Bone Marrow Transplantation (2003) 31, 525–530

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Mini review

Should we continue to study high-dose chemotherapy in metastatic breast cancer patients? A critical review of the published data

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Summary:

Data from eight randomised trials on high-dose chemotherapy (HDC) for metastatic breast cancer (MBC) have been published, but only seven studies are evaluable after the Bezwoda trial was discredited. Moreover, overall survival (OS) has been evaluated in only four out of seven studies since three had a crossover design. OS was similar for the HDC and standard-dose chemotherapy (SDC) group in the four evaluable trials, while disease-free survival (DFS) was improved in the HDC group in six of the seven trials. The delay in relapse for patients with metastatic disease represents an important clinical outcome; furthermore, since none of the reported studies randomised more than 220 patients, their statistical power may have been too limited to detect meaningful survival differences. Finally, preliminary experiences have shown that HDC seems to be the ideal platform upon which to build novel therapies. In conclusion, HDC remains an important field of clinical research for breast cancer patients with stage IV disease and, from the studies reported in this article, there is some evidence for offering this therapeutic modality to selected patients who are interested in a medically aggressive approach.
Bone Marrow Transplantation (2003) **31,** 525–530. doi:10.1038/sj.bmt.1703824
Keywords: high-dose chemotherapy; metastatic breast cancer

The development of high-dose chemotherapy (HDC) strategies for metastatic breast cancer (MBC) patients (pts) has a long and emotive history in medicine. In the late 1980s and mid-1990s, several phase II trials reported promising results for HDC in MBC pts[1–14] (Table 1). These results created positive expectations among oncologists and led to an increase in the number of MBC pts treated with HDC, not always within controlled studies. In the last decade, diversification of this approach has been possible, helped by the availability of haematopoietic growth factors and peripheral blood progenitor cells that significantly reduce transplant-related morbidity and mortality.[15] Simultaneously, multiple phase III trials are being conducted around the world to compare HDC with standard-dose chemotherapy (SDC) in MBC pts.

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Randomised trials

Data from eight randomised trials on HDC for MBC are currently available.[16–23] In 1995, Bezwoda *et al*[16] published the results of the first completed randomised trial; the authors reported a significant advantage in terms of overall response rate (ORR), overall (OS) and disease-free survival (DFS) for the HDC group compared with the SDC group. Recently, the results of this study were retracted after a full audit found unequivocal evidence of scientific misconduct and falsified data.[24] Two Dukes' studies were presented at the American Society of Clinical Oncology (ASCO) meeting in 1996 and 2000, respectively.[17,18] In the first Dukes' trial, with a crossover design, 100 MBC pts in complete response (CR) with conventional dose AFM (doxorubicin, 5-fluorouracil, methotrexate) were randomised to immediate HDC with CPB regimen (cyclophosphamide, cisplatin, carmustine) *vs* HDC at the time of relapse.[17] In the second Dukes' trial, a group of 69 pts with bone metastases only received induction chemotherapy with up to a maximum of four cycles of AFM; pts who did not progress were randomised to receive immediate consolidation with CPB or observation with CPB at the time of disease progression.[18] A significant DFS improvement in the immediate HDC arm was recorded in both studies. Two other randomised trials were presented at the ASCO meeting in 1999: the Philadelphia Intergroup study (PBT-1) and the PEGASE 04 study.[19,20,25] In the Philadelphia Intergroup study, responders after induction therapy with 4–6 cycles of CAF or CMF were randomised to receive HDC using the STAMP V regimen or maintenance CMF continued until progression, or for up to 24 cycles.[19,25] The authors reported no difference in DFS and OS in the two arms. A recent 5-year update of the PBT-1 study confirmed these results; in particular, with a median follow-up of 67.5 months, the median OS was 25.8 and 26.1 months for the HDC and the CMF group, respectively, while the median

Table 1 Several phase II trials with HDC in MBC pts in the late 1980s and mid-1990s

Authors	*Year*	*No. of pts*	*HDC regimen*	*CR (%)*	*OR (%)*	*Med surv (mos)*	*TRM (%)*
Peters *et al*[1]	1988	22	CBP	54	73	10	23
Kennedy *et al*[2]	1991	30	CT	46	100	22	0
Williams *et al*[3]	1992	27	CT	55	86	15	14
Antman *et al*[4]	1992	29	CTCb	45	100	>20	3
Dunphy *et al*[5]	1994	80	CVPx2	55	79	15	9
Perry *et al*[6]	1994	14	CTCb	36	86	NA	0
Ayash *et al*[7]	1995	62	CTCb	29	88	24	5
Silverman *et al*[8]	1995	17	CTCb	29	88	NA	0
Cameron *et al*[9]	1996	32	L-Pam/VP16/TSPA	53	100	15	0
Gisselbrecht *et al*[10]	1996	60	CMA	60	86	26	11
Weaver *et al*[11]	1996	118	CTCb	43	66	NA	0
Bitran *et al*[12]	1996	27	CT/L-PAM	56	67	>30	0
Ayash *et al*[13]	1996	67	L-PAM/CTCb	33	82	20	1
Lelli *et al*[14]	1997	18	ICE	78	100	36	0

CBP: cyclophosphamide + BCNU + cisplatin; CT: cyclophosphamide + thiotepa; CTCb: cyclophosphamide + thiotepa + carboplatin; CVP: cyclophosphamide + etoposide + cisplatin; ICE: iphosphamide + carboplatin + etoposide; CMA: cyclophosphamide + mitoxantrone + melphalan; TRM: transplant-related mortality; NA: not available.

Table 2 Arguments in favour (a) or against (b) the use of HDC in MBC Pts

(a)	(b)
• DFS improved in HDC arm in 6/7 randomised trials	• No evidence of survival advantage over conventional therapy from published randomised trials[a]
• Acceptable morbidity and mortality related to HDC	• Higher costs, morbidity and mortality
• Short intense treatment instead of multiple cycles of chemotherapy	• Procedure safely performed only in qualified centres
• HDC as a platform on which to add new treatments	• Priority for novel approaches

[a]Not considering the Bezwoda trial.

TTP was 9.6 months for HDC and 9.1 months for CMF.[26] The analysis also showed a trend towards improved survival with HDC in patients aged <43 years and with CMF in patients aged >42 years. In the PEGASE 04 study, 61 pts with MBC responding to four–six cycles of conventional chemotherapy were randomised to HDC *vs* two or four additional cycles of conventional chemotherapy.[20] In this small study, the median DFS was 20 and 35.3 months in the standard and HDC group ($P = 0.05$), respectively; OS was not statistically different in two groups, although there was a trend against an improved OS in the intensive arm. The results of a phase III National Cancer Institute of Canada (NCIC) trial were presented by Crump *et al*[21] at the ASCO meeting in 2001. This study randomised 219 MBC pts responding after four cycles of a first-line therapy to receive two–four additional cycles of standard chemotherapy or one–two cycles followed by HDC (cyclophosphamide 6 g/m^2, mitoxantrone 70 mg/m^2, carboplatin 1800 mg/m^2). DFS was significantly improved in the HDC arm, while no differences in 3-year OS were observed between the two groups. Finally, at the last ASCO meeting other two randomised trials, the PEGASE 03 study and the trial by Schmidt *et al*, were presented.[22,23] In the PEGASE 03 study, 180 pts with MBC with an objective response after four FEC were randomised to HDC (thiotepa 800 mg/m^2, cyclophosphamide 6 g/m^2) *vs* no further treatment. The 1-year DFS was 19 *vs* 46%, respectively, favouring the intensive arm; however, the 3-year OS was 38% in HDC arm *vs* 30% in the observation arm. In the Schmidt *et al*[23] trial, 92 MBC pts were randomised to six–nine courses of chemotherapy with doxorubicin and paclitaxel (AT) *vs* double HDC (cyclophosphamide 4.4 g/m^2, mitoxantrone 45 mg/m^2, etoposide 2.5 g/m^2). Crossover HDC was planned at relapse for pts showing a complete response to AT. In this study, HDC was associated with a significantly longer progression-free survival (PFS). Several randomised trials of HDC in MBC pts are ongoing, but unfortunately their accrual has dropped significantly after the 1999 ASCO meeting.[27]

Discussion

The role of HDC with autologous bone marrow or peripheral blood progenitor cells support in MBC pts is controversial (Table 2). An unreasonably high expectation for this approach until 1999 was followed by an unreasonably negative one since then, mainly because of the 'Bezwoda rebound effect' and the superficial evaluation of some phase III studies. In 1995, Bezwoda *et al*[16] published

Table 3 Summary of randomised trials with HDC in MBC Pts

Study	*Year*	*No. of pts (HDC/control)*	*Median age (years)*	*Median follow-up (years)*	*Regimens (HDC/control)*	*Results*	*Comments*
Dukes' study (complete responders only)[17]	1996	100 (51/49)	43	6	CBP/observation	DFS improved in the immediate HDC group[a]	OS not evaluable (crossover design); high TRM
Dukes' study (bone metastases only[18])	2000	69 (35/34)	NA	5	CBP/observation	DFS improved in the immediate HDC group[a]	OS not evaluable (crossover design)
PBT-1 study[19]	1999	184 (101/83)	45	5.6	STAMPV/continued CMF	No difference in DFS and OS	Significant drop-out rate; 13% of pts in the control arm received HDC; not conventional treatment used in the control arm
PEGASE 04 study[20]	1999	61 (32/29)	44	5	CMA/anthracycline-based CT	DFS improved in the HDC group[a]	Small study
NCIC study[21]	2001	219 (110/109)	47	3	CMCb/anthracycline or taxane-based CT	DFS improved in the HDC group[a]	High TRM (7.7%)
PEGASE 03 study[22]	2002	180 (91/89*)	46	4	CHUT/observation	DFS improved in the HDC group[a]	HDC *vs* observation
Schmid *et al* study[23]	2002	92 (48/44)	49	1.3	CME/AT	DFS improved in the HDC group[a]	Double HDC; crossover HDC at relapse for pts showing a CR to conventional chemotherapy

[a]Statistically significant. NA: not available; AT: doxorubicin + paclitaxel; Cbp: cyclophosphamide + BCNU + cisplatin; STAMP V: cyclophosphamide + thiotepa + carboplatin; CMA: cyclophosphamide + mitoxantrone + melphalan; CMCb: cyclophosphamide + mitoxantrone + carboplatin; CHUT: cyclophosphamide + thiotepa; CME: cyclophosphamide + mitoxantrone + etoposide.

the results of the first randomised trial comparing HDC *vs* SDC in patients with MBC. The results in favour of HDC of this small study were greatly magnified by the debates in oncological meetings and resulted in an increase in the number of pts treated with this approach, also outside controlled studies. Recently, this trial has been discredited with consequent loss of enthusiasm for HDC among oncologists.[24]

Besides the Bezwoda trial, seven randomised trials on the role of HDC in MBC patients have been published to date and are evaluable. Nevertheless, the OS has been evaluated in only four of the seven trials, since three studies had a crossover design. In the four evaluable trials, OS was similar in the HDC and SDC groups, while DFS was improved in the HDC group in six of seven trials (Table 3). The delay in relapse for patients with metastatic disease represents an important outcome, since it is associated with a longer off-therapy survival and a better quality of life. Thus, the results of these studies support a role for HDC in MBC patients. However, we believe that some aspects of these studies need to be highlighted before drawing definitive conclusions: (a) The Dukes' studies investigated the timing of the intensification (immediate *vs* delayed HDC). (b) The PBT-1 study randomised only 33% (184 pts) of the original number of patients; 10 pts (13%) randomised to the control arm received HDC, while five pts in the HDC arm received no therapy or conventional dose chemotherapy; three pts assigned to conventional dose chemotherapy received HDC after relapse; CMF was continued until progression or for up to 24 cycles, which cannot be considered a conventional treatment. (c) The NCIC study reported a high transplant-related mortality (7.7%). (d) In the PEGASE 03 study, after induction chemotherapy with standard FEC, the pts were randomised to HDC *vs* observation and not *vs* continued SDC. (e) Considering that none of the reported studies randomised more than 220 patients, their statistical power is too limited to detect meaningful survival differences. Recently, Berry *et al*[28] published a comparison of Cancer and Leukaemia Group B Trials (CALGB) with data from the Autologous Blood and Marrow Transplant Registry (ABMTR) with the aim of assessing survival of MBC pts treated with HDC *vs* SDC. In this nonrandomised analysis of two large data sets, women receiving HDC demonstrated a higher long-term probability of survival.

Table 4 Positive prognostic factors for MBC pts treated with HDC

Positive oestrogen receptor status
No liver or CNS metastases
Complete response to SDC
No prior adjuvant chemotherapy
Long disease-free interval after adjuvant chemotherapy

Prognostic factors for MBC patients treated with HDC

HDC might be of particular benefit for a subgroup of patients with MBC (Table 4). Rizzieri *et al*,[29] in a multivariate analysis of data from 425 MBC pts treated with HDC, reported that positive oestrogen receptor status, nonvisceral metastases and no prior adjuvant chemotherapy are positive prognostic factors for OS. Rowlings *et al*,[30] in a retrospective analysis of 1188 MBC pts treated with HDC identified age (older than 45 years), showed poor performance status, absence of hormone receptors, prior

Table 5 HDC as a platform on which to add novel therapies

Authors	*Study characteristics*	*Results*
Preti *et al*[36]	CD34 positive or positive/negative selection	Reduction of contaminating tumour cells in the PBPCs without delay of the autograft
Hempel *et al*[37]	Combination of *ex vivo* immunomagnetic purging of PBPCs and *in vivo* purging with Mab 17-1A	Reduction of the residual disease
Cowan *et al*[38]	Autotransplant of PBPCs transduced with a retrovirus containing the MDR1	Feasible
Reece *et al*[39]	Use of anti-idiotype breast cancer vaccine 11D10 + autotransplant of PBPCs	Improvement in PFS in patients with most vigourous immune response
Nieto *et al*[40]	Trastuzumab + HDC (STAMP-I)	Feasible
Carella *et al*[41]	HDC + autologous PBPCs followed by nonmyeloablative allograft	Feasible

adjuvant chemotherapy, short initial DFS, liver and central nervous system metastases, three or more sites of metastasis and incomplete response to standard chemotherapy as factors associated with increased risk of treatment failure. In particular, in this analysis women with no risk factors had a 3-year probability PFS of 43% *vs* 4% for women with more than three risk factors. In contrast to their predictive value for outcome after conventional chemotherapy, data from the literature about Her2/neu, p53 and Ki 67 in metastatic breast cancer patients treated with HDC are as yet inconclusive.[31–34] Induction duration and number of high-dose cycles might also influence long-term survival of women with MBC treated with HDC. Elias *et al*[35] compared the long-term outcomes of women with MBC enrolled in three phase I/II trials of the Dana–Farber STAMP program characterised by a different study design (long induction/single transplantation, long induction/double transplantation, short induction/double transplantation). The authors concluded that a short induction followed by a double transplant was associated with the longest DFS and OS.

New perspectives

Recent experiences have shown that HDC can be used as a platform on which to add novel approaches such as regimens including new agents, reduced-conditioning allogenic transplantation, molecular targeted therapy, use of antiangiogenesis factors, dendritic cell vaccines and *ex vivo* expansion or purging of the peripheral blood progenitor cells (PBPCs) (Table 5). Preti *et al*[36] demonstrated that CD34 selection alone or in combination with negative selection can result in a significant reduction of contaminating tumour cells in the PBPCs without a significant delay of the autograft. Hempel *et al*[37] reported that *ex vivo* immunomagnetic purging of PBPCs followed by *in vivo* purging with Mab 17-1A after HDC can reduce residual disease without severe toxicity. Cowan *et al*[38] showed the feasibility of autotransplanting PBPCs transduced with a retrovirus containing the multidrug resistance complementary DNA (MDR1) in MBC pts. Moreover, the authors suggest that MDR1 gene therapy may be able to reduce the haematological toxicity with subsequent enhancement of the chemotherapy dose intensity. Reece *et al*[39] published an interim analysis of the use of the anti-idiotype breast cancer vaccine 11D10 in conjunction with autologous stem cell transplantation in patients with MBC. The authors recorded a positive anti-anti-idiotype antibody humoral response at a median of 1.76 months postautotransplant; moreover, they reported a significant improvement in PFS in patients with the most vigorous humoral and cellular immune response. Recently, Nieto *et al*[40] demonstrated that the concurrent administration of trastuzumab and HDC (STAMP-I) in advanced HER2+ breast cancer patients is feasible, with no increase of cardiotoxicity. Finally, interesting results were reported by Carella *et al*[41] in a preliminary experience with HDC plus autologous stem cell rescue followed by nonmyeloablative allograft in MBC patients. The aim of this approach is to achieve a reduction in tumour burden after autograft and control of residual disease with immune-mediated effects after allograft. This therapeutic modality is under study in an ongoing European Group for Blood and Marrow Transplantation (EBMT) trial (Table 6). The eligibility criteria of this study include age <65 years Karnofsky score $\geqslant 70$, diagnosis of advanced breast cancer, previously not more

Table 6 Ongoing EBMT trial with autograft/immunosuppressive allograft for patients with MBC

Autograft
Autologous PBPCs mobilisation
(a) Cyclophosphamide 3 g/m^2 + G-CSF
(b) G-CSF alone

- Mitoxantrone 45 mg/m^2 on day -5
- Thiotepa 600 mg/m^2 on day -4
- Autologous PBPCs reinfusion on day 0

Allograft (30–60 days after autograft)
- Fludarabin 30 mg/m^2 on days -4, -3, -2
- Cyclophosphamide 300 mg/m^2 on days -4, -3, -2
- Donor PBPCs infusion on day 0

GVHD prophylaxis
- Cyclosporin A 1 mg/kg from day -5
- Methotrexate 10 mg/m^2 on day $+1$, $+3$, $+6$

than one line of chemotherapy and availability of one or more HLA-A/B/C/DR/DQ-matched sibling. In the EBMT trial, pts undergo autologous PBPC mobilisation with cyclophosphamide 3 g/m^2 + G-CSF, then HDC (mitoxantrone 45 mg/m^2 + thiotepa 600 mg/m^2) with an autograft, followed by an allograft 30–60 days later using a conditioning regimen with fludarabine 90 mg/m^2 + cyclophosphamide 900 mg/m^2. All pts receive graft-versus-host disease (GVHD) prophylaxis with cyclosporin A 1 mg/kg from day −5 (doses will be adjusted to maintain whole-blood through levels between 150 and 300 ng/ml) and methotrexate 10 mg/m^2 on days +1, +3, +6.

Conclusions

Analysis of the currently available randomised trials shows a significant DFS improvement in favour of HDC in six of the seven published studies, while OS for the HDC and SDC groups is similar in the four evaluable trials. The delay in relapse for patients with metastatic disease represents a very important outcome since it is associated with a longer off-therapy survival and better quality of life; however, it must be emphasised that the statistical power of these trials is too limited to detect meaningful survival differences. Moreover, given a similar survival with HDC or SDC and the present less than 2% transplant-related mortality, many patients might prefer a short intense treatment programme instead of multiple cycles of chemotherapy. Finally, although HDC alone may not be curative in most patients, interest is increasing in using the situation of minimal residual disease as a platform for additional post-transplantation therapy.

In conclusion, HDC remains an important field of clinical research for breast cancer patients with stage IV disease and, from the studies reported in this article, there is some evidence to propose this therapeutic modality for selected patients who are interested in a medically aggressive approach.

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