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ORIGINAL ARTICLE

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High-dose chemotherapy with autologous hematopoietic stem-cell transplantation in breast cancer

Abstract Since 1981 we have conducted four studies of the treatment of metastatic and postoperative high-risk breast cancer with high-dose chemotherapy supported by autologous hematopoietic stem-cell transplantation (AHSCT). Study I, involving 56 metastatic cancer patients, proved that induction chemotherapy produces a lasting complete response (CR) in only a few cases despite the achievement of a CR rate higher than that expected from standard chemotherapy. Study II was designed to examine consolidation chemotherapy in metastatic cancer patients responding to induction chemotherapy. At a median follow-up of 26 months (range 2–66), consolidation therapy produced a 5-year progression-free survival rate of 27.1% in 30 patients showing a CR or a partial response to induction therapy and 58.6% in 13 patients showing a CR to consolidation therapy. No treatment-related death occurred during study II. The same regimen used in study I was employed for 58 postoperative high-risk patients in study III. The 10-year disease-free survival rate recorded for patients with $\geq$10 positive axillary lymph nodes was significantly higher ($P < 0.05$) in the AHSCT-supported chemotherapy group than in the conventional chemotherapy group. A double high-dose regimen was adopted for 21 postoperative high-risk patients in study IV. The 3-year disease-free survival rate recorded for 9 patients with $\geq$10 positive axillary lymph nodes was 71.4% at a median follow-up of 25 (range 8–45) months. No treatment-related death occurred during study IV. Peripheral blood stem-cell transplantation shortened the duration of bone marrow suppression more effectively than did bone marrow transplantation, thereby optimizing high-dose chemotherapy.

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Introduction

Breast cancer generally responds well to chemotherapy and radiation therapy. Chemotherapeutic agents have been shown experimentally to have a dose-response relationship in drug-sensitive cancer [4]. This suggests that high-dose chemotherapy might improve the therapeutic outcome in breast cancer, and prospective studies have shown that increased dose intensity is useful for the clinical management of breast cancer [2, 7]. However, the problem of toxicity, particularly bone marrow suppression, has prevented the widespread use of chemotherapeutic agents. Autologous bone marrow transplantation (ABMT) was introduced to overcome this therapeutic barrier and has enabled the clinical use of chemotherapeutic agents at a dose 2- to 20-fold greater than the standard dose [3]. More recently, peripheral blood stem-cell transplantation (PBSCT) has come into use, contributing to the safer use of chemotherapeutic agents.

Between 1981 and 1991 we treated metastatic and postoperative high-risk breast cancer patients using high-dose chemotherapy supported by autologous hematopoietic stem-cell transplantation (AHSCT). On the basis of this experience we have employed two higher-dose regimens during recent years. We review the data obtained from our four studies and discuss the future prospects of this therapeutic strategy.

Patients and methods

The patients studied and the therapeutic regimens used are shown in Tables 1 and 2, respectively. Bone marrow was taken from the bilateral iliac bones of each patient under general anesthesia and was centrifuged using an IBM Blood Cell Processor (COBE Laboratories, Tokyo, Japan) to separate mononuclear cells. The mononuclear cells thus obtained were frozen using a programmed freezer and then preserved

Table 1 Patients studied

Parameter	Target disease			
	Metastatic breast cancer		Postoperative high-risk breast cancer	
	Study I	Study II	Study III	Study IV
Period of study	May 1981–October 1990	November 1990–June 1996	June 1981–December 1991	January 1992–June 1996
Number of patients	56	30	58	21
Median age in years (range)	48 (29–68)	49 (27–62)	47 (29–66)	41 (23–62)
Therapeutic regimen[a]	1	2	1	3

[a] For details, see Table 2

Table 2 Therapeutic regimens

Regimen	Cycle	Drug (dose)	Administration	
			Route	Day(s)
1	Induction (repeated twice)	Cyclophosphamide (800 mg/m² daily)	i.v.	−3, −2
		Doxorubicin (80 mg/m² daily)	i.v.	−3
		Nimustine (3 mg/m² daily)	i.v.	−2
		ABMT		0
2	Induction	Cyclophosphamide (1000 mg/m² daily)	i.v.	1
		Epirubicin (130 mg/m² daily)	i.v.	1
		G-CSF (125 μg daily)	s.c.	2–
	Consolidation	Cyclophosphamide (2000 mg/m² daily)	i.v.	−5, −4, −3
		Thiotepa (200 mg/m² daily)	i.v.	−5, −4, −3
		ABMT/PBSCT		0
		G-CSF (300 μg/m² daily)	i.v.	1–
3	Disease-oriented conditioning	Cyclophosphamide (1000 mg/m² daily)	i.v.	1
		Epirubicin (130 mg/m² daily)	i.v.	1
		G-CSF (125 μg daily)	s.c.	2–
	Double high-dose	Cyclophosphamide (1000 mg/m² daily)	i.v.	−5, −4, −3
		Thiotepa (100 mg/m² daily)	i.v.	−5, −4, −3
		Epirubicin (80 mg/m² daily)	i.v.	−5
		ABMT/PBSCT		0
		G-CSF (300 μg/m² daily	i.v.	1–

in liquid nitrogen with 10% dimethylsulfoxide (DMSO). Frozen mononuclear cells were promptly thawed in a 37 °C water bath immediately before their administration via i.v. drip [9]. Since November 1992 we have performed PBSCT. PBSCs were collected from each patient using a COBE Spectra apparatus (COBE Laboratories) and were preserved as described above. Nucleated cells and colony-forming units, granulocyte-macrophage (CFU-GM), were counted in bone marrow and peripheral blood using the method described elsewhere [9]. Table 3 shows the composition of the stem cells used in consolidation chemotherapy (study II) and double high-dose chemotherapy (study IV).

Results

Study I

Therapeutic regimen 1 was used in 56 patients who did not respond to standard chemotherapy and was assessed in 34 patients. The response rate was 76.5%; a complete response (CR) was observed in 35.3% (12/34) of patients and a partial response (PR), in 41.2% (14/34). The 10-year overall survival rate and the duration of 50% survival were 13.8% and 586 days, respectively, in the 56 patients at a median follow-up of 93 months (range 11–167 months; Fig. 1A) and 25.0% and 1693 days, respectively, in the 12 complete responders at a median follow-up of 131 months (range 41–167 months; Fig. 1B). The values recorded for the 12 complete responders were significantly higher than those noted for the 8 nonresponders ($P < 0.05$, log-rank test). The duration of 50% survival seen in the 14 partial responders was 334 days, which did not differ significantly from the duration of 505 days observed in the 8 nonresponders. In all, 8 of the 11 patients followed for >5 years showed a CR for a maximum of 13 years and 11 months.

Study II

Consolidation chemotherapy was performed in 30 (7 complete and 23 partial) responders to induction chemotherapy. The performance status was 0 in 11 patients and 1 in 19 patients. The dominant sites of disease were the lung (n = 11), lymph nodes (n = 8), liver (n = 6), chest wall

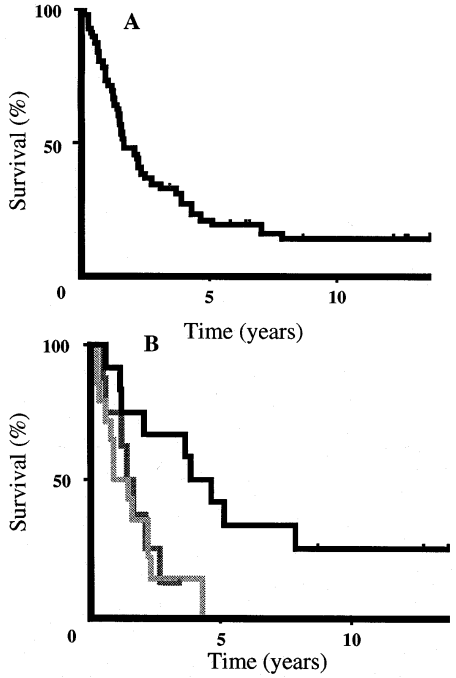

Fig. 1 A, B Overall survival of metastatic breast cancer patients undergoing induction chemotherapy. **A** All registered patients (n = 56). Median follow-up 93 months (range 11–167 months). **B** By response (■ CR – n = 12; ▒ PR – n = 14; ▨ no change/disease progression – NC/PD, n = 8); median follow-up 131 months (range 41–167 months)

(n = 3), and skin (n = 2). The 7 complete responders and 6 of the 23 partial responders showed CR to consolidation therapy; the 17 other partial responders to induction therapy remained partial responders after consolidation therapy. The overall 5-year progression-free survival rate observed at a median follow-up of 26 months (range 2–66 months) was 27.1% (Fig. 2A). Analysis by response to induction therapy revealed that the 5-year progression-free survival rate recorded for the 7 complete responders was 35.7%, which was not significantly different from the value of 24.6% noted for the 23 partial responders (Fig. 2B). However, after consolidation therapy the 5-year progression-free survival rate (58.6%) recorded for the 13 complete responders was significantly higher ($P < 0.05$) than that noted for the 17 partial responders (Fig. 2C). Analysis of AHSCT by graft source revealed that the duration of chemotherapy-induced bone marrow suppression was significantly shorter ($P < 0.01$) when PBSCT was used alone or in combination with ABMT than when ABMT was used alone (Table 4). The toxic effects of severity higher than Japan Clinical Oncology Group (JCOG) grade 3 [8] included hepatic disturbance (six patients), fever (four patients), stomatitis (one patient), and hematuria (two patients). However, neither toxicity higher than JCOG grade 4 nor treatment-related deaths occurred during the study.

Study III

Therapeutic regimen 1 was used as adjuvant chemotherapy in 58 patients with postoperative high-risk breast cancer; 22

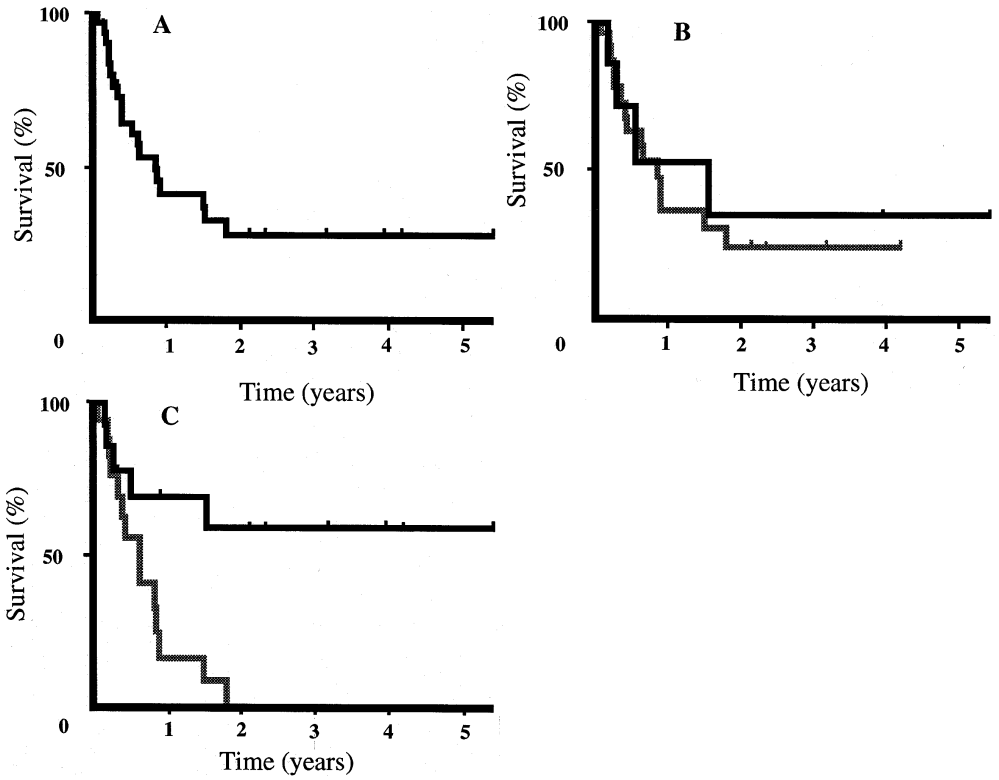

Fig. 2 A–C Progression-free survival of metastatic breast cancer patients undergoing consolidation chemotherapy after response to induction chemotherapy; median follow-up 26 months (range 2–66 months). **A** All registered patients (n = 30). **B** By response to induction therapy (■ CR – n = 7; ▨ PR – n = 23). **C** By response to consolidation therapy (■ CR – n = 13; ▨ PR – n = 17)

Table 3 Transfused stem cells

Cycle	Cell type transfused	ABMT	ABMT+PBSCT	PBSCT
Consolidation chemotherapy		(n = 12)	(n = 11)	(n = 6)
	Nucleated ($\times 10^7$/kg)	2.30 ± 0.85	50.0 ± 27.3	26.5 ± 7.0
	CFU-GM ($\times 10^4$/kg)	1.73 ± 0.89	32.4 ± 46.6	19.3 ± 8.9
Double high-dose chemotherapy		(n = 3)	(n = 4)	(n = 12)
1 bone marrow	Nucleated ($\times 10^7$/kg)	1.5 ± 0.7	1.7 ± 0.7	–
	CFU-GM ($\times 10^4$/kg)	0.9 ± 0.2	2.0 ± 0.4	–
1 PBSC	Nucleated ($\times 10^7$/kg	–	19.0 ± 3.0	23.0 ± 9.53
	CFU-GM ($\times 10^4$/kg)	–	15.0 ± 9.7	16.1 ± 11.3
2 bone marrow	Nucleated ($\times 10^7$/kg)	1.4 ± 0.6	1.2 ± 0.4	–
	CFU-GM ($\times 10^4$/kg)	1.0 ± 0.6	1.7 ± 0.7	–
2 PBSC	Nucleated ($\times 10^7$/kg)	–	17.5 ± 8.9	23.6 ± 12.5
	CFU-GM ($\times 10^4$/kg)	–	15.1 ± 8.6	22.6 ± 22.0

Table 4 Hematologic recovery during consolidation therapy

	ABMT (n = 12)	ABMT+PBSCT (n = 11)	P	PBSCT	P
Neutrophils $>500/mm^3$ (days after transplantation)	13.5 (11–16)	9 (7–11)	<0.0001	8.5 (7–10)	<0.0001
Neutropenia $<500/mm^3$ (duration)	11 (8–13)	7 (4–9)	<0.0001	5.5 (4–10)	0.0009
Platelets $>50\,000/mm^3$ (days after transplantation)	28.5 (22–45)	14 (9–32)	0.0004	12 (9–14)	<0.0001
Platelet transfusion $\times 10$ units (number of times)	5.5 (3–16)	2 (1–7)	0.0015	2 (1–3)	0.0054

patients had ≥10 positive axillary lymph nodes. The 10-year disease-free survival rate observed at a median follow-up of 112 months (range 27–201 months) was 30.3% in the 22 patients undergoing ABMT-supported chemotherapy, which was significantly higher ($P < 0.05$) than the 11.3% observed in the 30 patients who had ≥10 positive axillary lymph nodes and underwent conventional chemotherapy (Fig. 3). Multivariate analysis showed that the number of positive lymph nodes and the use of ABMT-supported high-dose chemotherapy had significantly more influence ($P < 0.05$) on the prognosis for postoperative high-risk breast cancer patients than did other factors (Table 5).

Table 5 Analysis with the Cox proportional-hazard model of the survival of 52 patients with ≥10 positive lymph nodes

Variable	Coefficient	SE	χ^2	P value
Age	0.00603	0.0149	0.164	0.686
Histology	–0.166	0.109	2.33	0.127
t factor	0.647	0.531	1.48	0.223
n factor	0.461	0.746	0.381	0.537
Number of positive nodes	0.0343	0.0175	3.84	0.0499
TNM stage	–0.911	0.894	1.04	0.309
Estrogen receptor	0.0799	0.194	1.69	0.681
ABMT treatment	–0.633	0.322	3.86	0.0494

[a] Of the 52 patients, 22 were undergoing ABMT-supported high-dose adjuvant chemotherapy and 30 conventional adjuvant chemotherapy

Study IV

Double high-dose chemotherapy was used in 21 patients (8 with stage II disease and 13 with stage III disease) with between 1 and 41 (median 8) positive axillary lymph nodes. These patients showed a 4-year disease-free survival rate of 76.0% at a median follow-up of 28 months (range 8–54 months); however, 9 patients with ≥10 positive axillary lymph nodes showed a 3-year disease-free survival rate of

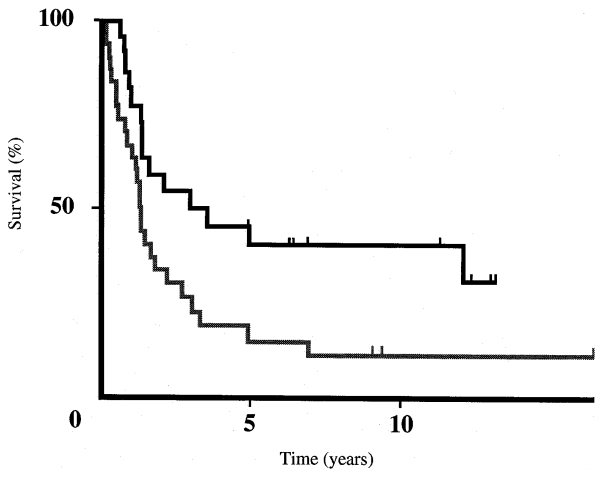

Fig. 3 Comparison of disease-free survival in stage II/III breast cancer patients with ≥10 positive axillary lymph nodes and receiving ABMT-supported high-dose adjuvant chemotherapy or conventional adjuvant chemotherapy (■ ABMT – n = 22; ▨ conventional adjuvant therapy – n = 30); median follow-up 112 months (range 27–201 months)

Table 6 Hematologic recovery in double high-dose chemotherapy: comparison between graft sources

Cycle	Parameter	ABMT (n = 3)[a]	ABMT+ PBSCT (n = 4)[a]	P	PBSCT (n = 12)[a]	P
1	Neutrophils >500/mm^3[b]	23, 21, 18	15, 14, 15, 18	0.0223	15 (14–16)	<0.0001
	Neutropenia <500/mm^3[c]	15, 12, 9	5, 5, 6, 8	0.0168	5.5 (4–7)	<0.0001
	Platelets >50,000/mm^3[b]	36, 26, 24	19, 20, 20, 19	0.0325	18.5 (15–26)	0.0008
	Platelet transfusion×10 units[d]	12, 5, 6	0, 2, 3, 2	0.0302	1 (0–3)	0.0001
2	Neutrophils >500/mm^3[b]	21, 20, 19	14, 15, 15, 17	0.0031	15 (13–16)	<0.0001
	Neutropenia <500/mm^3[c]	11, 11, 10	4, 6, 6, 8	0.0056	6 (4–7)	<0.0001
	Platelets >50,000/mm^3[b]	35, 41, 30	18, 21, 19, 20	0.0023	18 (16–25)	<0.0001
	Platelet transfusion×10 units[d]	9, 10, 6	1, 3, 2, 1	0.0023	2 (0–4)	<0.0001

[a] Data for individual patients treated using ABMT and ABMT+PBSCT are given; the median value (range) of data for patients treated using PBSCT is shown
[b] Data show the number of days after the start of chemotherapy
[c] Data show the duration of neutropenia in days
[d] Data show the number of times platelet transfusions were given

71.4% at a median follow-up of 25 months (range 8–45 months; Fig. 4). PBSCT used alone or in combination with ABMT allowed neutrophil and platelet recovery significantly more promptly than did ABMT alone ($P<0.05$; Table 6). There was no significant difference in the time required for hematologic recovery between the first and second cycles. Toxic effects more severe than JCOG grade 3 included hepatic disturbance, fever, and hemolytic anemia in two patients each during the first cycle and hepatic disturbance in two patients, fever in one patient, and skin disorder in one patient during the second cycle. The two patients who had hemolytic anemia during the first cycle were not registered for the second cycle. However, neither toxicity higher than JCOG grade 4 nor treatment-related deaths occurred during the study.

Discussion

ABMT-supported high-dose chemotherapy has been shown to produce a higher response rate in breast cancer patients than has conventional chemotherapy. An investigative group has reported that the response rate recorded for 307 patients undergoing this new treatment modality was 66%, including a CR rate of 19% [1]. However, the duration of response was as short as 2–10 months in most patients. With this in mind, they attempted high-dose consolidation chemotherapy in 442 patients who responded to induction chemotherapy. This resulted in a CR rate of 48%, with a continuous CR being seen in 31% of patients. Our study in metastatic breast cancer reveals that high-dose consolidation chemotherapy can produce a significantly higher progression-free survival rate in complete responders than in partial responders. Our protocol for AHSCT-supported high-dose consolidation chemotherapy is under in-depth evaluation in a multicenter phase II trial. A future proposal involves increasing the dose intensity in consolidation therapy to produce a cure-oriented therapy; tandem-repeated high-dose chemotherapy [6] represents an attempt to do this.

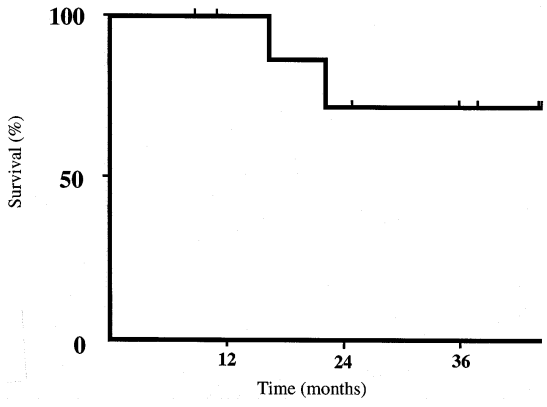

Fig. 4 Disease-free survival in stage II/III breast cancer patients with ≥10 axillary lymph nodes undergoing double high-dose chemotherapy (n = 9); median follow-up 25 months (range 8–45 months)

A continuous CR in metastatic breast cancer is observed in only a few cases despite the achievement of a high CR rate. This indicates that the tumor volume in metastatic breast cancer is beyond the scope of control with present regimens. Thus, AHSCT-supported high-dose chemotherapy is used as adjuvant chemotherapy for postoperative high-risk breast cancer. A phase II study has been conducted in postoperative breast cancer patients with ≥10 axillary lymph nodes, with the results showing that this treatment modality produces a disease-free survival rate of 72% at a median follow-up of 30 months [5]; this is higher than the 38–52% survival rate reported at the same median follow-up in a retrospective study of conventional adjuvant chemotherapy conducted by the Cancer and Leukemia Group B (CALGB) [5]. Similar results were obtained using our AHSCT-supported double high-dose chemotherapy regimen, except that treatment-related deaths, which occurred in 12% of patients in the CALGB study, were not observed in our study. The cost-benefit ratio of this new treatment modality is also under further examination in prospective comparative studies.

The superiority of PBSCT over ABMT in terms of neutrophil and platelet recovery during high-dose chemotherapy was confirmed in our studies. Recently, CD34$^+$ cells have come into use; this and the availability of larger numbers of nucleated cells and of CFU-GM that are less contaminated by cancer cells will make it possible to

increase patients' tolerance of chemotherapy, thereby enabling chemotherapy to be used at its maximal potency.

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