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CASE REPORT

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Advanced chemoresistant breast cancer responding to multidisciplinary treatment with hyperthermia, radiotherapy, and intraarterial infusion

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Abstract We employed multidisciplinary therapy, consisting of hyperthermia, radiotherapy, and intraarterial infusion, for a patient with progressive advanced breast cancer that was resistant to epirubicin hydrochloride and cyclophosphamide (EC) therapy as well as being resistant to docetaxel hydrate, and obtained a good therapeutic response. Because estrogen and progesterone receptors were both negative and HER2 was 3(+), administration of trastuzumab was started, and this patient has shown no signs of recurrence at 33 months after our treatment. The results suggested that our multidisciplinary therapy can be an effective method for the treatment of progressive breast cancer showing resistance to major chemotherapy agents such as anthracyclines and taxanes.

Key words Progressive breast cancer · Multidisciplinary therapy · Hyperthermia · Radiotherapy · Intraarterial infusion

Introduction

Many patients with advanced breast cancer show a relatively good response to treatment, due to various developments in chemotherapy, hormone therapy, and radiotherapy, but refractory tumors that do not show any satisfactory response are still common. Hyperthermia is often performed for inoperable or recurrent cancer, as a possible treatment, but, because it has little effect when used alone, it is generally applied as part of multidisciplinary therapy, together with radiotherapy and chemotherapy. In breast cancer patients, hyperthermia is easy to perform because the tumor is superficial, and a local beneficial response can be expected when it is used concomitantly with radiotherapy.[1] Treatment of inoperable localized progressive breast cancer is based on the assumption that intraarterial infusion increases local drug concentration, while a combination of radiotherapy and hyperthermia results in greater tumor shrinkage than radiotherapy alone. However, there have been no reports on the combination of radiotherapy, hyperthermia, and intraarterial infusion as the initial treatment for progressive breast cancer. Previously, we have used this multidisciplinary treatment of hyperthermia, radiotherapy, and intraarterial infusion for a patient with primary inflammatory breast cancer, but it had almost no effect. Here, we report our experience of a patient with advanced breast cancer (negative for hormone receptors and positive for HER2) that showed resistance to EC therapy (epirubicin hydrochloride [EPI] and cyclophosphamide [CPA]), and to docetaxel hydrate (DTX), but responded to multidisciplinary treatment of hyperthermia, radiotherapy, and intraarterial infusion. There have been no symptoms of recurrence at 33 months after our treatment. She continues to receive trastuzumab maintenance therapy. This case is reported here, with discussion of the relevant literature.

Case report

A 64-year-old woman noticed induration in the left breast from around August 2000, but received no medical examination. After pain and a mass developed, she presented as an out patient to the Department of Surgery at our hospital,

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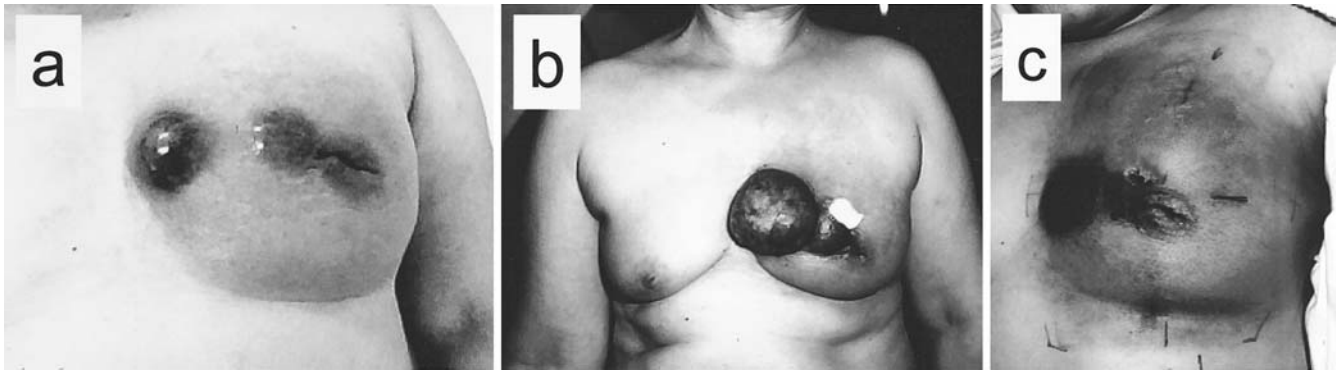


Fig. 1. **a** Generalized redness in the left breast, with two tumors, each measuring 4 × 3 cm in diameter, and an inverted nipple, were seen before treatment. **b** Five courses of EC therapy (epirubicin hydrochloride [EPI], 60 mg/m^2 and cyclophosphamide [CPA], 600 mg/m^2) and three courses of docetaxel hydrate (DTX; 60 mg/m^2, biweekly) were administered, but the tumor became larger and tumor markers were further elevated. Progressive disease was diagnosed. **c** The primary tumors and the left axillary lymph node metastases had almost disappeared after multidisciplinary treatment

in early 2001. Generalized redness in the left breast, with two tumors, each measuring 4 × 3 cm in diameter, and an inverted nipple were seen (Fig. 1a). An enlarged left axillary lymph node was palpable. Tumor markers were elevated, with carcinoembryonic antigen (CEA) being 364.9 ng/ml (normal, 5.0 ng/ml or less) and carbohydrate antigen (CA)15-3 being 49.2 U/ml (normal, 27 U/ml or less). In the left breast, a high-intensity tumor with unclear boundaries was observed on mammography. Breast ultrasonography revealed a solid hypoechoic mass with nonuniform characteristics, which had a boundary echo and an irregular, margin. Its shape was irregular, and relatively clear boundaries were observed. The left axillary lymph nodes were also enlarged. Chest computed tomography (CT) confirmed two lesions, measuring 6 × 5.5 × 3 cm and 4 × 4.5 × 3 cm in diameter, with variable density and suspected partial invasion to the pectoralis major muscle (Fig. 2a). The left axillary lymph nodes were enlarged (Fig. 2b). No metastases were found in the bones, lungs, liver, or other tissues. The tumor was biopsied, and a histopathological examination was performed. The diagnosis was invasive ductal carcinoma. Estrogen and progesterone receptors were both negative, and HER2 was 3(+).

From the above findings, left breast cancer (T4cN2MO, stage IIIB) was diagnosed, and preoperative chemotherapy was performed. From July 18, 2001, five courses of EC therapy (EPI 60 mg/m^2 and CPA 600 mg/m^2) were given. From October 17, 2001, three courses of DTX (60 mg/m^2) were administered biweekly, but the tumor continued to develop. Partial necrosis in the tumor was detected, but tumor markers were further elevated, and progressive disease (PD) was diagnosed (Fig. 1b). Informed consent for multidisciplinary therapy, consisting of hyperthermia, radiotherapy, and intraarterial infusion, was obtained from the patient, and the multidisciplinary therapy was initiated from November 27, 2001. Radiotherapy consisted of tangential irradiation for the whole left breast (total dosage of 60 Gy in 30 fractions), which was done using a 6-MV linear accelerator. Intraarterial infusion was done by implanting a catheter into the intrathoracic artery. We approached this artery from the right femoral artery, according to the Seldinger method. S. Fluorouracil (500 mg), adriamycin (20 mg), and mitomycin C (4 mg) were administered twice, with a 4-week interval. Hyperthermia was performed at a surface temperature of 38°C–41°C, once a week for 40 min, on a total of five occasions, using a microwave generator (Hyperthermis System HMS-015; Aloka, Tokyo, Japan). The primary tumors and left axillary lymph node metastases observed on the chest CT scans became larger after the EC therapy and DTX administration, but the primary tumors and left axillary lymph node metastases gradually shrank after the start of the multidisciplinary treatment, and had almost disappeared by the completion of therapy (Fig. 2c,d). Angiography showed strong tumor stains in the left breast and axillary lymph node before the multidisciplinary therapy, but the tumor stains were mostly absent after the multidisciplinary therapy (Fig. 3a,b). The tumor marker levels were 914.3 ng/ml for CEA and 98.7 U/ml for CA15-3 before the multidisciplinary therapy. However, after 3 months of multidisciplinary therapy, these levels were improved to 6.9 ng/ml for CEA and 4.1 U/ml for CA15-3. After the multidisciplinary therapy, no tumor was observed on mammography or on breast ultrasonography, and she was diagnosed as having a complete response (CR) (Fig. 1c). Acute skin reaction, due to the radiotherapy, was observed in the left breast, but it resolved within 2 months. Dermatitis, due to intraarterial infusion in the left breast, was severe (grade 3), and fibrosis persisted after the dermatitis resolved. After the completion of the multidisciplinary therapy, administration of trastuzumab was started, from October 4, 2002. To date, as of April 2004 (33 months after presentation), no localized recurrence or distant metastasis has been observed, the tumor marker levels are normal (CEA, 1.48 ng/ml and CA15-3, 14.4 U/ml), and the patient is healthy. She is still under observation as an outpatient. Her clinical course is shown in Fig. 4.

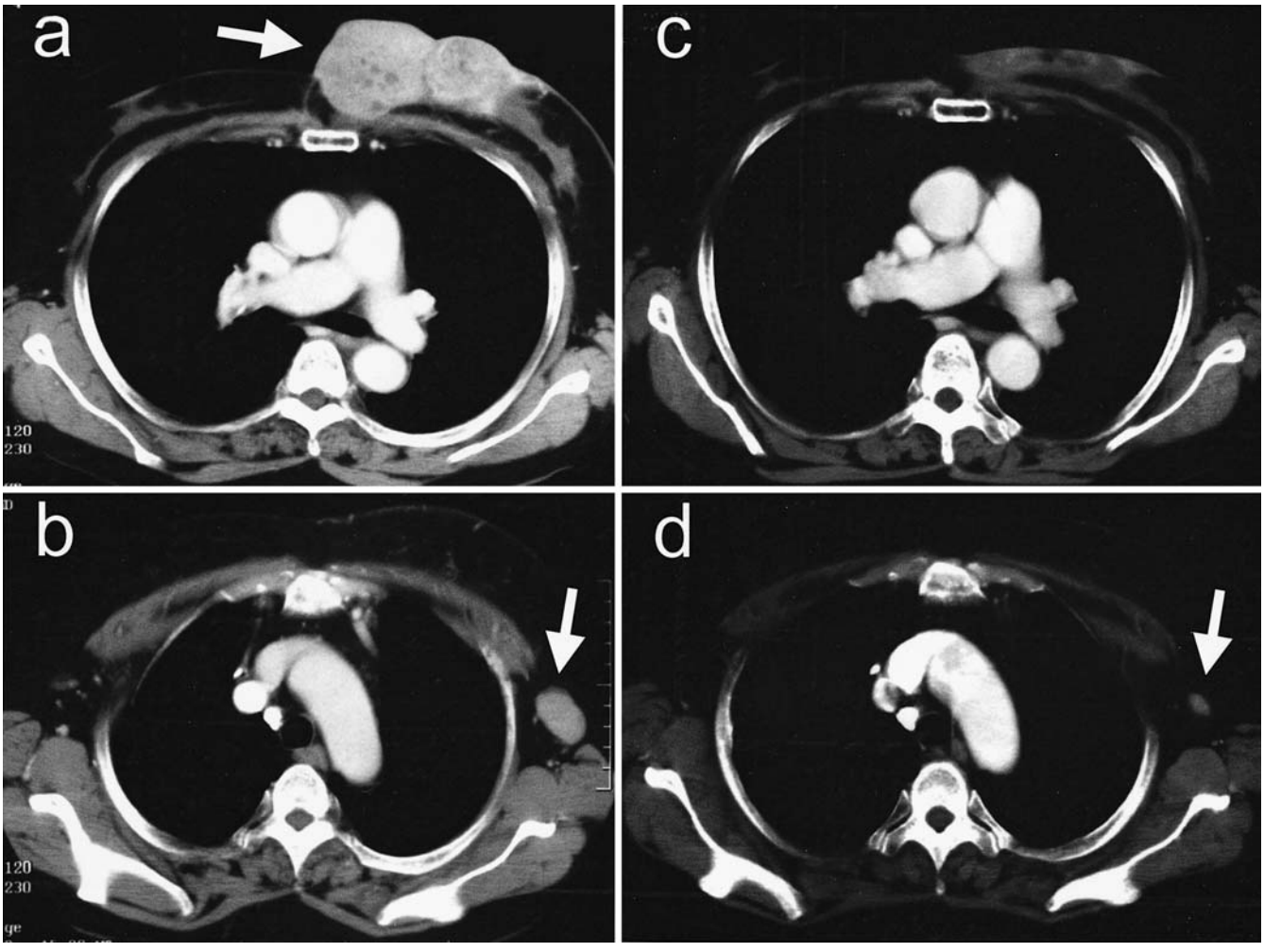
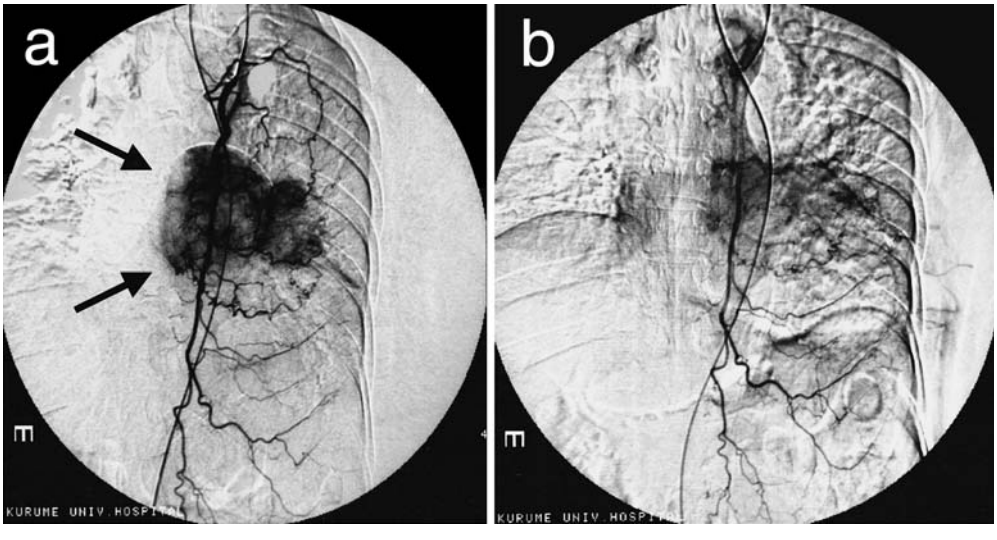


Fig. 2. **a** Chest computed tomography (CT) revealed two tumors, measuring 6 × 5.5 × 3 cm and 4 × 4.5 × 3 cm in diameter, with variable density and suspected partial invasion to the pectoralis major muscle (*arrow*). **b** The left axillary lymph nodes were enlarged (*arrow*). **c** The primary tumors gradually shrank after the institution of the multidisciplinary treatment and had almost disappeared by the completion of treatment. **d** The left axillary lymph node metastases were markedly reduced in size (*arrow*)

Fig. 3a,b. Angiography. Strong tumor stains were shown in the left breast and axillary lymph nodes before the multidisciplinary therapy (*arrows;* **a**), but the tumor stains were almost absent after completion of the multidisciplinary therapy (**b**)



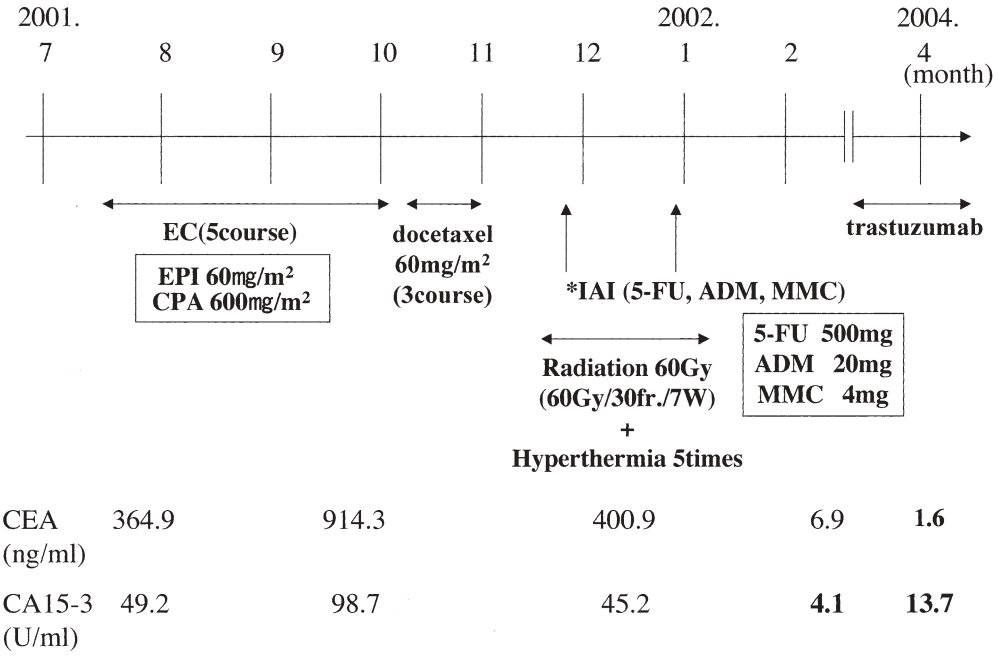


Fig. 4. Clinical course of the patient described in this report. The tumor marker levels were 914.3 ng/ml for carcino embryonic antigen (CEA) and 98.7 U/ml for carbohydrate antigen 15-3 (*CA15-3*) before the multidisciplinary therapy. However, after 3 months of the multidisciplinary therapy, these levels had improved, to 6.9 ng/ml for CEA and 4.1 U/ml for CA15-3. To date (April 2004), no localized recurrence or distant metastasis has been observed, and the tumor marker levels are normal (CEA, 1.6 ng/ml and CA15-3, 13.7 U/ml). *EC*, epirubicin hydrochloride (EPI) and cyclophosphamide (*CAP*); *5-FU*, 5-fluorouracil; *ADM*, adriamycin; *MMC*, mitomycin C; *fr*, fractions; *W*, weeks

Discussion

A complementary effect has been observed when hyperthermia and radiotherapy are combined for breast cancer, and many cases of effective treatments have been reported.[1,2–4] Joh et al.[5] reported that tumor shrinkage and control of pain were excellent in 30% and 40%, of patients respectively, and were good in 90% and 100%, respectively, after concomitant hyperthermia and radiotherapy for localized recurrent breast cancer. However, hyperthermia has been mainly used for recurrent breast cancer, and there have been few reports of its use in the treatment of primary tumors. Masunaga et al.[4] reported the effects of radiotherapy alone or in combination with hyperthermia in patients with localized progressive primary breast cancer and found a response of 55% to radiotherapy alone, and a response of 85% when it was combined with hyperthermia, immediately after completion of the therapy, while local tumor inhibition was seen in 50% and 89% of patients, respectively, at 3 months after the therapy. A better antitumor effect was obtained by the combination of radiotherapy and hyperthermia than by radiotherapy alone, and no localized recurrence was observed in patients evaluated as showing a CR after combination therapy. Three or more sessions of concomitant hyperthermia and radiotherapy have been reported to show a good antitumor effect.[4] Kimura et al.[6] performed multidisciplinary therapy, consisting of chemoendocrine therapy, radiotherapy, and hyperthermia, in a patient with progressive breast cancer who refused surgery, and they reported tumor shrinkage, with survival at 4 years after treatment. Kobayashi et al.[7] reported local control rates of 18.8% for CR and 81.3% for partial response (PR), with 5-year survival rates of 87%–100% after triple combination therapy was given to stage III or stage IV patients. Feyerabend et al.[8] observed grade 3 myelosuppression with triple combination therapy, but achieved CR in 70% of patients. These results indicate the possibility of achieving local control of breast cancer by a combination of chemoendocrine therapy, radiotherapy, and hyperthermia, or other methods, in patients with progressive cancer, but there have been no reports on the combination of radiotherapy, hyperthermia, and intraarterial infusion as the initial treatment for progressive breast cancer. Radiofrequency (RF) waves are usually used for treating a recurrent cancer mass in which the depth of invasion exceeds 4 cm. However, in the present patient, the tumor was located superficially, and there were widespread inflammatory skin changes caused by the cancer, and so we selected microwave treatment. We speculated that the radiation and intraarterial infusion would produce a beneficial effect on the deep part of the tumor, and we also expected that the radiation and intraarterial infusion would have a good effect on the axillary lymph node metastases.

Multidisciplinary therapy, with a combination of radiotherapy and chemotherapy, treatments which require high enzyme levels and high blood flow, and hyperthermia, which requires low enzyme levels and low blood flow, should be effective against any enzyme activity and blood flow conditions present in a particular tumor. Intraarterial injections of anticancer agents such as adriamycin should enhance tumor sensitivity to radiotherapy. The problems with such therapy are recurrence, due to insufficient irradiation and heating, in addition to local pain and skin changes. In the present patient, skin ulceration in the left breast was considered to be associated with the intraarterial infusion,

so it seems necessary to study further the administration rates and dosages of the anticancer agents used for this therapy.

After the completion of multidisciplinary therapy in our patient, trastuzumab was administered as maintenance therapy. Tumor markers have remained normal for 17 months to date, and imaging has shown no tumor, so this patient continues to show a good response to trastuzumab. It is necessary to investigate further which treatment should be used first after chemotherapy fails, i.e., multidisciplinary therapy or trastuzumab. However, we consider that the multidisciplinary therapy described in this report would be effective for HER2-negative patients. We also need to examine why the multidisciplinary therapy with hyperthermia, radiotherapy, and intraarterial infusion was effective when there was no response to systemic chemotherapy.

Our results suggested that multidisciplinary therapy consisting of hyperthermia, radiotherapy, and intraarterial infusion, was an effective method for the treatment of progressive breast cancer that showed resistance to major chemotherapy agents such as anthracyclines and taxanes.

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