High-dose Chemotherapy with Peripheral Blood Stem Cell (PBSCT) Support for Recurrent Breast Cancer

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ABSTRACT

Between May 1995 and June 1999 Seven patients with recurrent breast cancer received high dose chemotherapy (HDCT) with autologous peripheral blood stem cell transplantation (PBSCT). The HDCT regimen consisted of epirubicin (120-260 mg/m^2), cyclophosphamide (0-4000 mg/body). Medroxyprogesterone (1200 mg/day) was given more than 2 weeks prior to induction chemotherapy. HDCT with PBSCT support was performed on all patients on schedule. No toxic death by chemotherapy occurred. The clinical response was CR in 3, PR in 3 and NC in one patient. The rate of good clinical response was 86 %. The mean survival duration after recurrence was 24 months (range10-34). The mean survival period after HDCT was 12 months (range 8-25). The durations of efficacy were shorter than had been expected. While this treatment resulted in higher rates of clinical response, the prognosis for patients with metastatic tumor was not improved.

Key words : High-dose chemotherapy, PBSCT, Recurrent breast cancer

INTRODUCTION

Treatments for recurrent breast cancer may consist of surgery, endocrinechemotherapy, radiotherapy, thermotherapy and/or immunotherapy and among these endocrinechemothrapy is the main modality. Despite multidisciplinary treatments, survival rates for almost all patients with metastatic and recurrent tumors are very poor. It has been established that tremendously high doses of chemotherapy - 5 to 30 times higher than standard doses - are

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more effective for obtaining higher clinical or histological efficacy, for overcoming drug resistance, and for eradicating certain cancers such as acute leukemia. This approach may also work in breast cancer. Because of the poor prognosis for StageⅣ breast cancer, metastatic breast cancer and advanced breast cancer with over 10 positive lymph nodes, HDCT is considered to be the suitable treatment modality[1-4]. However, because this treatment induces severe bone marrow suppression, peripheral blood stem cell and /or bone marrow transplantation is also required. In the present study, 7 patients with recurrent breast cancer received this treatment under informed consent. The contribution of this aggressive therapy was evaluated in terms of clinical response and prognosis.

PATIENTS AND METHODS

Patients

Seven recurrent breast cancer patients were studied between January 1995 and June 1999. The mean age of these patients on recurrence was 43.6 years (range from 38 to 47). All patients were in pre-menopause status. The recurrent sites were various such as contrabreast, bone, lung, supraclavicular lymph nodes, parasternum lymph nodes, chest wall and mediastinal lymph nodes. The status of primary breast cancer is shown in Table 1. Six patients took modified radical mastectomy and 1 underwent partial mastec-

Table 1 Charcteristic of Patients and Tumor

Patient	Age	Stage	Histology	LN	ER	Adjuvant therapy
1	44	Ⅲa	scirrhous	n2	+	TAM, UFT, MMC
2	46	Ⅲa	scirrhous	n2	+	TAM, UFT
3	47	Ⅰ	scirrhous	n1β	NE	TAM, UFT, EPI
4	45	Ⅰ	solidtubular	n1α	-	TAM, UFT
5	42	Ⅰ	scirrhous	n0	-	(-)
6	43	Ⅱ	solidtubular	n1α	+	TAM, UFT
7	38	Ⅰ	papillotubular	n1α	-	RT, 5-FU

TAM: tamoxifen citrate 20 mg/day, UFT(tegafur and uracil) 400 mg/day, EPI: epirubicin hydrochloride 20mg/m2/month, MMC: mitomicin 12mg/m2/month, 5-FU: fluorouracil 200mg/day.Stage, histology and lymph nodes status were indicated according to classification of Japanese Breast Cancer Society.

tomy. The mean disease free interval was 27 months (range from 7 to 54) (Table 2). Regarding treatment after operation, 6 patients received Tamoxifen (20 mg/day) and UFT (400 mg/day) for 2 years. One took radiation

Table 2 Regimen of Chemotherapy

Patient	DFI (months)	Site of Recurrence	Induction Chemotherapy (mg)	High-Dose Chemotherapy (mg)
1	15	CBR, SC	EPI 180 iv	EPI 400 ia
2	54	OSS	CMitF	EPI 180 iv, CPA 2000
3	19	SC, PS	EPI 210 ia	EPI 300 ia, CPA 2000
4	13	SC, MEDI	EPI 210 ia	EPI 100 ia, 400 iv, CPA 4000
5	24	PS	EPI 210 ia	EPI 400 iv, CPA 4000
6	54	PS,OSS,Chest Wall	EPI 210 ia, CPA 1000	EPI 100 ia, 300 iv, CPA 4000
7	7	PUL	EPI 210 iv, Docetaxel 100	EPI 320 iv, CPA 4000

DFI: disease free interval, CBR: contra breast, SC: supraclavicular lymph node, OSS: bone, PS: parasternum lymph node, MEDI: mediastinum lymph node, PUL: lung, ia: intraarterial infusion, iv: intravenous infusion, CMitF: cyclophosphamide, mitoxantron, fluorouracil.

therapy (46Gy) for the conserved breast and one patien didn't take any adjuvant therapy at all, because of lymph node negativity and ER (-).

Chemotherapy

The regimen of induction chemotherapy with medroxyprogesterone (MPA) was as follows. All patients were administrated 1200 mg/day of MPA from 2 weeks before the start of induction chemotherapy. Induction chemotherapy consisted of epirubicin (EPI) 120-140 mg/㎡, cyclophosphamide (CPA) 0-1000 mg/body and docetaxel 0-100 mg/body, rapidly infused via the subclavian artery and/or intravenously. For HDCT, EPI 120-260 mg /㎡ and CPA 0-4000 mg/body were administrated intraarterially and/or intravenouly with doses divided by 2 day intervals, as shown in Table 2. After HDCT had been performed, all patients were given EPI 30 mg/㎡ /month, 5' DFUR 800 mg/day (for 2 weeks/month), CPA 100 mg/day (for 2 weeks/month), and MPA 800 mg/day. Fig.1 shows the protocol of the chemotherapy.

PBSCH and PBSCT

PBSCs were collected at the time of hematopoietic recovery after induction chemotherapy and G-CSF (5 μg/kg/day) administration. Harvesting was performed by aphereses for 2-3 days using a blood cell separator (AS 104, Fresenius, Germany). The product was suspended in a freezing medium (CP-1, Kyokuto, Japan) and then stored at -80℃. PBSCs were identified as CD34 positive cells. A FACScan (Becton-Dickinson, San Jose, USA) using FITC conjugated anti CD34 (BIRMA-K3) (Dako Japan, Tokyo, Japan) was performed for the analysis. When PBSCT was performed, cells were thawed

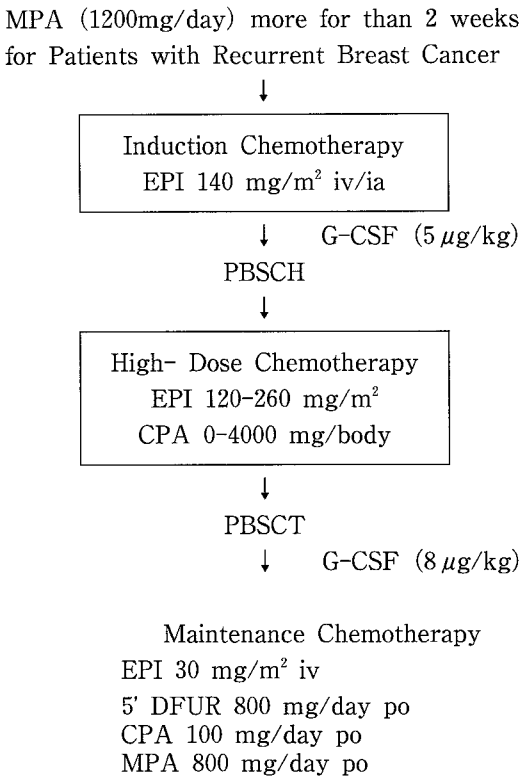

Fig. 1 Protocol of Chemotherapy. Peripheral blood stem cell harvest (PBSCH) was performed for 3 days after the number of WBC started to increase after nadir. Half the dosage of HDCT was administrated by 2 day interval.

in a 37℃ water bath and infused via a central venous catheter for 2 days after HDCT.

Clinical response

Complete response (CR), partial response (PR), no change (NC) and progessive disease (PD) were defined according to UICC criteria[5]. CR means the disappearance of all lesions assessed clinically. PR was defined as a decrease of at least 50% in all lesions. NC indicates a lack of change between conditions PR and PD. PD means an increase in tumor size and appearance of new lesions after chemotherapy.

The case of patient number 7

This 38-year old, premenopausal female with no past or family history of

the diseae noticed a small mass on the right breast in Oct. 1997. She was diagnosed as having breast cancer (T1a N1a M0) by excisional biopsy at another hospital. After being admitted to our hosipital, partial mastectomy was performed followed by radiation therapy (46 Gy) to conserved breast tissue. Pathological findings showed papillotubular carcinoma, n1 α , negative in estrogen receptor and negative in surgical margin. She was given 5-FU (200mg/body/day) as adjuvant chemotherapy. Seven months later, multiple lung metastases were detected by a check-up for recurrence at regular intevals. The tumor markers CA15-3, CEA and NCC-ST-439 were all normal. Informed consent was given to perform HDCT .

RESULTS

Hematopoietic progenitor cells

Aphereses were performed without significant complications. The mean numbers of CD34 positive cell were 2.32×10^6 ($1.6\text{-}3.6\times10^6$)/kg. The mean number of days for hematopoietic recovery (number of WBC, PLT $\geqq$1000/μl, $\geqq$50000/μl respectively) was 6.8 (5-11days). CD 34 positive cells greater than 2.0×10^6/kg were enough for PBSCT[6]. The nadir was longer compared with primary advanced breast cancer cases in which the mean number of days was 3.8 (0-8 days)[7]. When PBSCs were infused to patients intravenously, no complication occurred.

Clinical response

HDCT was performed on all patients on schedule. The rate of clinical response to HDCT was 86% (6/7 cases), as shown in Table 3. 3 patients achieved

Table 3 Outcome of High Dose Chemotherapy

Patient	Clinical Response	Survival periods after Recurrence (months)	Survival periods after HDCT (months)	alive/dead
1	PR	181	8	dead
2	NC	28	12	dead
3	PR	34	9	dead
4	CR	13	9	dead
5	PR	16	13	dead
6	CR	30	25	dead
7	CR	10	8	dead

Table 4 Overview of Randomized Study

	3-year Survival rate	Complete Response (n=45)	Partial Response (n=139)	All Patients (n=184)
Stadtmauer E.A.	High-Dose Chemotherapy	42%	27%	32% ┐ns
ECOG	Standard Chemotherapy	49%	36%	38% ┘

ECOG: the European Cooperative Oncology Group, regimen of HDCT: cyclophosphamide 1500mg/m^2/day, thiotepa 125mg/m^2/day, carboplatin 200mg/m^2/day for 4 days.

		5 -year Survival rate	Relapse rate at 3 years	Relapse rate at 5 years
Lotz J.P. et al	High-Dose Chemotherapy	29.8%	50.8%	90.7%
	Standard Chemotherapy	18.5%	79.3%	90.8%

regimen of HDCT: mitoxantron 45mg/m^2, cyclophosphamide 120mg/kg, L-PAM 140mg/m^2

CR, 3 had PR and the other patient with bone metastases had NC. Nonetheless, the periods of survival were short after HDCT. The mean survival periods after recurrence were 24 months (range from 10-34) and the mean survival period after HDCT was 12 months (range from 8-25). Two patients developed metastasis in the brain. One patient had metastases to the skin. All patients died of cancer progression. The prognosis for recurrent breast cancer was pretty poor in spite of the performance of HDCT.

Patient number 7

Induction chemotherapy, PBSCH, HDCT and PBSCT were carried out on schedule. The periods of nadir in WBC were 1 week, as shown in Fig.2. She had no severe toxicity except bonemarrow suppression. She had several bilateral metastatic lung tumors, the largest two being 2.5×1.6 cm and 2.2 ×1.7 cm at the right and left side respectively on the day of admission. After induction chemotherapy, these tumors decreased to 2.0×1.2 cm and 1.3×1.1 cm in size respectively. All tumors detected on chest x-ray had disappeared after HDCT, as shown in Fig.3. The symptoms, like cough, sputum and general malaise also vanished on leaving the hospital. Nontheless, one tumor was detected at the left lobe by a check-up 2 months later. Despite administration of more systemic chemotherapy, a metastatic brain tumor developed more 2 months later, as shown in Fig.4. Although radiation treatments to the brain metastasis were carried out and endocrinetherapy was continued, she died due to progression of the metastatic tumor and the

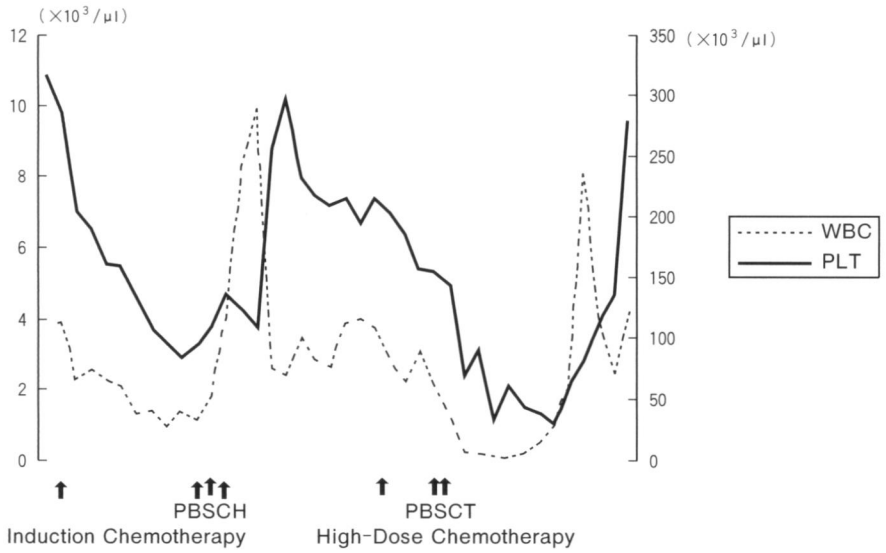

Fig. 2 The change of numbers of white blood cell and platelet after chemotherapy. The periods of nadir in WBC were 1 week.

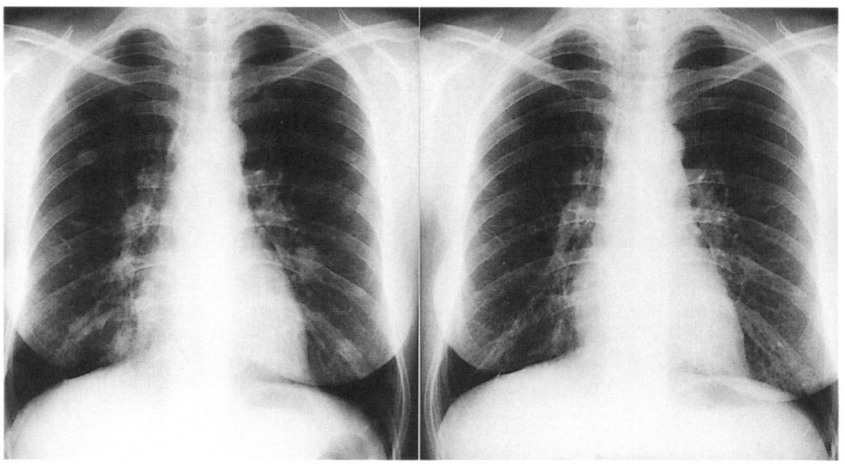

Fig. 3 Left photograph shows multiple lung tumors in patient number 7 on the day of admission. The chest x-ray (right) after HDCT shows no abnormal tumor shadows.

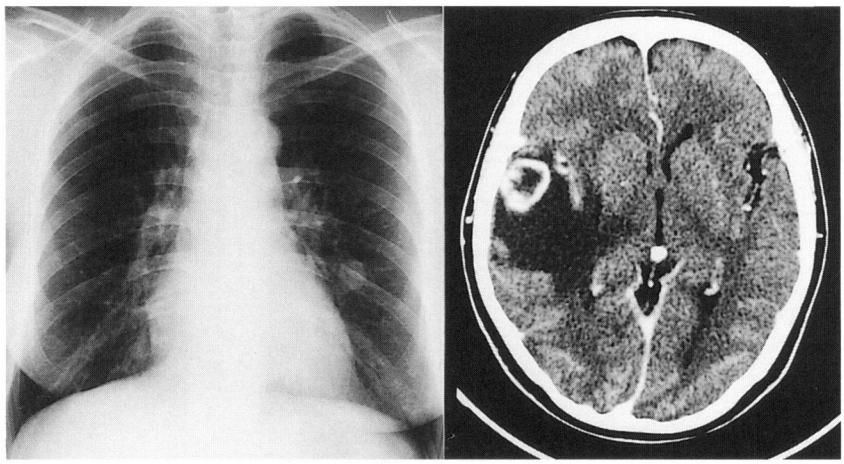

Fig. 4 Two months after HDCT, re-growth of metastatic lung tumor on the left lobe was detected (right). Metastatic brain tumor also appeared more than 2 months later (left)

appearance of pleural effusion. Only eight months had passed since HDCT was performed.

DISCUSSION

It has been established that extremely high doses of chemotherapy (5-30 times higher than standard doses) are more effective in overcoming drug resistance, eradicating certain cancers and curing otherwise incurable patients such as those with acute leukemia and lymphomas. It has been hypothesized that this approach might work in breast cancer as well[8]. We started this treatment for advanced breast cancer and recurrent breast cancer on May 1995. We reported previously as to the efficacy of HDCT for patients with locally advanced breast cancer in which all patients took neoadjuvant intraarterial HDCT[7]. The conclusion was that HDCT plus MPA supported by PBSCT had resulted in higher rates of clinical and histological response when compared with our previous intraarterial chemotherapy protocol[9]. At the ASCO Annual Meeting in 1999 the outcomes of an HDCT randomized study for metastatic breast cancer were presented. Stadtmauer and the ECOG showed that there was no significant difference statistically between HDCT and standard chemotherapy in 3-year survival rates[10]. Lotz et al stated that the relapse rate at 3-years was lower in HDCT than in standard chemotherapy. However, the relapse rate at 5-years was the same for both and there was no difference statistically in the 5-year survival rates. They concluded that this delay in relapse with HDCT could potentially offer a better quality

of life with a longer "off-therapy" period[11]. These results indicate the possible direction of future treatment. In the present study, HDCT for recurrent breast cancer was evaluated. 3 cases of CR and 3 of PR were achieved by this treatment. Although the rate of clinical response was high (86%), the efficacy was, against expectations, only short lived. In the cases with short disease free intervals, the survival periods after HDCT were particularly short (8-9 months). This may have been due to the biological characteristics of the tumors, the rapid acquirement of drug resistance against anti-cancer drugs, and/or the decrease of immune ability. The immune ability in patients with cancer is deceased compared with people without cancer[12]. The immune system may possibly be destroyed in patients with recurrent breast cancer compared to patients with primary breast cancer. Peripheral blood stem cells can produce new cells to replace those destroyed by chemotherapy. Stem cell support may be used to shorten the recovery time from HDCT. In the present study, the hematopoietic recovery periods were a little longer (mean 6.8 days) compared with cases with primary advanced breast cancer (mean 3.8 days). Something such as a kind of cytokine may exist in the blood to suppress activation of stem cells.

Our regimen basically consisted of EPI and MPA. The daily administration of MPA (1200mg/body) 2 weeks prior to infusion of EPI contributed to the high rate of clinical and histological efficacy[13] and protected against bone marrow suppression caused by cytotoxic drugs[14]. Also, promotion of appetite and inhibition of angiogenesis[15] were reported. EPI exceeded Doxorubicin in cardiotoxicity and myelosuppression[16]. We consider that a regimen with a high-dose of EPI plus MPA is a good modality for treatment of primary advanced breast cancer, because it achieved a high rate of clinical and hitological efficacy[17]. In the present study, the use of this regimen in conjunction with HDCT and PBSCT support for recurrent breast cancer didn't improve the patients' survival periods. Ito et al reported that EPI-containing HDCT for metastatic breast cancer was able to induce a high rate of CR, but, its benefits in terms of survival was still unclear[18]. Huber et al tried tandem and triple HDCT in metastatic breast cancer. They concluded that triple HDCT seemed not to improve patient outcome compared to tandem HDCT[19]. The limitation of HDCT was indicated by these studies. Nonetheless, Rowlings et al analysed the factors correlated with progression free survival after HDCT for metastatic breast cancer. They suggested that the existence of any of the following criteria made patients inappropriate candidates for HDCT treatment : older than 45 years, absense of hormone receptor, DFI of no more than 18 months or metastases in the liver etc[20]. The possibility

that HDCT can be advantageous still remains, depending on the selection of patients for treatment.

In conclusion, although a high rate of clinical response was achieved through HDCT with PBSCT support, the prognosis for recurrent breast cancer wasn't improved. However, further studies using patients who have survived for longer disease free periods and regimens with new anticancer drugs are needed before a definitive evaluation of the efficacy of HDCT can be made.

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