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Late intensification with high-dose melphalan and autologous bone marrow support in breast cancer patients responding to conventional chemotherapy

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Summary. Fifteen patients with advanced breast cancer who had achieved either a good partial or a complete response to conventional chemotherapy were selected to receive intensification treatment with high-dose melphalan 140–200 mg/m^2 (HDM). All patients received autologous bone marrow rescue. All patients experienced marked haematological toxicity, and most experienced moderate or mild gastrointestinal side effects. There were three treatment-related deaths. Of twelve assessable patients eleven have relapsed; median time to relapse after HDM is 7 months. Nine of these eleven have died from recurrent breast cancer. Of the three patients remaining alive, only one is disease-free, at 18 months after HDM. Analysis of the pattern of metastatic relapse suggests that recurrence was due to failure of HDM to eradicate residual disease in the patient, rather than reinfusion of viable tumour cells. Treatment intensification with HDM has not succeeded in prolonging survival in patients already in good remission.

Introduction

Conventional combination chemotherapy induces a significant proportion of remissions in advanced breast cancer. These responses are frequently short-lived, and patients generally relapse between 6 and 13 months later [7]. Continuation of conventional chemotherapy after response has not been shown to be successful in maintaining remission or prolonging survival [13].

It is possible that intensive treatment may eradicate small tumour residua in patients with good responses to conventional doses of cytotoxic drug combinations. Hence, we selected 15 such patients in complete or good partial remission for further treatment with high-dose melphalan (HDM). The dose of melphalan necessitated subsequent rescue with autologous bone marrow [9].

Patients and methods

The 15 patients studied (Table 1) were selected from a pool of 128 who had received conventional chemotherapy at the Royal Marsden Hospital, Sutton, between September 1982 and November 1984. Eligibility was based on informed consent, a partial or complete response to chemotherapy, age less than 60 years, an histological diagnosis of breast cancer, and general medical fitness; patients who had significant renal or hepatic disorders or who had experienced frequent marrow depression during induction were excluded.

Staging procedures, performed on all patients before and after conventional chemotherapy, included clinical examination, liver scan/ultrasound, chest X-ray, bone scan, skeletal survey (if the bone scan was positive), full blood count, biochemical profile and bone marrow aspirate and trephine.

The median age was 49 years (range 29–59); 8 patients were premenopausal. The ER status was known in 13 patients (6 positive, 7 negative). At the start of chemotherapy, 4 had pulmonary involvement, 8 had hepatic metastases, 8 had soft tissue disease, 4 had bone metastases and 1 had a cerebral secondary. Complete response was achieved by 7, and partial response also by 7; 1 patient with minimal bone disease and a pleural effusion, which were also locally treated, was not formally assessable for response.

The overall treatment plan is summarised in Fig. 1, and details are as follows:

Conventional chemotherapy. Each patient was allocated to one of three first-line chemotherapy regimens. These were four to seven 3-weekly cycles of vincristine, 1.4 mg/m^2 i.v., adriamycin 60 mg/m^2 i.v., and either 5-fluorouracil 750 mg/m^2 i.v. (VAF: 4 patients) or cyclophosphamide 750 mg/m^2 i.v. (VAC: 8 patients); or 3-weekly cycles of melphalan 6 mg/m^2 p.o., methotrexate 35 mg/m^2 i.v., and mitomycin C 8 mg/m^2 i.v., with the last omitted every alternate cycle (MMM; 3 patients).

An inadequate response resulted in a change to one of the other protocols; two MMM patients required further therapy with VAF (6 cycles) and VAC (8 cycles), respectively. Appropriate modifications were made for marrow depression.

High-dose melphalan. Four weeks after the last course of chemotherapy patients received HDM by i.v. bolus injection. Doses administered were 140 mg/m^2 (1 patient), 180 mg/m^2 (2 patients) and 200 mg/m^2 (12 patients). In three cases this was preceded by a small "priming" dose of cyclophosphamide (300 mg/m^2). The full technique is described elsewhere [9], and the rationale for priming has been discussed by Millar and McElwain [10].

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Table 1

Unique number	Age and menopausal status at presentation	Age and menopausal status at time of HDM	ER status and titre	Induction chemotherapy	Response	HDM dose (mg/m^2)	Marrow processing	Cyclo-priming	Time to relapse post HDM (months)	Status and time to death or last FU (months)	Cause of death
1	40 (PRE)	43 (PRE)	POS 30	MMM×4 VAF×6	NC CR	180	No	No	7	Dead 10	Recurreent disease
2	50 (POST)	50 (POST)	POS 15	MMM×6 VAC×3	NC PR	200	Yes	No	N/A	Dead <1	Septicaemia while pancytopenic
3	39 (PRE)	48 (POST)	POS 15	MMM×6	CR	140	Yes	No	N/A	Dead 4	Failure of engraftment
4	59 (POST)	59 (POST)	NEG	VAC×6	CR	180	No	No	11	Dead 11	Recurrent disease
5	34 (PRE)	34 (PRE)	NEG	VAC×6	CR	200	No	No	2	Dead 6	Recurrent disease
6	48 (PRE)	51 (POST)	NEG	VAC×7	PR	200	No	No	2	Dead 12	Recurrent disease
7	27 (PRE)	29 (PRE)	NEG	VAF×5	CR	200	Yes	No	2	Dead 9	Recurrent disease
8	46 (PRE)	49 (PRE)	?	VAF×4	N/A	200	No	Yes	N/A	Alive, disease-free 24	–
9	54 (POST)	54 (POST)	NEG	VAC×7	PR	200	No	No	N/A	Dead <1	Cerebral toxicity
10	38 (PRE)	39 (PRE)	POS 18	VAC×5	PR	200	No	Yes	4	Dead 12	Recurrent disease
11	56 (POST)	59 (POST)	NEG	VAC×5	PR	200	No	No	13	Alive, further chemotherapy 23	–
12	36 (PRE)	39 (PRE)	POS 42	VAC×6	CR	200	Yes	Yes	12	Dead 14	Recurrent disease
13	55 (POST)	59 (POST)	POS 31	VAC×5	PR	200	Yes	No	7	Alive, further chemotherapy 15	–
14	36 (PRE)	38 (PRE)	NEG	VAF×5	CR	200	Yes	No	7	Dead 10	Recurrent disease
15	47 (PRE)	50 (PRE)	?	VAF×6	PR	200	Yes	No	8	Dead 9	Recurrent disease

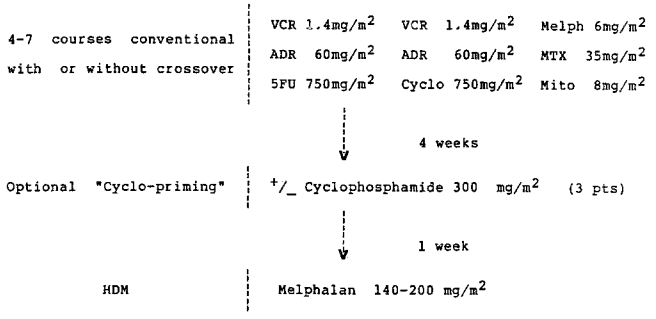

Fig. 1. Summary of overall treatment plan. VCR, Vincristine; ADR, adriamycin; 5FU, 5-Fluorouracil; Cyclo, cyclophophamide; Melph, melphalan; MTX, methotrexate; Mito, mitomycin-C

Autologous bone marrow rescue. All patients underwent autologous bone marrow harvest under general anaesthetic on the same day as receiving HDM. Bone marrow was kept at 4° C and reinfused i.v. over 4 h, starting 14 h after the administration of melphalan. Aliquots of marrow, examined histologically for involvement by tumour cells, were negative in all cases. To remove any infiltrating tumour cells [1, 3, 4, 5, 11], whole marrow was processed in vitro (7 patients only) with the monoclonal antibody Fib^{75} (with rabbit complement: 2 patients; Fib^{75}-Abrin conjugate: 5 patients), as described previously [1, 5]. Processing of marrow with complement led to unacceptable damage to colony-forming cells and was abandoned in favour of Fib^{75}-Abrin. Where possible, between one-third and one-half of the marrow was cryopreserved as a back-up. Cellularity of marrow returned to the patients ranged between 2 and 5×10^8 per kilogram of body weight.

Response and toxicity. Tumour response (complete or CR, partial or PR) was defined according to UICC criteria [6]. Toxicity was graded according to the standard WHO criteria [14].

Results

Response to conventional chemotherapy

Eight patients received VAC as first-line chemotherapy; three of these achieved CR and five achieved PR. Two of four VAF recipients achieved a CR, while one other achieved a PR; one was not evaluable because of local treatments to both known sites of disease. Of the three MMM patients, one achieved a CR and the other two stabilised; one of these two went on to receive VAC, achieving a PR, and the other received VAF with a resulting CR. Thus there were eventually seven patients with a CR, seven with a PR and one unevaluable patient without evidence of disease activity.

Relapse after HDM

Of the 12 evaluable patients, 11 relapsed after HDM. Median time to relapse was 7 months, with a range of 2–13 months. The other patients included 3 who died from the procedure and were not assessable in this respect. One of these, who died 4 months after HDM, had possibly viable tumour in the liver at post mortem. A single patient (case 8) is alive and disease-free at 18 months.

There was no difference in the time to relapse between those receiving antibody-processed marrow (average 6 months, range 2–8 months) and those receiving unprocessed marrow (average 7 months, range 2–13 months). There was also no significant difference in time to relapse between those achieving CR after induction chemotherapy (average 7 months, range 2–12 months) and those achieving PR (average 7 months, range 2–13 months).

The site distribution by clinical staging and, in two cases, at post mortem, is illustrated in Tables 2 and 3. In

Table 2. Patterns of metastatic relapse in patients receiving antibody processed marrow compared with those receiving unprocessed marrow. Number outside brackets represent unique numbers, numbers within brackets are subtotals. (Eleven patients assessable) Differences are not significant

	Same site(s) only	Same plus other	Other site(s) only
Marrow processed (4)	15 (1)	7, 13, 14 (3)	– (0)
Not processed (7)	1 (1)	4, 5, 6, 10, 11, 12 (6)	– (0)

Table 3. Extent of metastatic relapse in eleven evaluable patients

	Local	Bone	Lung	Pleura	Liver	CNS	Other	Comment
1. PRE	+	+	0	0	+	0	0	Same site only
RELAPSE	+	+	0	0	+	0	0	
PM	N/A	N/A	N/A	N/A	N/A	N/A	N/A	
4. PRE	+	0	0	+	0	0	0	Same plus other
RELAPSE	+	0	0	0	0	++	0	
PM	Yes	No	Yes	Yes	Yes	Yes	Yes	
5. PRE	+	+	0	0	+	0	+	Same plus other
RELAPSE	0	+	0	0	++	++	+	
PM	N/A	N/A	N/A	N/A	N/A	N/A	N/A	
6. PRE	+	0	0	+	0	0	+	Same plus other
RELAPSE	++	++	0	++	0	0	+	
PM	N/A	N/A	N/A	N/A	N/A	N/A	N/A	
7. PRE	+	0	0	0	0	0	0	Same plus other
RELAPSE	+	0	0	++	0	++	0	
PM	N/A	N/A	N/A	N/A	N/A	N/A	N/A	
10. PRE	0	+	0	0	+	0	0	Same plus other
RELAPSE	0	++	0	++	+	0	++	
PM	N/A	N/A	N/A	N/A	N/A	N/A	N/A	
11. PRE	0	+	+	+	0	0	0	Same plus other
RELAPSE	0	++	++	+	0	0	0	
PM	N/A	N/A	N/A	N/A	N/A	N/A	N/A	
12. PRE	0	0	0	0	+	0	0	Same plus other
RELAPSE	0	++	0	0	+	0	0	
PM	No	Yes	Yes	Yes	Yes	No	Yes	
13. PRE	0	0	0	0	+	0	0	Same plus other
RELAPSE	0	0	0	++	++	0	0	
PM	N/A	N/A	N/A	N/A	N/A	N/A	N/A	
14. PRE	0	0	0	0	0	0	+	Same plus other
RELAPSE	0	++	++	++	0	0	++	
PM	N/A	N/A	N/A	N/A	N/A	N/A	N/A	
15. PRE	0	+	0	0	+	0	0	Same site only
RELAPSE	0	+	0	0	+	0	0	
PM	N/A	N/A	N/A	N/A	N/A	N/A	N/A	

PRE, Before induction chemotherapy; RELAPSE, clinical evaluation at relapse after HDM; PM, post mortem; +, positive; ++, new lesions; 0, no disease evident

every patient who experienced relapse, all, or nearly all, sites that had been involved prior to HDM exhibited disease activity at recurrence. Most patients (9/11) in addition relapsed at other, new sites; only two patients relapsed in the same site(s) only. No patient relapsed in a new site only.

Of the nine patients who relapsed in the "same plus other" category, three had received antibody-processed marrow and six had not; this difference is not significant. There was no difference in the number of individual lesions between these two subgroups insofar as this could be assessed. Of the two in the "same site only" category, one had received processed marrow and the other had not. The single patient who is alive and disease-free received unprocessed marrow.

Survival and cause of death, after HDM

Twelve patients have died since receiving HDM. Three of these deaths were attributable to the procedure; two died after prolonged periods of pancytopenia and the third, who had had cranial irradiation 6 months prior, died from massive cerebral necrosis in less than 1 month. The other nine deaths were caused by recurrent breast cancer.

There were no major differences in the likelihood, or length, of survival in the marrow-processed versus the non-processed group. One of the two patients who died from pancytopenia received marrow processed by complement as well as antibody. Antibody-toxin conjugates have since been used, with no significant delay in bone marrow recovery. One patient died whilst pancytopenic from overwhelming infection uncontrolled by antibiotics. Both had received MMM induction chemotherapy.

Only one marrow-processed patient is alive, and she continues to receive chemotherapy following a relapse at 7 months. Two further patients are alive in the non-processed group; one is disease-free (18 months) and the other, alive at 23 months, is receiving chemotherapy after relapsing at 13 months. Overall median survival is 12 months (Table 4).

Survival, measured from the start of conventional chemotherapy, is no different in these HDM patients than in all those patients who achieved a CR or PR with conventional chemotherapy without HDM intensification (Fig. 2).

Table 4. Survival after HDM as a function of marrow processing with antibody[a]

	Processed marrow	Non-processed marrow
Total number	6	9
Deaths (total):	5	7
Deaths from procedure	2 (pancytopenia)[b]	1 (cerebral necrosis)
Deaths from recurrent disease	3	6
Median survival	9 months	12.5 months

[a] One patient (case 12) in whom engraftment with processed marrow failed received back-up unprocessed marrow at 3 weeks; she is included in the "non-processed" group

[b] One of these two received marrow processed with complement and antibody

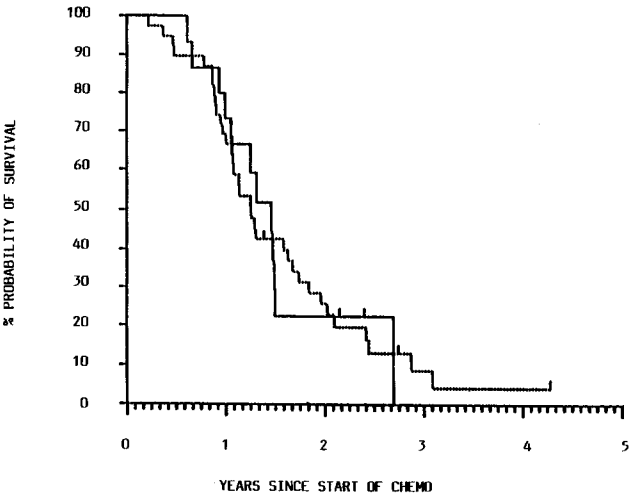

Fig. 2. Survival of HDM intensified patients (−) compared with survival of good chemotherapy responders not receiving HDM (. . .). Difference is not significant. ($P > 0.1$)

Response to subsequent treatment

Four patients (cases 6, 11, 12 and 13) have had further systemic treatment following relapse after HDM. One (ER+) experienced a transient PR to tamoxifen combined with CMF. Another (ER−) was resistant to tamoxifen and methotrexate. A third achieved a PR and a fourth has stabilised on MMM.

Toxicity

Severe (WHO grade IV) neutropenia occurred in all patients. Peripheral leucocyte counts fell to less than 500/mm^3 (median) day 7 (range day 6–8) after treatment. Leucocyte counts rose to greater than 500/mm^3 on (median) day 15 (range day 13–16) in the group receiving unprocessed marrow, and on (median) day 16 (range day 14–24) in the group receiving marrow processed with the antibody-toxin conjugate. The processed marrow group did not experience a significant prolongation in the duration of leucopenia. Figures for the 1000/mm^3 leucocyte level reflect a similar pattern (Table 5).

A platelet nadir of less than 25000/mm^3 (WHO grade IV) occurred in all patients (Table 6). The median nadir for the processed group was 9000/mm^3 (range 4000–13000/mm^3) and that for the unprocessed group was 11000/mm^3 (range 4000–13000/mm^3). The median duration of thrombocytopenia (less than 100000/mm^3) was 23 days for the unprocessed group (range 17–50 days) and 28 days for the processed group (range 21–36 days). In all 15 patients prophylactic platelet transfusions were given.

Nausea and vomiting occurred in two-thirds of these patients, but was severe (WHO grades 3 and 4) in only two. It usually lasted 48 h. Anorexia and stomatitis occurred in similar proportions of patients (67% and 80%, respectively). Stomatitis tended to appear between days 5 and 8 and usually lasted about 7–10 days. Diarrhoea, experienced by 74%, appeared a few days after treatment and lasted about 7–10 days. Non-haematological toxicity is detailed in Tables 7 and 8.

Table 5. Haematological toxicity after HDM: leucocyte depression in all patients and marrow processed[a] and non-processed subgroups. (Time in days) Differences are not significant

	Time to $<0.5\times10^9$/l			Duration $<0.5\times10^9$/l			Time to $<1\times10^9$/l			Duration $<1\times10^9$/l		
	All patients	Processed	Non-processed	All patients	Processed	Non-processed	All patients	Processed	Non-processed	All patients	Processed	Non-processed
Median	7	7	7	8	10	8	7	7	7	14	13	13
Range	6–8	6–8	6–8	5–17	5–17	6–10	5–8	5–8	5–8	18–22	8–22	11–17

[a] Two patients receiving complement- and antibody-processed marrow have been excluded

Table 6. Haematological toxicity after HDM: platelet depression in all patients and in marrow-processed[a] and non-marrow-processed subgroups. (Time in days) Differences are not significant

	Time to $<100\times10^9$/l			Duration $<100\times10^9$/l			Nadir		
	All	Processed	Non-processed	All	Processed	Non-processed	All	Processed	Non-processed
Median	6	6	7	24	28	23	9	9	11
Range	4–10	4–9	5–10	17–50	21–36	17–50	4–20	4–13	4–20

[a] Two patients receiving complement- and antibody-processed marrow have been excluded

Table 7. Gastrointestinal toxicity in 15 patients
Toxicity (WHO grade)

	1–2	3–4	Total
Nausea, vomiting	8	2	10 (67%)
Anorexia	7	3	10 (67%)
Stomatitis	7	5	12 (80%)
Diarrhoea	7	4	11 (74%)

Table 8. Other non-haematological toxicity, adverse effects

Infection: pyrexia	12 (80%)
positive culture	1 (7%)
Purpuric rash	4 (27%)
Peripheral oedema	2 (14%)
Hypertension	3 (20%)
Pneumothorax	1 (7%)
Grand mal fits	1 (7%)

The majority (80%) of patients experienced sustained pyrexia, which was promptly treated by a combination of broad-spectrum antibiotics. In only one patient was a positive blood culture obtained. Various other adverse effects were found in a minority of patients (Table 8).

None of the three patients who received a priming dose of cyclophosphamide experienced severe gastrointestinal side effects, and only one of them experienced diarrhoea (versus 74% for the group as a whole). Haematological toxicity was not different in the primed and non-primed groups.

Discussion

This study demonstrates the feasibility of giving high-dose chemotherapy to selected patients with advanced breast cancer at the time of their best response to conventional chemotherapy. Mostly, side effects and complications were treatable. We believe that two of the three procedure-related deaths were avoidable. One patient, who had a cerebral death, had had whole-brain radiotherapy 6 months before. In the other case death was caused by failure of engraftment, related to a particular technique of marrow processing (with antibody and complement) which was rapidly abandoned. In both cases where death was caused by pancytopenia, the MMM combination had been used during induction. This combination may well be too myelosuppressive for bone marrow to be used for subsequent autoreconstitution.

Successful engraftment was observed in five of seven patients who received in vitro antibody-processed marrow. This technique did not prolong the time to haematological recovery, but given the lack of survival benefit, requires more justification than this study provides.

It is also worth noting that in the three patients who received a priming dose of cyclophosphamide 1 week prior to HDM, gastrointestinal side effects were mild or non-existent.

When the survival of the 15 HDM patients is compared with that of a previous group of chemotherapy responders who did not receive high-dose late intensification it is evident that no benefit has resulted from HDM. Given that these patients were selected on the basis of an excellent response to conventional chemotherapy, the almost universal recurrence of widespread, usually fatal breast cancer within a short time is a major disappointment. (In the single patient who is alive and disease-free, radiotherapy and intrapleural chemotherapy were also given to all known sites of disease before HDM. It is possible that these were the only sites of disease.) The question is whether these relapses resulted from a failure of HDM to eradicate residual disease in the patient or from the reinfusion of contaminated marrow at autotransplant, or both. We believe the pattern of metastatic relapse is instructive.

Relapse could have occurred in the same sites only, other sites only, or the same plus other sites. The recurrent disease faithfully reappeared in the pre-HDM sites in virtually every site in every patient. No patient relapsed at

"other sites" only. This pattern does not support the explanation that reseeding by contaminated marrow is the sole cause of relapse; rather, failure to eradicate disease by HDM is the main or only explanation. Further evidence is provided by the similarity in relapse pattern between the marrow processed and the non-processed group. If recontamination had been significant, there would presumably have been more multiple-site relapses in the non-processed group. This would only have become evident had our patients survived longer; we cannot, therefore, draw any conclusions about marrow processing.

Most patients relapsed in the "same plus other" category. These "other" sites presumably resulted from pre-existing micrometastases which HDM, by inference, was also not able to eradicate at this dose level. This interpretation does not support the use of HDM (200 mg/m^2) in an adjuvant setting.

In this series, drug resistance is the only tenable explanation for failure. The low rate and short duration of response of advanced breast cancer to normal-dose melphalan [2], coupled with the very poor results obtained with HDM as first-line treatment (I. E. Smith, personal communication), lead to the conclusion that breast cancer is inherently quite insensitive to this drug. We were unable to overcome this, despite prior debulking with conventional drug combinations. Indeed, by prior exposure of the tumour to a variety of cytotoxic agents (including melphalan itself in 3 patients, cyclophosphamide in 9, 5-fluorouracil in 5 and vincristine/adriamycin in 14 patients), we may have induced an additional element of pleotropic acquired resistance, perhaps as described by Ling et al. [8] or Schmid et al. [12].

Four of the patients, in relapse after HDM, were judged fit enough to receive further chemotherapy. In two cases (possibly three) this was not only feasible but beneficial. Whatever the nature of resistance to HDM, it is drug-specific [12], or genetically unstable or both; earlier HDM is not an absolute bar to further successful combination chemotherapy at conventional doses with agents like cyclophosphamide, methotrexate, 5-fluorouracil, mitomycin C and perhaps even melphalan itself.

There is only a remote possibility that new combinations of existing agents at conventional dose will cure advanced breast cancer. Cure will require either new agents or radically different ways of using available ones; this latter option may be realized in terms of higher dose. This study establishes the feasibility of this approach; however, melphalan up to a dose of 200 mg/m^2 is by itself insufficient.

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