. **c, d** After 4 cycles of high-dose TOR and DOC, pleural effusion disappeared from the left thoracic cavity.

CA15-3 while continuing the therapy (for a total of 12 cycles). However, in January 2007, he complained of dyspnea and severe chest pain. Clinical examination showed thickening of the left pleura with elevation of the CA15-3 level, suggesting tumor invasion to the pleura. Although oral capecitabine was administered, the patient developed severe bilateral interstitial pneumonia, and eventually died of respiratory failure in February 2007.

Discussion

From the very limited sample sizes, no randomized clinical trials of chemotherapy and endocrine therapy for MBC have been conducted [1]. Data are only available from small-scale prospective or retrospective studies. These indicate that adjuvant chemotherapy with CMF and CAF provide survival benefits for node-positive MBC [1, 2], while the role of taxanes or other dose-dense chemotherapy regimens in MBC has not yet been clarified [1].

TAM is the most accepted first-line additive therapy, since MBC has high rates of hormone receptor positivity. Adjuvant TAM has improved survival for MBC [2, 7], and for metastatic disease TAM has demonstrated objective response rates comparable to gonadal ablation without significant negative events [1, 2]. Recently developed selective AIs such as ANA have been shown to provide a superior disease-free survival advantage for breast cancer in post-menopausal women, compared to TAM [8]. However, the efficacy in MBC is controversial because only a few case reports have shown limited responses [1, 9]. Theoretically, AIs only block approximately 80% of estrogen production which is derived through peripheral aromatization of androgens in men. The inability to shut down the remaining 20%, which is secreted directly from the testes, may explain the lower response rate observed in MBC [9].

Experimentally, high-dose TOR has been showed to have the effects on ER-negative cells through mechanisms such as

apoptosis induction or inhibition of angiogenesis [10, 11]. Clinically, however, high-dose TOR showed only limited responses for TAM-refractory breast cancer [5, 6], while high-dose TOR as well as other SERMs have been reported to reverse chemotherapeutic drug resistance of cancer cells by modulation of p-glycoprotein (Pgp) function [12]. Pgp is associated with multiple drug resistance which means resistance not only to the initially exposed drugs but also to a range of structurally and functionally unrelated compounds. In addition, an active metabolite of TOR was shown to have a higher affinity to tumor tissues than normal tissues [13]. These facts indicate that high-dose TOR may act as a chemosensitizer to overcome multiple drug resistance and diminish side effects. Following the idea, several reports have demonstrated the efficacy of high-dose TOR as an enhancer for treatment beyond second-line chemotherapy in TAM-refractory recurrent female breast cancers [14, 15].

In the current case, CMF and TAM were adopted as adjuvant therapy after surgical treatment of the primary lesion due to advanced disease. When the bone metastases were recognized, CAF therapy was administered because of doubts regarding the efficacy of selective AIs on MBC. Finally, TAM was switched to ANA due to worsening of the bone metastases. However, ANA appeared to be ineffective because the

CA15-3 level continued to increase. Then, carcinomatous pleuritis indicated that the patient was in a life-threatening state and needed more dense therapy to save his life. In addition, the occurrence of multiple drug resistance was feared due to prior use of CMF and CAF, since both anthracyclines and taxanes are active substrates transported by Pgp [16]. Therefore, combination therapy with high-dose TOR and DOC was administered, which remarkably improved the carcinomatous pleuritis without any side effects while controlling the disease for about 1 year without re-increase in tumor markers. Based on the above findings, high-dose TOR and DOC are thus considered to be effective beyond second-line chemotherapy and endocrine therapy in MBC as well as in female cases. Although further trials in a large population are needed, high-dose TOR and DOC can be considered as a useful choice for the treatment of advanced and recurrent MBC to overcome potential multiple drug resistance and diminish inevitable side effects.

Conflict of Interest

The authors declare no conflict of interests, no external funding was obtained for this study.

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