ELSEVIER

European Journal of Cancer 41 (2005) 71–80

European Journal of Cancer

www.ejconline.com

High-dose chemotherapy with haematopoietic stem cell transplantation for metastatic breast cancer patients: final results of the French multicentric randomised CMA/PEGASE 04 protocol☆

Jean-Pierre Lotz [a,b,c,d,e,*], Hervé Curé [b,c,d,e], Maud Janvier [b,c,d,e], Bernard Asselain [b,c,d,e], François Morvan [b,c,d,e], Michel Legros [b,c,d,e,†], Bruno Audhuy [b,c], Pierre Biron [b,c,d,e], Maryse Guillemot [e], Jocelyne Goubet [b,c], Abderrahmane Laadem [a], Christian Cailliot [b,c], Christine Le Maignan [a], Thierry Delozier [b,c], Sylvie Glaisner [b,c], Dominique Maraninchi [b,c,d,e], Henri Roché [b,c,d,e], Christian Gisselbrecht [a,b,c,d,e]

[a] *Tenon and Saint-Louis Hospitals, Assistance Publique-Hôpitaux de Paris, 3 avenue Victoria, 75003 Paris*
[b] *The PEGASE Group, Institut C. Regaud, 20-24 rue du Pont St. Pierre, 31052 Toulouse*
[c] *Fédération Nationale des Centres de Lutte Contre le Cancer, 101, rue de Tolbiac, 75013 Paris*
[d] *Société Française de Greffe de Moelle et de Thérapie Cellulaire, Hôpital Edouard Herriot, 69000 Lyon*
[e] *BLUESTAT, 20, rue Duperré, 75009 Paris*

Received 19 May 2004; received in revised form 14 July 2004; accepted 2 September 2004
Available online 13 October 2004

Abstract

The aim of our study was to evaluate the impact on time to progression (TTP) and overall survival (OS) of high-dose chemotherapy (HD-CT) over conventional CT in metastatic breast cancer patients. Between 09/92 and 12/96, 61 patients with chemosensitive metastatic breast cancer were randomised between HD-CT using the CMA regimen (Mitoxantrone, Cyclophosphamide, Melphalan) applied as consolidation (32 patients) or maintenance CT (29 patients). At randomisation, 13 patients were in complete response, 47 in partial response and one had stable disease. The median TTPs from randomisation were 6 and 12 months in the standard and intensive groups, respectively ($P < 0.0056$), with a relapse rate of 86.2% *vs.* 62.5% at 2 years, and 100% *vs.* 81.3% at 5 years. The median OS times were 19.3 and 44.1 months, with an OS rate of 13.8% *vs.* 36.8% at 5 years ($P < 0.0294$). The CMA regimen could prolong the TTP of patients with chemosensitive metastatic breast cancer. Further studies are needed to determine if this translates into an effect on OS.

Keywords: Metastatic breast cancer; High-dose chemotherapy; Survival; Time to progression

1. Introduction

Median survival times of metastatic breast cancer patients still remains poor [1]. Based on the relationship between dose intensity and response in breast cancer, new approaches with high-dose chemotherapy (HD-CT) have been developed worldwide [2–5]. These studies

☆ Supported in part by the French National League Against Cancer (Ligue Nationale Contre le Cancer), and Amgen, Pharmacia-Upjohn and Lederle Laboratories.
* Corresponding author. Present address: Hôpital Tenon, Service d'Oncologie Médicale, 4 rue de la Chine, 75970 Paris Cedex 20, France. Tel.: +33 1 56 01 60 58; fax: +33 1 56 01 68 75.
E-mail address: jean-pierre.lotz@tnn.ap-hop-paris.fr (J.-P. Lotz).
† deceased.

0959-8049/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ejca.2004.09.006

allowed their authors to conclude that HD-CT should only be proposed for chemosensitive diseases [6–11]. Among these phase II studies, Gisselbrecht and colleagues have published a trial in which 61 patients with chemosensitive metastatic breast cancer were proposed for HD-CT using the CMA regimen [Mitoxantrone, Cyclophosphamide, Melphalan]. In this trial, high-dose consolidation resulted in a median overall survival (OS) time of 33 months, a median event-free survival (EFS) time of 20 months from the start of therapy, and 13 ± 2 months from the time of HD-CT [11]. These results laid the foundation for an evaluation in a randomised trial including chemosensitive metastatic breast cancer patients. Hence, the CMA/PEGASE (Programme d' Etudes des Greffes Autologues daus les cancers de SEin) 04 protocol was developed by the French Society of Bone Marrow Transplantation and Cellular Therapy, and the French Federation of Cancer Centers, with the aim of determining the impact on OS and time to progression (TTP) of HD-CT *vs.* anthracycline-based conventional CT in chemosensitive metastatic breast cancer patients. We hereby report the results of this French national multicentric randomised protocol.

2. Patients and methods

2.1. Aim of the study

The main objective of this study was to evaluate in metastatic breast cancer patients responding to anthracycline-based conventional CT, the impact on TTP of

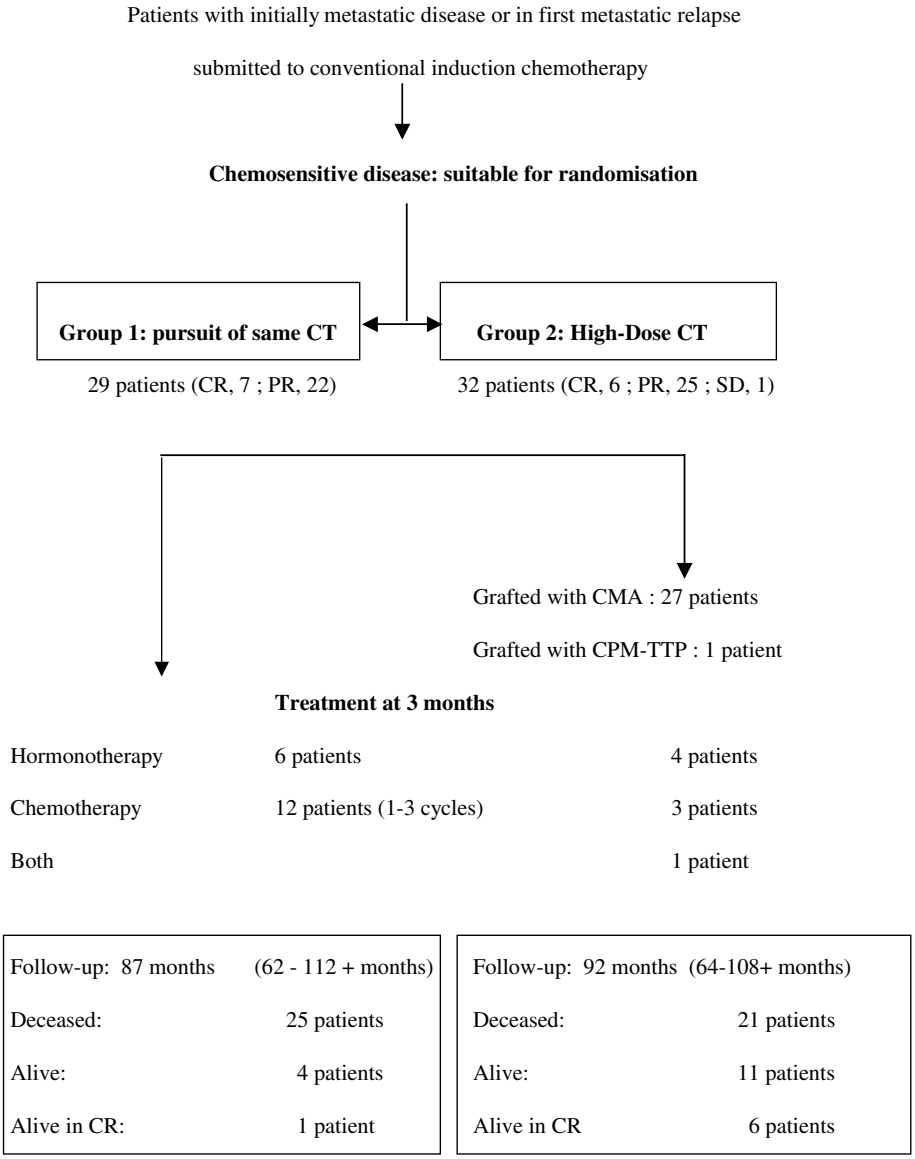


Fig. 1. Description of treatment and outcome of the population.

Table 1
Characteristics of the 2 groups (demographic data and history of breast disease)

	Group 1	Group 2
	Conventional CT	HD-CT
Total number of patients	29	32
Median age in years (range)	44 (31–60)	44 (29–59)
Menopausal status		
Premenopausal	20	19
Post-menopausal	9	13
Median delay between diagnosis of breast cancer and onset of metastases (range)	504 days (1–3693 days)	622 days (1–2389 days)
Median delay between the first day of conventional CT and randomisation	81 days (52–351 days)	78 days (63–276 days)
Median delay between randomisation and high-dose therapy	NA	71 days (33–165 days)

CT, chemotherapy; HD, high-dose; NA, not available.

HD-CT supported by haematopoietic stem cell transplantation (HSCT) over additional courses of the same therapeutic regimen administered after randomisation. In addition, the study investigated the complete response (CR) rate and the impact on OS.

2.2. Statistical considerations

To detect a difference of 25% in the 2-year progression-free rate (from 25% to 50%), 156 patients were planned to be enrolled within 3 years ($\alpha = 5\%$, $\beta = 5\%$); α was one-sided. The statistical analysis was an intent-to-treat analysis. The duration of TTP and OS was calculated from the date of randomisation. Survival curves were obtained using the Kaplan–Meier method and compared using the Log-rank test [12,13]. The number of patients required was determined according to Freedman's method [14]. Impact of HD-CT on the CR rate could be assessed 3 months after completion of intensive therapy. All endpoints were updated on December 31, 2002. The study was reviewed in 2001 by the Quintiles Quality Assurance Services and Consultancy Strategic Business Unit and the French Federation of Cancer Centers for confirmation of the following data: number of patient medical files and informed consents, date of birth, date of primary/metastatic diagnosis, date of randomisation, date of intensive therapy, date of relapse, date of last news, status of living patients and finally, the date and cause of death.

2.3. Patient selection

Patients were referred to participating centres only if they were considered to be responders to a conventional induction regimen. No pre-registration was done. For induction therapy, it was recommended to use an anthracycline-based regimen. Using a pragmatic approach, prolongation of the induction period to a maximum of 9 cycles of conventional chemotherapy was permitted. Patients were retrospectively assessed by history of the

Table 2
Characteristics of the breast disease

	Group 1	Group 2
Characteristics of breast disease		
Tumour size		
T*x*	2	2
T1–T2	16	18
T3–T4	11	12
Nodal status		
N*x*/N0	1/6	0/14
N1	18	10
N2–N3	4	8
SBR classification		
Not available	7	8
I	1	3
II	13	13
III	8	8
Number of positive nodes		
N*x*	6	7
0–3	21	20
$\geqslant 4$	2	5
Hormonal receptors		
Oestrogen/Progesterone receptor		
Negative	14/13	11/7
Positive	8/9	8/11
Unknown	7/7	13/14
Metastatic status at diagnosis		
M0	18	19
M1	11	13
Previous therapy		
Radiotherapy		
No	11	12
Yes	18	20
Adjuvant chemotherapy		
No	14	14
Yes[a]	15	18
Adjuvant hormonotherapy[b]		
No/?	20/2	24/3
Yes	7	5

SBR, Scarff-Bloom-Richardson.
[a] CMF (cyclophosphamide–methotrexate-5-fluorouracil (5FU)) for 4 patients, anthracycline-based chemotherapy for 29 patients.
[b] Tamoxifen for 8 patients, ovarian ablation for 4 patients.

Table 3
Description of the disease status in the 2 groups at the time of randomisation

	Group 1	Group 2
Local relapse[a]		
No	27	27
Yes	2	5
Lung metastases		
No	23	17
Yes[b]	6	15
Liver metastases		
No	18	23
Yes	11	9
CNS metastases		
No	29	30
Yes	0	2
Bone metastases		
No	13	20
Yes	16	12
Median number of tumour sites [c](range)	2 (1–4)	2 (1–5)
CA 15–3		
Normal/abnormal	9/19	14/15
Not done	1	3
LDH level		
Normal/abnormal	15/7	16/5
Not done	7	11
Disease status at randomisation		
Complete response	7	6
Partial response	22	25
Stable disease	0	1

CNS, central nervous system; LDH, lactate dehydrogenase.
[a] All patients with local relapse were also metastatic patients.
[b] ($P = 0.009$).
[c] 11 patients had one metastatic site (8 in Group 1 and 3 in Group 2) and 50 patients had 2 or more metastatic sites (21 in Group 1 and 29 in Group 2). Two patients in Group 1 and one in Group 2 only had evaluable bone metatstases.

disease, physical examination, hepatic and renal chemistries, cardiac function tests, chest roentgenogram, liver ultrasound, computed tomography of all metastatic sites, and bone scintigram.

2.4. Inclusion and exclusion criteria

Inclusion criteria were: histologically proven adenocarcinoma of the breast, first metastatic relapse or metastatic disease at presentation, age $\leqslant 60$ years, performance status <2, adequate hepatic, renal and cardiac functions, measurable disease, and chemo-responsive disease. Patients with brain metastases were eligible provided that the lesions did not require treatment, were not life-threatening, and were chemosensitive. Patients with marrow metastases were eligible if it was possible to assess the chemo-sensitivity of all other metastatic sites. Prior cumulative doses of anthracycline derivatives had to be: <450 mg/m^2 for doxorubicin, <800 mg/m^2 for epirubicin and <100 mg/m^2 for mitoxantrone. All patients gave their informed consent. Before randomisation, patients were classified as complete responders or partial responders according to the World Health Organisation (WHO) classification [15].

2.5. Treatment

In the case of complete (CR) or partial response (PR) to conventional CT, patients were randomised between maintenance CT with 2–4 additional courses using whenever possible the same protocol (Group 1) and HD-CT (Group 2).

Table 5
High-dose chemotherapy (Group 2)

CD34+ collection (10^6/kg)	3.4 (1.1–27.5)
No. of patients grafted (with CMA)	28 (27)/32[a]
Median value of HD-CT	
Mitoxantrone (mg/m^2)	44 (23–50)
Cyclophosphamide (mg/kg)	119.5 (64–141)
Melphalan (mg/m^2)	139 (105–155)
Median delay of autograft (range)	8 days (6–11)
Median no. of CFU-GM re-infused (10^4/kg)	12.4 (0.2–74)
Median no. of CD34+ re-infused (10^6/kg)	3.40 (1.1–8.0)
Median no. of days of treatment by filgrastim	14 days (8–32)
Median no. of days of hospitalisation	25 days (20–44)

CFU-GM, colony-forming units-granulocyte macrophage; CMA, mitoxantrone, cyclophosphamide and melphalan.
[a] Five patients could not be grafted with the CMA regimen: 3 patients because of progressive disease, 1 patient for failure of stem cell collection, and 1 for alteration of her cardiac function tests. This last patient was nevertheless treated with high-dose CPM (6000 mg/m^2) and Thiotepa (800 mg/m^2). Twenty-seven have received the CMA regimen so far.

Table 4
Induction chemotherapy before randomisation

Induction chemotherapy				
Number of cycles	Group 1:5 (3–9)		Group 2:6 (3–7)	
Protocols (no. of patients and median doses of anthracyclines)				
Doxorubicin	$N = 8$	199 mg/m^2	$N = 7$	228 mg/m^2
Epirubicin	$N = 13$	351 mg/m^2	$N = 16$	393 mg/m^2
Mitoxantrone	$N = 4$	36 mg/m^2	$N = 2$	36 mg/m^2
THP–doxorubicin	$N = 2$	249 mg/m^2	$N = 4$	242 mg/m^2
Other protocols	$N = 2$		$N = 3$	

THP, Pirarubicin.

2.5.1. Mobilisation and collection of stem cells

Mobilisation of blood progenitors was performed with high-dose cyclophosphamide (3 g/m^2 on day 0) and filgrastim, 5 μg/kg/day from day 1 until the level of polymorphonuclear (PMN) cells reached 1.5×10^9/l. Leucocytapheresis continued until at least 3.0×10^6 CD34 cells per kilogram were collected. The product of leucocytapheresis was cryopreserved according to standard methods in the liquid or vapour phase of liquid nitrogen at −196 °C. Bacteriological tests and determination of the level of colony forming units-granulocyte macrophage (CFU-GM) were performed according to standard methods.

2.5.2. High-dose therapy

All patients were hospitalised in a protected environment. Patients were treated with the CMA regimen as follows: mitoxantrone 45 mg/m^2 (30-min infusion) on day 1, cyclophosphamide 60 mg/kg/day (1-h infusion) plus mesna (100% of total dose of cyclophosphamide) for 2 days, on days 2 and 3, and melphalan 140 mg/m^2 (1-h infusion) on day 5. Progenitor cells were re-infused on day 7 and filgrastim was administered at a daily dose of 5 μg/kg from day 8 until PMN reached $>1.5 \times 10^9$ cells/l. Anti-5HT3 were used prophylactically. All patients received prophylactic antibiotics for selective bowel decontamination. Large broad-spectrum antibiotics were administered when required. Irradiated platelet transfusion was performed to maintain the platelet count above 20×10^9 cells/l and irradiated leucocyte-free red blood cells were transfused if haemoglobin level became <80 g/l.

2.5.3. Subsequent therapies

For the patients who attained a CR or a PR at the time of randomisation and who were allocated to the conventional group, continuation with 2–4 additional courses of the same regimen was proposed. Investigators were asked to use a non-anthracycline-based regimen if limiting doses of anthracycline were reached, or in case of alteration in the cardiac function tests. Hormonotherapy using tamoxifen, 20 mg daily for 5 years, was recommended for all oestrogen receptor-positive (ER+ patients). Radiotherapy could be proposed if necessary. Relapses could be treated according to each oncologist's habits.

3. Results

3.1. Population and randomisation

Between 09/29/1992 and 12/04/1996, only sixty-one patients with chemosensitive metastatic breast cancer could be referred to the seven participating bone marrow transplant centres Fig. 1. It was therefore decided to interrupt the enrollments in the study and to perform the statistical analysis.

Median age for the whole population was 44 years (range: 29–60 years). Dates of diagnosis of breast cancer ran from June 01, 1983 to July 12, 1996. Thirty-nine patients (64%) were premenopausal and twenty-two (36%) were post-menopausal. Twenty-nine patients (48%) were randomised to standard CT (Group 1) and 32 (52%) were randomised to intensive CT (Group 2) Table 1. Median delay between diagnosis of breast cancer and onset of metastases was 504 days in Group 1 and 622 days in Group 2. Most patients (27/29 patients in Group 1, and 29/32 patients in Group 2 had been treated with an anthracycline-based regimen for a median number of courses of 6 cycles (median 5, range: 3–9

Table 6
Toxicity of high-dose chemotherapy

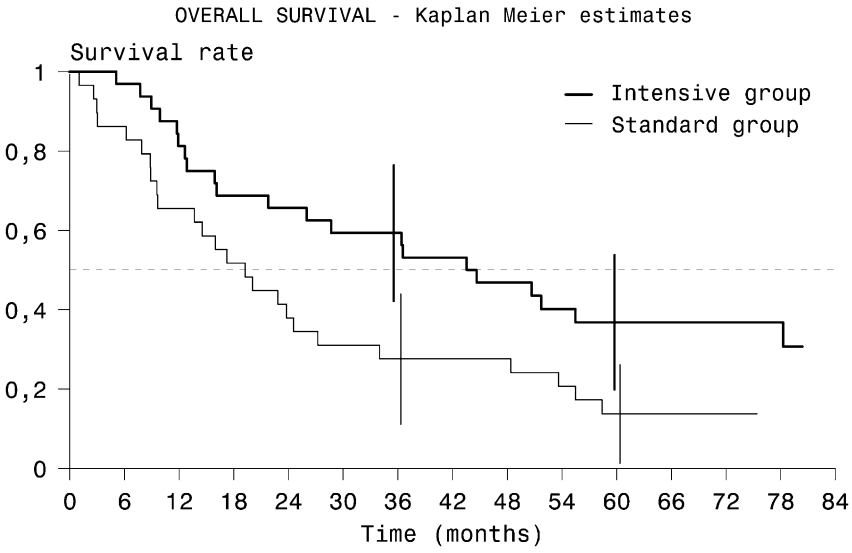
PMN < 0.5×10^9 cells/l	13 days (9–26 days)
PMN < 1.0×10^9 cells/l	13.5 days (10–48 days)
Platelets < 20×10^9 cells/l	9.5 days (3–30 days)
Platelets < 50×10^9 cells/l	11 days (4–27 days)
Duration of antibiotic therapy	9 days (5–30 days)
Red cell transfusion (no. of packs)	2 (0–5)
Platelet transfusion (no. of episodes)	4 (0–10)
WHO grade III–IV toxicity	
Infection[a]	7
Mucositis	8
Liver	1
Cardiac	0
Toxic-related deaths	0

PMN, polymorphonuclear; WHO, World Health Organization.
[a] Including one episode of pulmonary aspergillosis requiring curative partial pneumonectomy.

Table 7
Time to progression and overall survival from randomisation for the 2 groups of patients

	Group 1	Group 2
Overall survival		
Median	19.3 months	44.1 months
2 year survival	37.9%	65.6%
95%CI (2 years)	20.3–55.6	49.2–82.1
5 year survival	13.8%	36.8%
95%CI (5 years)	1.2–26.3%	19.9–53.7%
Log-rank test	$P < 0.0294$	
Relative risk (95%CI) [a]	1.890 (1.055–3.390)	
Time to progression		
Median	6 months	12 months
2-year relapse rate	86.2%	62.5%
95%CI (2 years)	73.7–98.8	45.7–79.3
5-year relapse rate	100%	81.3%
95%CI (5 years)	–	67.7–94.8%
Log-rank test	$P < 0.0056$	
Relative risk (95%CI)[a]	2.123 (1.232–3.650)	

95% CI, 95% Confidence Interval.
[a] Using the Cox model.



		0 month	12 months	24 months	36 months	48 months	60 months
Standard	At risk	29	19	11	8	8	4
	Died	0	10	18	21	21	25
Intensive	At risk	32	26	21	19	14	11
	Died	0	6	11	13	17	20

Fig. 2. Overall survival from randomisation for the 2 groups of patients (Group 1: conventional chemotherapy; Group 2: high-dose chemotherapy).

for Group 1, and median 6, range: 3–7 for Group 2) Table 2.

Thirty-seven patients (61%) were treated for metastatic chemosensitive relapse: 18 patients in Group 1, 19 patients in Group 2. Twenty-four patients (39%) were metastatic at presentation: 11 in Group 1 and 13 in Group 2. The populations were well balanced in terms of staging except for pulmonary and central nervous system (CNS) metastatic spread. Eleven patients in Group 1 and 9 in Group 2 had liver metastases (Tables 3 and 4).

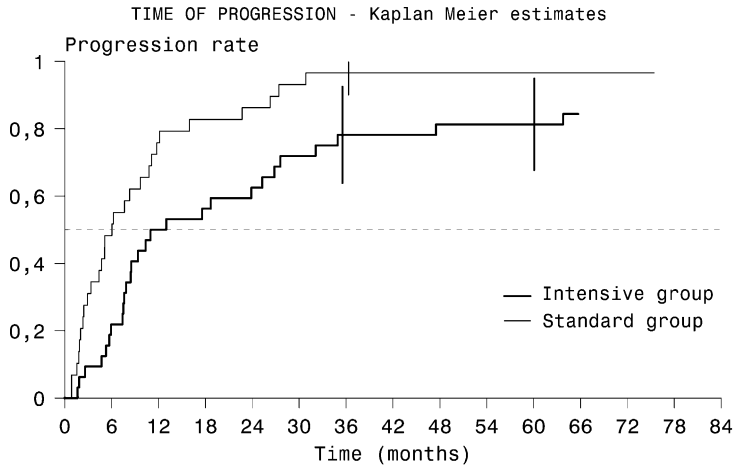
At the time of randomisation, 13 patients (21%) were in CR (7 in Group 1 and 6 in Group 2), 47 patients (77%) were in PR (22 patients in Group 1 and 25 patients in Group 2), and one patient in Group 2, who was first considered to be in PR at randomisation, was retrospectively assessed as having stable disease (SD).

3.2. High-dose chemotherapy

Following randomisation, five patients could not be grafted with the CMA regimen: 3 patients because of progressive disease, 1 patient for failure of stem cell collection and 1 for alteration of her cardiac function tests (this patient was nevertheless grafted with a high-dose regimen combining CPM at 6000 mg/m^2 and thiotepa at 800 mg/m^2). For the 27 patients submitted to the CMA regimen, the median delay between randomisation and high-dose therapy was 71 days (range: 33–165 days). Data on HD-CT are reported in Table 5.

3.3. Toxicity of high-dose chemotherapy

No cardiac toxicity and no therapy-related deaths occurred in this trial Table 6. A number of expected extra-haematological grade III–IV toxicities were observed in the high-dose arm. These toxicities concerned 16 patients out of the 28 who given intensified treatment. One patient needed surgery for a pulmonary aspergillosis infection. The median time to haematological recovery to a neutrophil count of more than 0.5×10^9 cells/l was 13 days (range: 9–26 days) and that for untransfused platelet count of more than 50×10^9 cells/l was 11 days (range: 4–27 days). The median duration of hospitalisation was 25 days (range: 20–44 days) in the high-dose arm.



		0 month	12 months	24 months	36 months	48 months	60 months
Standard	At risk	29	7	4	1	1	1
	Prog.	0	22	25	28	28	28
Intensive	At risk	32	16	12	7	6	6
	Prog.	0	16	20	25	26	26

Fig. 3. Time to progression from randomisation for the 2 groups of patients (Group 1: conventional chemotherapy; Group 2: high-dose chemotherapy).

3.4. Response and survival

High-dose chemotherapy permitted 2 patients in Group 2 who were in PR before randomisation to reach a CR, so that 8 patients of this group were in CR at 3 months. Due to progression occurring during the first three months following high-dose therapy, subsequent courses of chemotherapy were delivered in 4 patients of this group (one of them received concomitant hormonotherapy). Hormonotherapy using tamoxifen was given to 1 patient for 2 years and 3 other patients for three years. None of them were treated at 5 years (Fig. 1).

Among the 29 patients allocated to Group 1, 12 had received subsequent chemotherapy using the same anthracycline-based regimen in the first three months following randomisation because no cardiotoxicity was reported, for a median number of 1 cycle (range: 1–3 cycles). Hormonotherapy using tamoxifen, 20 mg daily, was started in 6 patients during the same period. Of these, 2 were treated for 1 year, 1 was treated for 3 years, but none achieved 5 years of treatment. Four patients from this group who were in PR before randomisation obtained a CR status with subsequent chemo- and/or hormonotherapy. Results are summarised in Table 7. With a median follow-up duration of 87 months in Group 1 (range: 62–112+ months) and of 92 months in Group 2 (range: 64 –108+ months) from the date of randomisation, the OS (Fig. 2) was statistically different between the 2 groups ($P < 0.0294$). The median time to progression (Fig. 3) was statistically different between the 2 groups ($P < 0.0056$). At the time of analysis, 4 patients from Group 1 were alive, one in CR, and eleven patients from Group 2 were alive and 6 of them are in CR.

4. Discussion

Despite the availability of new chemotherapeutic drugs, the median duration of survival still remains close to 24 months. A dose–response relationship in the conventional-dose range has been clearly demonstrated and HD-CT produces a high response rate in patients with metastatic breast cancer, even in refractory diseases where most remissions are temporary [16–20]. Patients with chemosensitive metastatic breast cancer seem to do better, with a 5-year progression-free survival (PFS) rate of 15–20% [8,11,17]. However, most patients die of their disease. In phase II studies, patient selection is a major factor that has a substantial influence on outcome, and all authors agree that HD-CT has no definitive influence on the outcome of resistant disease.

The CMA/PEGASE 04 trial was targeted at chemosensitive patients. Tolerance to HD-CT was that usually

associated with high-dose therapies [20]. Fifty-seven percent of patients experienced grade III–IV extra-haematological toxicities, without any therapy-related deaths. We observed, in a small population, a statistically significant difference in terms of TTP and OS. These results might indicate that HD-CT would be able to delay the time to relapse in patients with chemosensitive metastatic breast cancer, without any major risk of toxicity. One could surmise that this delay in time to relapse would offer the patients a better quality of life with a longer period "off-therapy". However, it is difficult, even impossible, to conclude here that HD-CT has a real impact on OS because of the small size of our population included over a long period of time, with a probable selection bias due to the absence of pre-registration, leading oncologists to refer only patients who would be good candidates for HD-CT. Moreover, we have to point out 3 factors that could have favoured the HD arm: (a) there was a prevalence in the HD group of patients with pulmonary lesions, that are more responsive than other visceral lesions, (b) only 12 of the 29 patients of Group 1 received subsequent CT after randomisation suggesting the arms were unbalanced with regard to the duration of CT in favour of the HD group, and (c) all patients in the HD arm became postmenopausal, whereas many patients remained premenopausal in the standard arm, suggesting a possible impact of hormone deprivation on survival. All of these reasons and the small study size means the results must be intrepreted with extreme caution.

A retrospective analysis of the observation database of the American Bone Marrow Transplant Registry indicates that 13–30% of patients with chemosensitive tumours remain relapse-free after transplant [4]. However, breast cancer is a heterogeneous disease in which outcome can depend on a large number of prognostic factors and it is therefore very difficult to interpret the results of published phase II HD-CT studies. In 1994, Dunphy and colleagues [17] concluded that three variables were independent negative predictors for *OS* : liver site ($P = 0.001$), soft tissue site ($P = 0.039$) and prior adjuvant CT ($P = 0.028$). Ayash and colleagues [8] have also suggested that patients with chemosensitive disease, minimal tumour bulk, and a prolonged disease-free interval between the diagnosis of breast cancer and onset of metastases appear to benefit most. In multivariate analysis, single metastatic site ($P = 0.002$) and attainment of a CR to induction CT ($P = 0.04$) were the most significant predictors for PFS. Rahman and colleagues [21] suggested in 1997 that encouraging results of single-arm trials of HD-CT could partially be due to the selection of patients with a better prognosis. These results have been confirmed by Schneeweiss and colleagues [22] who observed long-term DFS in young metastatic breast cancer patients with limited, hormone-responsive and chemotherapy-sensitive disease. Thus, more randomised studies are clearly warranted.

In a prospective trial comparing HD-CT as consolidation and HD-CT as front-line therapy at the time of relapse, Peters and colleagues [23] have shown that the metastatic breast cancer patients who attained a CR after anthracycline-based CT could benefit from HD-CT as consolidation in terms of relapse-free survival (RFS). Conversely, patients assigned to HD-CT in the case of relapse had a longer OS. Stadtmauer and colleagues [24] demonstrated in a prospective randomised study that HD-CT (STAMP-V regimen) did not improve the OS of metastatic breast cancer patients, in comparison with maintenance CT using the cyclophosphamide-methotrexate-5 fluorouracil (CMF) regimens. In their study, 199 out of the 553 metastatic patients enrolled between 12/90 and 12/97 were randomised after 4–6 cycles of induction CT using the CMF or 5 fluorouracil-doxorubicin-cyclophosphamide (FAC) regimens between HD-CT and maintenance therapy. The 2-year OS was 46% in the high-dose group and 52% in the standard group ($P = 0.52$). By contrast, one could conclude that one cycle of HD-CT is equivalent to 2 years of maintenance CMF therapy. On behalf of the National Cancer Institute of Canada, Crump and colleagues [25] reported positive results in term of EFS, but not in terms of OS. For 224 responsive patients, the high-dose regimen was associated with an EFS rate of 38% *vs.* 24% in the control arm for a median follow-up of 19 months ($P = 0.01$). The median OS times were not different, 24 and 28 months, respectively, ($P = 0.09$). In the French PEGASE 03 protocol, in which 304 patients were randomised between observation or HD-CT (cyclophosphamide, 6 mg/m^2 plus thiotepa, 800 mg/m^2) following 4 cycles of FEC100, Biron and colleagues [26] have reported positive results in term of DFS without any significant impact upon OS. Crown and colleagues [27] recently concluded tandem HD-CT was superior to optimised conventional-dose chemotherapy. In this International Randomised Breast Cancer Dose Intensity Study, 110 patients were randomly assigned to conventional CT (4 cycles of doxorubicin/docetaxel followed by 4 cycles of CMF) or to a high-dose arm (4 cycles of doxorubicin/docetaxel followed by one cycle of the ICE regimen – ifosfamide, carboplatin and etoposide – and one second HD-CT regimen combining thiotepa and cyclophosphamide). The results, in terms of an intent-to-treat analysis, were significantly positive for 3-year PFS ($P = 0.007$), but not for OS ($P = 0.15$). However, the 3-year OS became significantly positive in terms of actual treatment received ($P = 0.02$).

In light of these studies, we are presently unable to define the situation(s) in which HD-CT could be of benefit for patients with metastatic breast cancer and we therefore recommend that new randomised studies

should be conducted. First of all, the best clinical and biological prognostic factors of the population have to be clearly defined (hormonal status, chemosensitivity, HER2/neu overexpression and so on) as well as who could be considered for HD therapy [23,28,29]. By contrast, one of the reasons for the failure of HD-CT in breast cancer was the choice of drugs used (mainly alkylating agents and platinum) in most of the studies; we should look at intensifying chemotherapy with more active drugs, given in different schedules, with the aim to reach the status of CR, which remains the only way to cure metastatic disease [30]. Front-line HD-CT, tandem HD-CT, sequential semi-intensive CT using taxanes and, for some authors, allogeneic transplantation merit consideration for these studies, considering also the patient's quality of life. It is clear that HD-CT on its own will not solve the problem of breast cancer, but should be considered as part of the overall therapeutic plan for a patient with this disease. New therapeutic advances (e.g. antibodies) should also be evaluated as part of this strategy to reach a CR status, and not as concurrent strategies.

Conflict of interest statement

None declared.

Acknowledgements

The authors thank the PEGASE Group, the staff of the French Federation of Anti-Cancer centres and the nurses of the Bone Marrow Transplant Units for their involvement in the care of their patients.

References

1. Flamm Honig S. Hormonal therapy and chemotherapy (for metastatic disease). In Harris JR, Lippman ME, Morrow M, Hellman S, eds. *Diseases of the Breast*. Philadelphia, PA, Lippincott-Raven, 1996, 669–734.
2. Hryniuk W, Bush H. The importance of dose intensity in chemotherapy of metastatic breast cancer. *J Clin Oncol* 1984, **2**, 1281–1288.
3. Henderson IC, Hayes DF, Gelman R. Dose–response in the treatment of breast cancer: a critical review. *J Clin Oncol* 1988, **6**, 1501–1515.
4. Antman KH, Rowlings PA, Vaughan WP, *et al*. High-dose chemotherapy with autologous hematopoietic stem-cell support for breast cancer in North America. *J Clin Oncol* 1997, **15**, 1870–1879.
5. Gratwohl A, Passweg J, Baldomero H. European group for blood and marrow transplantation: blood and marrow activity in Europe in 1996. *Bone Marrow Transpl* 1998, **22**, 227–240.
6. Rodenhuis S, Westermann A, Holtkamp MJ, *et al*. Feasibility of multiple courses of high-dose cyclophosphamide, thiotepa, and carboplatin for breast cancer or germ cell cancer. *J Clin Oncol* 1996, **14**, 1473–1483.
7. Ghalie R, Richman CR, Adler SS, *et al*. Treatment of metastatic breast cancer with a split-course high-dose chemotherapy regimen and autologous bone marrow transplantation. *J Clin Oncol* 1994, **12**, 342–346.
8. Ayash LJ, Wheeler C, Fairclough D, *et al*. Prognostic factors for prolonged progression-free survival with high-dose chemotherapy with autologous stem-cell support for advanced breast cancer. *J Clin Oncol* 1995, **13**, 2043–2049.
9. Broun ER, Sridhara R, Sledge GW, *et al*. Tandem autotransplantation for the treatment of metastatic breast cancer. *J Clin Oncol* 1995, **13**, 2050–2055.
10. Bitran HD, Samuels B, Llein L, *et al*. Tandem high-dose chemotherapy supported by hematopoietic progenitor cells yields prolonged survival in stage IV breast cancer. *Bone Marrow Transpl* 1996, **17**, 157–162.
11. Gisselbrecht C, Extra JM, Lotz JP, *et al*. Cyclophosphamide/mitoxantrone/melphalan (CMA) regimen prior to autologous bone marrow transplantation in metastatic breast cancer. *Bone Marrow Transpl* 1994, **18**, 857–863.
12. Kaplan EL, Meier P. Nonparametric estimation for incomplete observations. *J Am Stat Assoc* 1958, **53**, 457–481.
13. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother Rep* 1966, **50**, 163–170.
14. Freedman LS. Tables of the number of patients required in clinical trials using the log-rank test. *Stat med* 1982, **1**, 121–129.
15. Miller AB, Hoogstraten B, Staquet M, Winckler A. Reporting results of cancer treatment. *Cancer* 1981, **47**, 207–214.
16. Bergh J. Dose intensity in patients with metastatic breast cancer – time for a novel thoughts. *Ann Oncol* 1997, **8**, 109–110.
17. Dunphy FR, Spitzer G, Fornoff JE, *et al*. Factors predicting long-term survival for metastatic breast cancer patients treated with high-dose chemotherapy and bone marrow support. *Cancer* 1994, **73**, 2157–2167.
18. Dunphy FR, Spitzer G, Buzdar AU, *et al*. Treatment of estrogen receptor-negative or hormonally refractory breast cancer with double high-dose chemotherapy intensification and bone marrow support. *J Clin Oncol* 1990, **8**, 1207–1216.
19. Peters WP, Shpall EJ, Jones RB, *et al*. High dose combination alkylating agents with bone marrow support as initial treatment for metastatic breast cancer. *J Clin Oncol* 1988, **6**, 1367–1376.
20. Eddy DM. High-dose chemotherapy with autologous bone marrow transplantation for the treatment of metastatic breast cancer. *J Clin Oncol* 1992, **10**, 657–670.
21. Rahman ZU, Frye DK, Buzdar AU, *et al*. Impact of selection process on response rate and long-term survival of potential high-dose chemotherapy candidates treated with standard-dose doxorubicin-containing chemotherapy in patients with metastatic breast cancer. *J Clin Oncol* 1997, **15**, 3171–3177.
22. Schneeweiss A, Hensel M, Sinn P, *et al*. Characteristics associated with long-term progression-free survival following high-dose chemotherapy in metastatic breast cancer and influence of chemotherapy dose. *Ann Oncol* 2002, **13**, 650–652.
23. Peters WP, Jones RB, Vredenburgh J, *et al*. A large prospective randomized trial of high dose combination alkylating agents (CPB) with autologous cellular support as consolidation for patients with metastatic breast cancer achieving complete remission after intensive doxorubicin-based induction therapy (AFM). *Proc Am Soc Clin Oncol* 1996, **15**, 121. (abstract 149).
24. Stadtmauer EA, O'Neill A, Goldstein LJ, *et al*. Phase III randomized of high-dose chemotherapy (HD-CT) and stem cell support (SCT) shows no difference in overall survival or severe toxicity compared to maintenance chemotherapy with cyclophosphamide, methotrexate, and 5-Fluorouracil (CMF) for women with metastatic breast cancer who are responding to conventional chemotherapy: the Philadelphia Intergroup Study (PBT-1). *New Eng J Med* 2000, **342**, 1069–1076.

25. Crump M, Gluck S, Stewart D, *et al*. A randomized trial of high-dose chemotherapy (HDCT) with autologous peripheral blood stem cell support (AHPCT) compared to standard chemotherapy in women with metastatic breast cancer: a National Cancer Institute of Canada (NCIC) Clinical Trials Group study. *Proc Am Soc Clin Oncol* 2001, **20**, 21a. (abstract 82).
26. Biron P, Durand M, Roché H, *et al*. High dose thiotepa (TTP), cyclophosphamide (CPM) and stem cell transplantation after 4 FEC100 compared to 4 FEC100 alone allowed a better disease free survival in first line chemotherapy metastatic breast cancer. *Proc Am Soc Clin Oncol* 2002, **21**, 42a. (abstract 167).
27. Crown J, Pey L, Lind M, *et al*. Superiority of tandem high-dose chemotherapy (HDC) versus optimised conventionaly-dosed chemotherapy (CDC) in patients-pts) with metastatic breast cancer (MBC): the International Randomized Breast Cancer Dose Intensity Study (IBDIS 1). *Proc Am Soc Clin Oncol* 2003, **22**, 23. (abstract 88).
28. Hensel M, Ho AD, Bastert G, *et al*. Prognostic markers for survival after high-dose chemotherapy with autologous stem-cell transplantation for breast cancer. *Ann Oncol* 2003, **14**, 341.
29. Rodenhuis S, Bontenbal M, Beex LV, *et al*. High-dose chemotherapy with hematopoietic stem-cell rescue for high-risk breast cancer. *N Engl J Med* 2003, **349**, 7–16.
30. Greenberg PA, Hortobagyi GN, Smith TL, *et al*. Long-term follow-up of patients with complete remission following combination chemotherapy for metastatic breast cancer. *J Clin Oncol* 1996, **14**, 2197–2205.