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High-Dose Toremifene for Fulvestrant-Resistant Metastatic Breast Cancer: A Report of Two Cases

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Key Words

Secondary breast neoplasm · Hormone therapy · High-dose toremifene

Abstract

Introduction: Hormone receptor (HR)-positive metastatic breast cancer (MBC) is usually treated with hormone therapy. In postmenopausal females, aromatase inhibitors (AIs) are usually used as first-line therapy, and fulvestrant is used subsequently. The optimal treatment beyond fulvestrant has not been established. We experienced two cases in which high-dose toremifene (hdTOR) was effective after the failure of AIs and fulvestrant. ***Case 1:*** A 73-year-old female with HR-positive left breast cancer (T2N1M0) underwent preoperative chemotherapy and mastectomy with axillary dissection. Computed tomography (CT) revealed liver tumors in S7 (23 mm) and S8 (25 mm) during adjuvant letrozole therapy, so fulvestrant was started. The tumors initially decreased in size (23 and 22 mm), but then progressed (36 and 25 mm). Treatment was changed to hdTOR, and the tumors shrunk to 26 mm (S7) and 24 mm (S8), and she was stable for 6 months while receiving hdTOR. ***Case 2:*** An 81-year-old female with HR-positive left breast cancer (T2N1M0) underwent left mastectomy and axillary dissection. CT revealed liver tumors in S7 (20 mm) and S8 (11 mm) during adjuvant letrozole therapy, so fulvestrant treatment was started. The tumor in S7 shrunk (13 mm), but the tumor in S8 slightly progressed (13 mm), and both tumors progressed (14 and 18 mm) after 6 months. Treatment was changed to hdTOR, and the tumors slightly shrunk (12 and 14 mm) after 6 months. hdTOR has been continued for 9 months. ***Conclusion:*** hdTOR was effective for MBC after multiple hormone therapies, likely because it acts via a different mechanism of action.

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Introduction

According to various guidelines, such as the NCCN guidelines [1] and Hortopagyi's [2] algorithm, hormone receptor (HR)-positive metastatic breast cancer (MBC) without a life-threatening tumor is usually treated with hormone therapy because of its mild side effects. There are several drugs used for hormone therapy, and if a hormone therapy becomes ineffective, another one is administered as long as the disease does not become life-threatening. In many cases, postmenopausal females with HR-positive MBC are treated with a nonsteroidal aromatase inhibitor (AI) as the first-line therapy [3, 4], and when it becomes ineffective, many physicians use fulvestrant based on the results of previous clinical trials [5, 6]. The optimal treatment after fulvestrant has not been established, and selective estrogen receptor (ER) modulators, steroidal AIs or progestins are often used based on the physician's choice.

Toremifene (40 mg) is a selective ER modulator with equivalent activity to tamoxifen (20 mg) [7]. Toremifene can also be used at a high dose (120 mg) because of its safety. High-dose toremifene (hdTOR) is considered to have a different mechanism of action from the standard doses of tamoxifen or toremifene, and it can be more effective than the standard dose, likely because of the different mechanism of action [8].

In this paper, we describe the cases of 2 patients who benefited from hdTOR after their MBC became resistant to an AI and fulvestrant.

Case Reports

Case 1

The patient was a 73-year-old female with a history of angina pectoris. She had a left breast tumor measuring 4 cm in diameter, and apparent axillary lymph node swelling. She received six cycles of epirubicin + cyclophosphamide therapy and underwent a mastectomy and axillary lymph node dissection. The postoperative diagnosis was invasive ductal carcinoma with an ER-positive, progesterone receptor (PgR)-positive, and human epidermal growth factor receptor 2 (HER2)-negative status, and six node metastases. She received postmastectomy radiation therapy for a total dose of 50 Gy, and letrozole was started as adjuvant therapy.

After 4 years and 5 months from the start of letrozole treatment, CT revealed liver tumors in S7 (23 mm) and S8 (25 mm). Bone scintigraphy revealed no abnormal uptake (fig. 1a), and the results of the blood tests were almost normal. She was diagnosed to have liver metastases during the adjuvant AI, so the hormone therapy was changed to fulvestrant.

After 3 months, the liver tumors had slightly shrunk to 23 mm (S7) and 22 mm (S8). However, the tumors progressed to 36 mm (S7) and 25 mm (S8) during the next 3 months (fig. 1b). Therefore, the treatment was changed to hdTOR.

Three months after starting hdTOR, the tumors had shrunk to 26 mm (S7) and 24 mm (S8). After another 3 months, the tumors grew slightly larger, and chemotherapy with TS-1 (Taiho, Japan) was started (fig. 1c). The levels of the tumor markers CEA and CA15-3 paralleled her disease progression (fig. 1d).

Case 2

The patient was an 81-year-old female with a history of paroxysmal atrial fibrillation. She underwent a left mastectomy and axillary dissection for breast cancer, and her postoperative diagnosis was T2N1M0 invasive ductal carcinoma with an ER-positive, PgR-

positive and HER2-negative status. She received letrozole as adjuvant therapy. Four years and seven months after the operation, positron emission tomography with computed tomography (PET/CT) revealed liver tumors in S7 (20 mm) and S8 (11 mm), and lymph node swelling in her mediastinum (fig. 2a). She was diagnosed to have liver and lymph node metastases, so the hormone therapy was changed to fulvestrant.

Three months after the first administration of fulvestrant, the tumor in S7 shrunk to 13 mm. However, the tumor in S8 slightly grew to 13 mm. After another 3 months, the tumor sizes increased to 14 mm (S7) and 18 mm (S8) (fig. 1b), and she was diagnosed with progressive disease. Therefore, the hormone therapy was changed to hdTOR.

During the next 6 months, the tumors slightly shrunk to 12 mm (S7) and 14 mm (S8) (fig. 2c), and the administration of hdTOR has been continued for 9 months.

Discussion

We experienced 2 patients with MBC who benefited from hdTOR after their disease became resistant to an AI and fulvestrant. The standard dose of toremifene is 40 mg. However, a high dose of up to 120 mg can be used for MBC in Japan, and toremifene is considered to have a different mechanism of action at this high dose compared to the standard dose.

In a retrospective study, hdTOR for MBC produced a 15% objective response rate and a 45% clinical benefit rate [9]. This study included patients receiving second- or higher-line therapy, as well as first-line therapy. In a prospective phase II study investigating the efficacy of hdTOR for recurrence during adjuvant AI therapy, the objective response rate was 7.7%, the clinical benefit rate was 46.2% and the median progression free survival (PFS) was 5.9 months [10]. These results indicated that hdTOR has a benefit even if the MBC had become resistant to another hormone therapy.

Vergote et al. [11] reported that even when MBC has become resistant to fulvestrant, another hormone therapy, such as tamoxifen or a steroidal AI, can still be effective. Moreover, Yamamoto et al. [9] reported that hdTOR was effective even for MBC with tamoxifen resistance. Therefore, hdTOR can be used even after MBC has become resistant to antiestrogen therapies.

In many cases, exemestane is used for MBC, which has acquired resistance to nonsteroidal AIs. However, the Hi-FAIR ex trials, which compared the efficacy between exemestane and hdTOR in MBC patients, revealed that hdTOR had a significantly longer median PFS compared with exemestane (7.3 vs. 3.7 months) [12], and we consider that hdTOR should be used in such situations due to its apparently better efficacy.

The Hi-FAIR fx study is still ongoing in Japan, and is comparing the efficacy between hdTOR and 500 mg of fulvestrant in MBC patients [13]. This study will elucidate which drugs should be used first as the second-line hormone therapy after the failure of nonsteroidal AIs.

In terms of basic research, there have been some reports describing that hdTOR inhibits insulin-like growth factor 1 and phosphorylation of ERK in breast cancer cells, which can inhibit cell proliferation [8]. These findings further support the use of hdTOR.

In conclusion, we experienced the cases of 2 patients who benefitted from hdTOR after the failure of an AI and fulvestrant. hdTOR seems to be very effective for MBC after multiple hormone therapies because it seems to have other mechanism(s) of action in addition to its antiestrogen effects.

References

1 National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Breast Cancer (Version 3.2014). http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.
2 Hortobagyi GN: Treatment of breast cancer. N Engl J Med 1998;339:974–984.
3 Nabholtz JM, Bonneterre J, Buzdar A, et al: Anastrozole (Arimidex) versus tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: survival analysis and updated safety results. Eur J Cancer 2003;39:1684–1689.
4 Mouridsen H, Gershanovich M, Sun Y, et al: Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group. J Clin Oncol 2003;21:2101–2109.
5 Robertson JF, Osborne CK, Howell A, et al: Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma in postmenopausal women: a prospective combined analysis of two multicenter trials. Cancer 2003;98:229–238.
6 Di Leo A, Jerusalem G, Petruzelka L, et al: Final overall survival: fulvestrant 500 mg versus 250 mg in the randomized CONFIRM trial. J Natl Cancer Inst 2014;106:337.
7 Milla-Santos A, Milla L, Rallo L, Solano V: Phase III randomized trial of toremifene vs tamoxifen in hormonodependant advanced breast cancer. Breast Cancer Res Treat 2001;65:119–124.
8 Kuroiwa S, Maruyama S, Okamoto K, Morino T: Ther Res 2012;33:571–578.
9 Yamamoto Y, Masuda N, Ohtake T, et al: Clinical usefulness of high-dose toremifene in patients relapsed on treatment with an aromatase inhibitor. Breast Cancer 2010;17:254–260.
10 Sawaki M, Wada M, Sato Y, et al: High-dose toremifene as first-line treatment of metastatic breast cancer resistant to adjuvant aromatase inhibitor: a multicenter phase II study. Oncol Lett 2012;3:61–65.
11 Vergote I, Robertson JF, Kleeberg U, Burton G, Osborne CK, Mauriac L: Postmenopausal women who progress on fulvestrant ('Faslodex') remain sensitive to further endocrine therapy. Breast Cancer Res Treat 2003;79:207–211.
12 Yamamoto Y, Ishikawa T, Hozumi Y, et al: Randomized controlled trial of toremifene 120 mg compared with exemestane 25 mg after prior treatment with a non-steroidal aromatase inhibitor in postmenopausal women with hormone receptor-positive metastatic breast cancer. BMC Cancer 2013;13:239.
13 https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&type=summary&recptno=R000010802&language=J.

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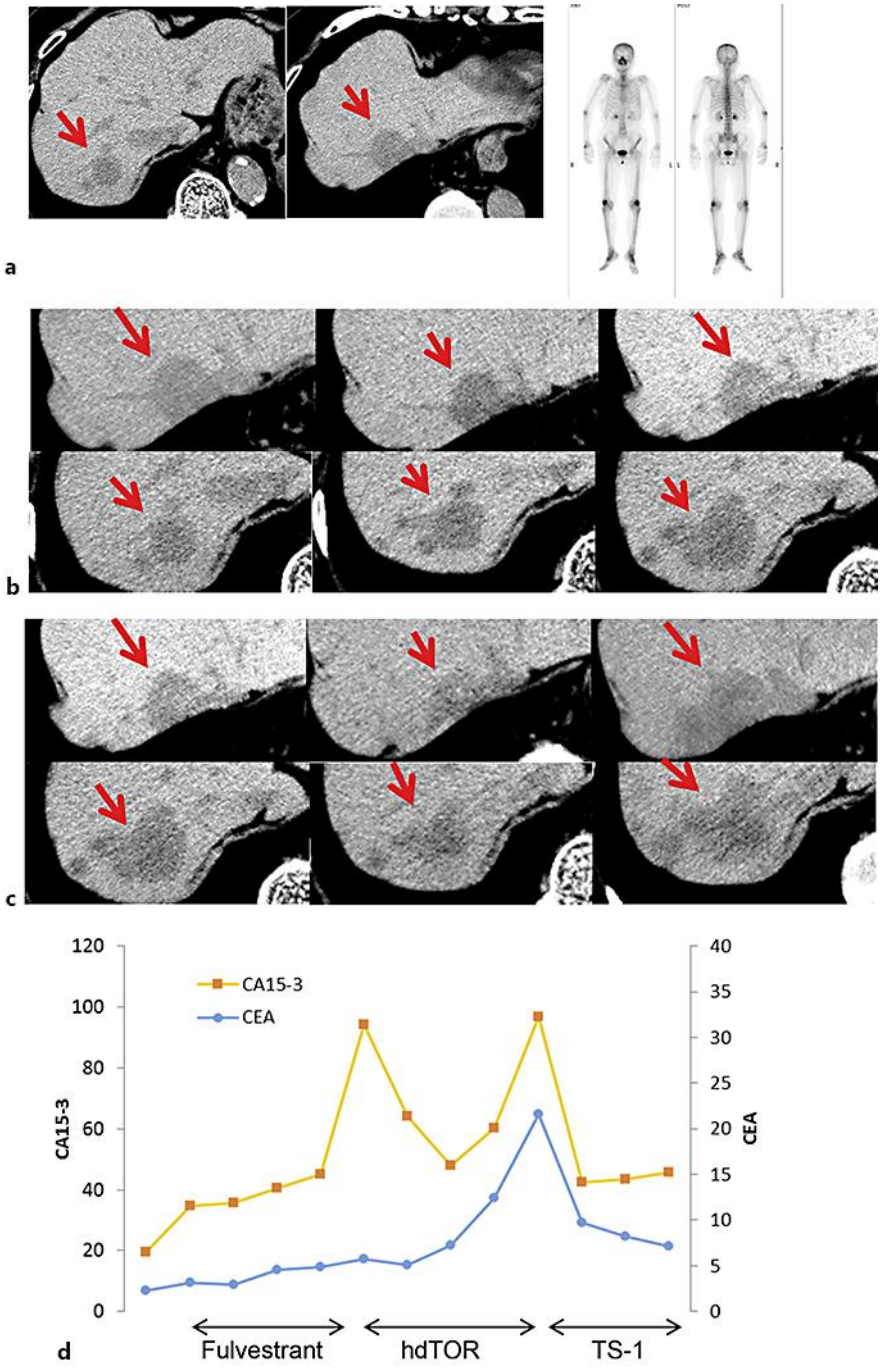

Fig. 1. Images and tumor marker levels of case 1. **a** CT and bone scintigraphy findings at diagnosis of recurrence. **b** Liver tumors in S7 (upper) and S8 (lower) at the start of fulvestrant (right), after 3 months (middle) and after 6 months (right). **c** Liver tumors in S7 (upper) and S8 (lower) at the start of hdTOR (right), after 3 months (middle) and after 6 months (right). **d** Changes in the tumor marker levels (CEA and CA15-3).

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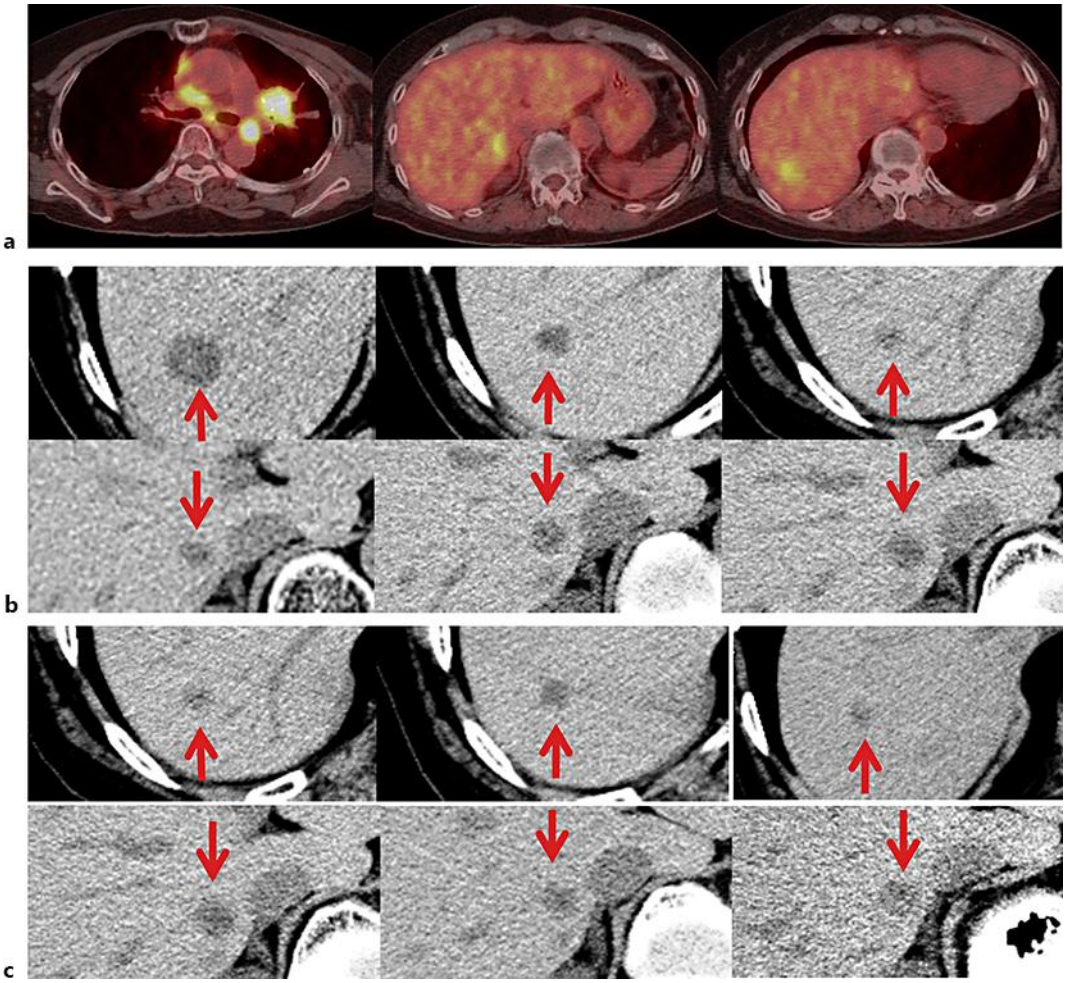

Fig. 2. Images of case 2. **a** PET/CT images at diagnosis of recurrence. **b** Liver tumors in S7 (upper) and S8 (lower) at the start of hdTOR (right), after 3 months (middle) and after 6 months (right). **c** Liver tumors in S7 (upper) and S8 (lower) at the start of hdTOR (right), after 3 months (middle) and after 6 months (right).