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ORIGINAL ARTICLE

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Epirubicin-containing high-dose chemotherapy followed by autologous hematopoietic progenitor cell transfusion for patients with chemotherapy-sensitive metastatic breast cancer: results of 5-year follow-up

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Abstract *Purpose*: Conventional chemotherapy for metastatic breast cancer results in very few long-term survivors. With a view to overcoming this problem, we hypothesized that a higher rate of complete response (CR) would lead to more long-term survivors. Therefore, we conducted a phase II study of epirubicin-containing high-dose chemotherapy (HDC) followed by autologous hematopoietic progenitor cell transfusion in patients who were sensitive to induction chemotherapy. *Methods*: The induction chemotherapy consisted of doxorubicin 60 mg/m^2, cyclophosphamide 750 mg/m^2 and fluorouracil 750 mg/m^2 on day 1. Supported by G-CSF, this chemotherapy was repeated for at least three cycles at intervals of 2 weeks until the achievement of $>50\%$ tumor regression. The HDC comprised epirubicin 120 mg/m^2 on day 1, cyclophosphamide 60 mg/kg on days 1 to 3 and thiotepa 6 mg/kg on days 1 to 3, followed by autologous bone marrow transplantation and peripheral blood stem cell transfusion. *Results*: Of 25 patients who achieved a partial response to the induction chemotherapy, 17 were treated with the HDC. Of the 15 patients evaluable for response, 10 achieved a CR (67%), giving an overall CR rate of 43% (10/25). The disease-free survival rate at 5 years was 27%. The median duration of overall survival was 21 months and the overall survival rate at 5 years was 31%. However, the survival curves were not significantly different from those of the historical controls who achieved a CR or PR to conventional chemotherapy. There were three early deaths, one as a consequence of disease progression and two treatment-related (sepsis and heart failure). Diarrhea (grade 3, 76%) and stomatitis (grade 3–4, 29%) were the dose-limiting toxicities. *Conclusions*: The present study suggests that epirubicin-containing HDC is able to induce a high rate of CR, but its benefit in terms of survival is still unclear. To determine whether HDC can achieve a cure in some patients, further studies in a larger number of patients, with a longer follow-up, are necessary.

Key words Metastatic breast cancer · High-dose chemotherapy · Bone marrow transplantation · Peripheral blood stem cell transfusion

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Introduction

Metastatic breast cancer cannot be cured [5]. Conventional chemotherapy, which consists of anthracycline-containing combination regimens, achieves a complete response (CR) in 10–20% of patients [5], and approximately 20% of these are still in remission at 5 years [5, 9]. However, absolute cure cannot be expected with these chemotherapies [5]. High-dose chemotherapy (HDC) supported by hematopoietic progenitor cells is able to achieve a CR in 40–60%, but long-term efficacy has not yet been determined [1, 2, 4, 7, 11, 12]. We conducted a phase II study of epirubicin-containing HDC followed by autologous bone marrow transplantation (BMT) and peripheral blood stem cell transfusion (PBSCT) in patients who had responded to induction chemotherapy. Our results suggest that this regimen is able to produce a high CR rate, but its effect on survival is still unclear.

Materials and methods

Patients

Between October 1990 and February 1993, patients with metastatic breast cancer were consecutively enrolled in this study. All patients gave informed consent. The protocol was approved by the Institutional Review Board. Patients aged ≦60 years were eligible. The eligibility criteria included no significant impairment of cardiac (ejection fraction ≧60%), hepatic (bilirubin in the normal range; transaminase less than twice normal) and renal (creatinine clearance ≧60 ml/min) functions, or performance score (Eastern Cooperative Oncology Group performance status not more than 2). Cardiac ejection fraction was determined by radionuclide-gated blood pool imaging or echocardiogram.

Induction chemotherapy

Intensive induction chemotherapy, which preceded the HDC, consisted of doxorubicin 60 mg/m^2, cyclophosphamide 750 mg/m^2 and fluorouracil 750 mg/m^2 on day 1. This treatment was repeated at intervals of 2 weeks, supported by G-CSF (2 μg/kg subcutaneously). A minimum of three cycles or a maximum of six cycles were administered until the achievement of >50% tumor reduction. Once this had been achieved, HDC was carried out as soon as possible, without obtaining a CR by repeating induction chemotherapy.

Peripheral blood stem cell/bone marrow collection

Peripheral blood stem cells (PBSC; $>5 \times 10^8$/kg) were collected by leukapheresis, which was performed during the marrow recovery phase after the last two cycles of induction chemotherapy. Bone marrow (BM) nuclear cells numbering more than 3×10^8/kg were harvested after completion of induction chemotherapy. The collected PBSC and BM were cryopreserved in liquid nitrogen. A colony-forming unit assay was not performed and CD34 antigen expression was not determined.

HDC and PBSCT/BMT

The HDC consisted of epirubicin 120 mg/m^2 on day 1, cyclophosphamide 60 mg/kg per day on days 1 to 3 and thiotepa 6 mg/kg per day on days 1 to 3. Both autologous BM and PBSC were infused on days 5 to 7. Intravenous G-CSF at a dose of 5 μg/kg was administered from day 8. Mesna was administered for uroprotection.

Post high-dose therapy

Patients with a positive or unknown estrogen receptor status received tamoxifen at 20 mg/day. Tamoxifen was started after ensuring marrow recovery, approximately 1 month after HDC.

Evaluation and statistical analysis

CR was defined as the disappearance of all measurable and assessable lesions for at least 4 weeks. A partial response (PR) was >50% decrease in the product of the two longest perpendicular diameters of bidimensionally measurable lesions for at least 4 weeks. We evaluated toxicities according to the criteria of the Japan Society for Cancer Therapy [6] which are a modification of those of the WHO. The disease-free survival and overall survival curves were estimated by the Kaplan-Meier method. Survival curves were tested for significance by the generalized Wilcoxon test.

Results

Patient characteristics

Table 1 shows the characteristics of the 25 patients enrolled. All patients had a good performance status (0 or 1). The median age was 42 years (27 to 56 years). The disease involved predominantly the lymph nodes (ten patients) and lung (ten patients), and 15 patients had only one metastatic tissue. Six patients had a positive estrogen receptor (ER) and positive progesterone receptor status, and nine patients had negative estrogen and negative progesterone status. At diagnosis, 13

Table 1 Patient characteristics and complete response rates

	No. of patients	%CR (patients)
Age		
<40	10	50 (5)
41–50	11	45 (5)
51–60	4	0 (0)
Performance status		
0	19	53 (10)
1	6	0 (0)
Disease involvement		
Lymph node	10	40 (4)
Lung	10	70 (7)
Liver	3	33 (1)
Bone	10	10 (1)
Pleura	6	0 (0)
Chest wall	2	50 (1)
Primary breast	3	0 (0)
No. of involved tissues		
4	1	0 (0)
3	1	0 (0)
2	7	43 (3)
1	15	47 (7)
Estrogen/progesterone receptor status		
E+, P+	6	33 (2)
E+, P–	2	50 (1)
E–, P+	2	50 (1)
E–, P–	9	44 (4)
Unknown	6	33 (2)
Initial stage at diagnosis		
I	1	100 (1)
II	13	54 (7)
IIIA	1	0 (0)
IIIB	4	25 (1)
IV	6	17 (1)
Interval from diagnosis to recurrence		
0[a]	6	17 (1)
<24 months	6	83 (5)
≧24 months	13	31 (4)
Interval from diagnosis to transplant		
<24 months	7	72 (5)
≧24 months	10	50 (5)
Prior treatment to metastatic lesions		
No	20	40 (8)
Yes[b]	5	40 (2)

[a] Primary advanced case
[b] Radiation, fluorouracil or cyclophosphamide

patients were in stage II. The median interval from diagnosis to recurrence was 28.5 months (5 to 98 months). The median interval from diagnosis to transplant was 29 months (5 to 78 months). Five patients had prior mild treatment of metastatic lesions, such as radiation, fluorouracil or cyclophosphamide.

Response

A total of 25 patients were treated with three to six cycles of the induction chemotherapy; 17 achieved a PR. The response rate was 68%. These 17 patients then received the HDC. Two of the 17 were inevaluable for the response to the HDC: one patient died of heart failure on day 23, and the other with primary advanced breast cancer in stage IIIB had no measurable lesion because mastectomy was performed before the HDC. Ten patients achieved a CR. The CR rate for HDC was therefore 67% (10/15). One PR was observed, and four patients did not respond. The overall CR rate of the induction chemotherapy and HDC was 43% (10/23). Table 1 presents the CR rates by each characteristic. Those aged < 50 years (48%, 10/21) or with a PS of 0 (53%,10/19) tended to show a favorable response. Those with metastases of the lymph nodes and lung showed response rates of 40% (4/10) and 70% (7/10), respectively. Those with initial advanced stage IIIB or IV at diagnosis showed a poor response rate (20%, 2/10). A short interval from diagnosis to recurrence or to transplant (< 24 months) tended to be associated with a favorable response [83% (5/6) and 72% (5/7), respectively]. Estrogen/progesterone receptor status and prior treatment of metastatic lesions did not influence response.

Duration of CR after HDC

The median follow-up was 69 months, ranging from 39 to 79 months. Median duration of CR in 11 patients was 20 months as determined by the Kaplan-Meier method. These 11 patients included a patient with stage IIIB disease who underwent mastectomy before HDC and relapsed with lung metastasis 2 months later. The disease-free survival rate at 5 year was 27% (Fig. 1). The median overall survival was 21 months, and the overall survival rate at 5 years was 31% (Fig. 2). As with the historical controls, patients who achieved a CR or PR on conventional chemotherapy were chosen [5]. The disease-free survival curve with HDC was not significantly different from that with conventional chemotherapy (generalized Wilcoxon test, $P = 1.26$). The overall survival rate at 5 years after HDC appeared to be superior to that with conventional chemotherapy (31% vs 19%, Fig. 2), but the difference between the two survival curves was not significant by the generalized Wilcoxon test ($P = 0.64$).

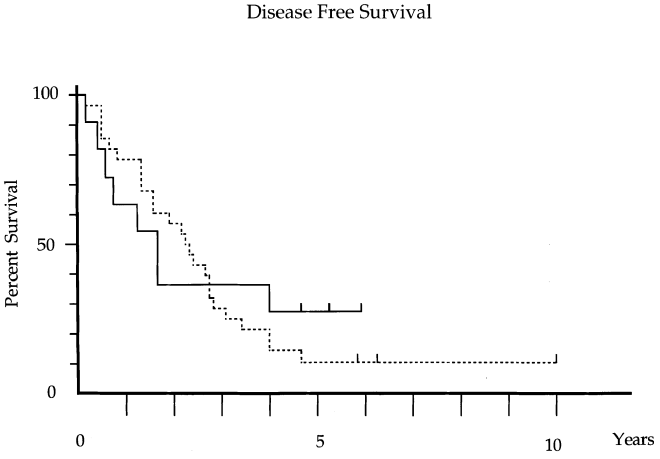

Fig. 1 Disease-free survival as determined by the Kaplan-Meier method. *Solid line* survival curve for 11 patients who achieved a CR by high-dose chemotherapy, including one patient who underwent mastectomy. The median duration of disease-free survival was 20 months. The disease-free survival rate at 5 years was 27%. *Dotted line* survival curve for 28 patients who achieved a CR on conventional chemotherapy, which included an anthracycline. There was no significant difference between the two survival curves by the generalized Wilcoxon test ($P = 1.26$)

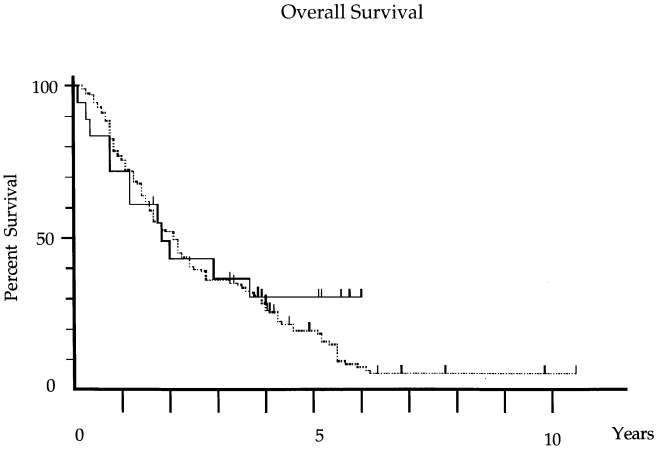

Fig. 2 Overall survival as determined by the Kaplan-Meier method. *Solid line* survival curve for 17 patients who received high-dose chemotherapy. The median duration of overall survival was 21 months, and the survival rate at 5 years was 31%. *Dotted line* survival curve for 131 patients who achieved a PR or a CR on conventional chemotherapy, which included an anthracycline. The survival rates at 5 years with high-dose chemotherapy and conventional chemotherapy were 31% and 19%, respectively. There was no significant difference between the two survival curves by the generalized Wilcoxon test ($P = 0.64$)

Toxicities

The toxicities are summarized in Table 2. Three early deaths occurred, one owing to disease progression and two treatment-related. The patient who died of her disease had progressive disease in spite of the HDC and she received additional chemotherapy, but died on day 52. One of the treatment-related deaths was a patient who showed no response to the HDC with prolonged

Table 2 Toxicities of high dose chemotherapy

Treatment related deaths	2
Median days to $>500/\mu l$ of neutrophils[a] (range)	11.5 (10–46)
Median days to $>10 \times 10^4/\mu l$ of platelet[a] (range)	17 (13–48)
Last day of platelet transfusion[a] (range)	12 (8–26)
Fever[b]	
Grade 0	0% ($n = 0$)
Grade 1	35% ($n = 6$)
Grade 2	29% ($n = 5$)
Grade 3	6% ($n = 1$)
Grade 4	29% ($n = 5$)
Nausea and vomiting[b]	
Grade 0	0% ($n = 0$)
Grade 1	0% ($n = 0$)
Grade 2	0% ($n = 0$)
Grade 3	100% ($n = 17$)
Diarrhea[b]	
Grade 0	6% ($n = 1$)
Grade 1	0% ($n = 0$)
Grade 2	18% ($n = 3$)
Grade 3	76% ($n = 13$)
Grade 4	0% ($n = 0$)
Stomatitis[b]	
Grade 0	12% ($n = 2$)
Grade 1	47% ($n = 8$)
Grade 2	12% ($n = 2$)
Grade 3	23% ($n = 4$)
Grade 4	6% ($n = 1$)
Elevation of transaminases[b]	
Grade 0	76% ($n = 13$)
Grade 1	12% ($n = 2$)
Grade 2	12% ($n = 2$)
Grade 3	0% ($n = 0$)
Grade 4	0% ($n = 0$)

[a] Excluding one case with engraftment failure
[b] Excluding one case with heart failure

myelosuppression and who died of sepsis and multiorgan failure during the 11th week, and the other was a patient who unexpectedly developed heart failure with a declining ejection fraction and who died on day 23. The latter patient had received only three cycles of the induction chemotherapy.

The total dose of doxorubicin was 180 mg/m^2. The median time to recover to a neutrophil count of more than 500/μl was 11.5 days (10–46 days). The median time to recover to a platelet count of more than $10 \times 10^4/\mu l$ was 17 days (13–48 days). Neutropenic fever (grade 3–4) was observed in 35% of patients (6/17). Nausea and vomiting (grade 3) occurred in all patients. The incidence was 76% (13/17) for diarrhea (grade 3), 29% (5/17) for stomatitis (grade 3–4) and 24% (4/17) for transient elevation of transaminases (grade 1–2). Therefore, the dose-limiting toxicities of this regimen were gastrointestinal toxicities.

Discussion

One approach to overcoming the incurability of advanced breast cancer is HDC followed by hematopoietic progenitor cell transfusion. The present study, in which the effectiveness of induction chemotherapy followed by HDC was evaluated, showed a 43% CR rate, which is double or triple that with conventional chemotherapy. Other authors have reported similar CR rates of 40 to 67% [1, 2, 4, 7, 11, 12]. The initial aim of a high CR rate may have been achieved. However, the final goal is to achieve more patients with persistent CR. Unfortunately, our results demonstrate that a majority of patients who show a CR will relapse, while only approximately 20% will maintain a CR for 5 years after HDC. The disease-free survival curve with HDC did not differ from that with conventional chemotherapy. This curve is very similar to that reported by others [9]. There are very few data on survival beyond 5 years in patients treated with HDC. The main question in establishing the benefit of HDC is whether the patients who show a CR for 5 years will achieve a cure or not. It is possible that the three long-term disease-free survivors in the present study may achieve a cure. To answer this question requires further follow-up. It is still unclear whether HDC has any impact on the survival of patients with metastatic breast cancer.

There has been only one randomized study reported. Bezwoda et al. [3] demonstrated that a high-dose regimen was significantly superior to conventional chemotherapy. Their results, however, do not appear to be conclusive because of the small numbers of patients treated (two groups of 45 patients), the short survival with standard chemotherapy and the unbalanced use of tamoxifen. Therefore, further investigation by means of a larger randomized trial is necessary. The best combination regimen of anticancer drugs at high doses is unknown. We have tried high-dose epirubicin, which is one of the key drugs for metastatic breast cancer, but mucositis and diarrhea interfered with the administration of the higher doses. Epirubicin at a dose of 120 mg/m^2 is only 1.5 to 2 times the conventional dose. It is of interest that Bezwoda et al [3] demonstrated the usefulness of a high-dose regimen containing mitoxantrone, which is an anthracycline derivative. They employed mitoxantrone at a dose four times the conventional dose. Recently, Vries et al. have reported encouraging results with a mitoxantrone-containing HDC regimen [10]. However, without stem cell support, the dose intensification of mitoxantrone does not improve the response or its duration [8]. The failure to achieve marked improvement in the present study may have been because of the use of epirubicin at a relatively low dose.

The toxicities of HDC should be assessed to clarify its usefulness. Two treatment-related deaths occurred in the present study. One patient had prolonged myelosuppression. This patient may not have had enough progenitor cells in the PBSC and BM collected. Such a delayed recovery of the BM can now be avoided because sufficient CD34 antigen-positive cells to recover BM function can be collected. It is important to monitor CD34 antigen expression or colony-forming activity of collected hematopoietic progenitor cells. The other

treatment-related death was due to cardiac toxicity. The patient had no basic heart disease and received a modest total cumulative dose of anthracyclines, i.e. 180 mg/m^2 of doxorubicin and 120 mg/m^2 of epirubicin. However, it is possible that additional epirubicin and cyclophosphamide in the HDC may aggravate their cardiac toxicity. A high-dose regimen containing an anthracycline requires very careful monitoring of cardiac function.

In conclusion, our results suggest that epirubicin-containing HDC is able to produce a high CR rate compared with conventional chemotherapy, but its benefit in terms of survival is still unclear. To improve the efficacy and safety, a novel strategy is required.

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References

1. Ayash LJ, Elias A, Wheeler C, Antman K (1994) Double dose-intensive chemotherapy with autologous marrow and peripheral-blood progenitor-cell support for metastatic breast cancer: a feasibility study. J Clin Oncol 12: 37
2. Ayash LJ, Wheeler C, Fairclough D, Schwartz G, Reich E, Warren D, Schnipper L, Antman K, Frei E III, Elias A (1995) Prognostic factors for prolonged progression-free survival with high-dose chemotherapy with autologous stem-cell support for advanced breast cancer. J Clin Oncol 13: 2043
3. Bezwoda WR, Seymour L, Dansey RD (1995) High-dose chemotherapy with hematopoietic rescue as primary treatment for metastatic breast cancer: a randomized trial. J Clin Oncol 13: 2483
4. Dunphy FR, Spitzer G (1992) Use of very-high dose chemotherapy with autologous bone marrow transplantation in treatment of breast cancer. J Natl Cancer Inst 84: 128
5. Inoue K, Ogawa M, Horikoshi N, Aiba K, Mukaiyama T, Mizunuma N, Itami S, Hirano A, Matsuoka A, Matsumura T (1991) Evaluation of prognostic factors for 233 patients with recurrent advanced breast cancer. Jpn J Clin Oncol 21: 334
6. Japanese Society for Cancer Therapy (1993) Criteria for evaluation of the clinical effects of solid cancer chemotherapy. J Jpn Soc Cancer Ther 28: 101
7. Peters WP, Shpall EJ, Jones RB, Ross M (1990) High-dose combination cyclophosphamide (CPA), cisplatin (cDDP) and carmustine (BCNU) with bone marrow support as initial treatment for metastatic breast cancer: three-six follow up. Proc Am Soc Clin Oncol 9: 10
8. Shpall EJ, Jones RB, Holland JF, Bhardwaj S, Paciucci PA, Wilfinger CL, Strashun A (1988) Intensive single-agent mitoxantrone for metastatic breast cancer. J Natl Cancer Inst 80: 204
9. Tomiak M, Piccart F, Mignolet T, Sahmoud R, Paridaens M, Nooy L, Beex L, Fentiman IS, Muller A, Schueren E van der, Ruben RD (1996) Characterisation of complete responders to combination chemotherapy for advanced breast cancer: a retrospective EORTC breast group study. Eur J Cancer 32: 1876
10. Vries EGE de, Rodenhuis S, Schouten HC, Hupperets PSCJ, Dolsma WV, Lebesque JV, Blijham GH, Bontenbal M, Mulder NH (1996) Phase II study of intensive chemotherapy with autologous bone marrow transplantation in patients in complete remission of disseminated breast cancer. Breast Cancer Res Treat 39: 307
11. Williams SF, Mick R, Dresser R, Golick J, Beschorner J, Bitran JD (1989) High-dose consolidation therapy with autologous stem cell rescue in stage IV breast cancer. J Clin Oncol 7: 1824
12. Williams SF, Gilewski T, Mick R, Bitran JD (1992) High-dose consolidation therapy with autologous stem cell rescue in stage IV breast cancer: follow-up report. J Clin Oncol 10: 1743