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Breast Cancer

Autologous hematopoietic stem cell transplantation for breast cancer in Europe: critical evaluation of data from the European Group for Blood and Marrow Transplantation (EBMT) Registry 1990–1999

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Summary:

The aim of this study was to identify trends in high-dose chemotherapy (HDC) with autologous hematopoietic stem cell transplantation (ASCT) and to assess survival in a large cohort of breast cancer (BC) patients receiving this therapy in Europe from 1990 to 1999. A total of 7471 patients who received HDC with ASCT between January 1, 1990 and December 31, 1999 were reported to the European Group for Blood and Marrow Transplantation Registry. Data required for demographics and survival analysis were available for 2679 patients with high-risk primary BC; 921 patients with inflammatory BC (IBC), and 2295 patients with metastatic disease. The main evaluation parameters were progression-free survival (PFS) and overall survival (OS). Between 1990 and 1998, autotransplants for BC increased 30-fold. Significant trends included use of blood-derived rather than marrow-derived stem cells, increment of reporting centers and decrease of mortality within 100 days from transplantation. The 5-year PFS and OS probabilities were 53 and 68% for high-risk disease and 42 and 53% for IBC, respectively. For metastatic disease 5-year PFS and OS probabilities in the whole cohort were 18 and 27%, respectively, while for women transplanted in complete remission the 5-year PFS was 29%. In conclusion, HDC with ASCT has been increasingly used until 1998 and the 100-day mortality rate has been constantly less than 2% from 1995 to date. The 5-year survival of high-risk BC is related to the number of axillary nodes involved at surgery. Outcome of patients with IBC is encouraging, suggesting the need for randomized trials. Patients with metastatic disease responding to pretransplant chemotherapy and harboring ER+ tumors have a better outcome.

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Despite improvements in early detection and adjuvant therapies, breast cancer (BC) remains a leading cause of cancer death in Western countries. Mortality at 10 years exceeds 60% for those patients with 10 or more involved nodes at surgery or large primary tumors, and nearly all women diagnosed with metastatic BC ultimately die of their disease.[1,2] Nowhere has there been more controversy in recent years than in the use of high-dose chemotherapy (HDC) with autologous hematopoietic stem cell transplantation (ASCT) for BC. Early trials of HDC, based on favorable laboratory and clinical indicators,[3,4] initiated in the early 1980s, suggested that this approach might favorably affect the course of operable, high-risk primary and metastatic BC (MBC).[5] Phase II studies created positive expectations among physicians and their patients, to such an extent that HDC with ASCT also became widely used as a therapeutic option outside controlled trials. The use of peripheral blood (PB) cells instead of bone marrow (BM) for ASCT[6,7] significantly reduced the morbidity and mortality related to HDC[8,9] and allowed the utilization of this procedure also outside specialized or academic centers.[10]

However, after almost two decades of clinical research in this field and thousands of women with BC receiving HDC, the appropriate role of this approach remains today uncertain. Most of the randomized trials reported in the last few years,[11–15] although demonstrating the noninferiority of HDC, have failed to show a survival benefit, although the follow-up was generally short and the number of patients was in some cases too small to reach the expected survival benefit.[16] In addition, because of the heterogeneity of intensity and duration of the standard dose chemotherapy (SDC) in the control arm, the outcomes of these studies have been quite variable.[17] Recently, Berry *et al*[18] have reported on a large retrospective analysis comparing survival of 1079 women with metastatic BC receiving either HDC (Autologous Blood and Marrow

Transplant Registry of North America, ABMTR) or SDC (CALGB database), indicating a statistically significant survival advantage for HDC *vs* SDC.

As a contribution to the ongoing discussion on HDC for BC we report here the results of this therapeutic approach in almost 6000 women receiving ASCT at 370 European Group for Blood and Marrow Transplantation (EBMT) centers between 1990 and 1999.

Methods

Patients

The EBMT Solid Tumors Registry was set up in 1984 to collect information regarding patients undergoing HDC and ASCT in Europe and the Middle East. EBMT centers are required to send patient data each year to the Central EBMT Database either directly, or through a National Registry where it exists. There are two levels of data: Minimal Essential Data type A (MED A) which are compulsory and consider major items such as demographic data, disease classification, type of transplant outcomes and follow-up; and Minimal Essential Data B (MED B) referring to items sent on a volunteer basis (type of conditioning or mobilization regimens, complications, number of cells transplanted, etc). A total of 10 centers each year are randomly requested to be audited by an EBMT committee in order to verify the quality of the reported data and to compare them with the ones of a general European survey performed yearly on behalf of the EBMT where only number of patients and type of graft and disease are requested.[19,20] Before starting the present evaluation regarding the decade 1990–1999, all centres were recontacted for missing data. Among 7471 BC patients reported to the EBMT Registry, 5895 were eligible for this retrospective analysis and represent the body of this paper. A total 2679 were reported as having high-risk BC, 921 inflammatory BC (IBC) and 2295 metastatic disease. Cases with an incomplete data set have been excluded from the analysis.

Statistical analysis

Probabilities of 100-day mortality, progression-free survival (PFS) and overall survival (OS) were calculated using the Kaplan–Meier product limit estimate.[21] The log-rank test was used for comparisons of PFS and survival between groups.[22] OS and PFS rates were measured from the date of transplant to the date of last follow-up or death and the date of progression, respectively.

Results

Between January 1, 1990 and December 31, 1999, 7471 patients with BC receiving HDC and HSCT were reported to the EBMT Registry, which represents 49% of all cases of solid tumors in the database. Demographics and essential clinical data are reported in Table 1.

During the decade, the number of ASCT, along with the number of reporting centers for BC, increased progressively until 1998 (Table 1) for all disease stages. During the following years, a rapid decline in the number of ASCT for BC has been observed, that is, 1115 (−32%) in 1999 and 762 (−32%) in 2000 (EBMT Solid Tumor Working Party, annual reports). Between 1992 and 1994, a dramatic shift toward a widespread use of PB progenitors occurred (19 and 91%, respectively). Transplant-related mortality, that is, any death not related to the disease occurring within the first 100 days after the graft, declined in the second half of the decade, to 1–2%.

Owing to the elevated number of phase II studies, the conditioning regimens employed are quite different (Tables 2 and 3). The cyclophosphamide/thiotepa/carboplatin (STAMP V) or its variants was the most frequently used schedule in the adjuvant setting, while high-dose sequential chemotherapy[15] or its variants, largely used in Italy, ranked second. STAMP V was the most frequently used regimen also in MBC while mitoxantrone/cyclophosphamide/melphalan, which is utilized mainly in France, ranked first in IBC. Overall, 25 different regimens in stage

Table 1 Demographics and essential clinical data of BC patients reported to the EBMT registry from 1990 to 1999

	1990	*1991*	*1992*	*1993*	*1994*	*1995*	*1996*	*1997*	*1998*	*1999*
Number of cases	54	113	198	344	579	789	1234	1407	1638	1115
No. of reporting centers	18	30	37	58	82	119	153	175	224	184
Median ASCT procedures per center/year (range)	3 (1–8)	2 (1–16)	4 (1–28)	3 (1–39)	4 (1–49)	4 (1–48)	5 (1–69)	6 (1–45)	4 (1–61)	4 (1–52)
Median patient age (range)	41 (25–53)	42 (26–61)	42 (27–59)	42 (23–67)	43 (23–66)	44 (18–64)	44 (22–70)	45 (21–69)	45 (22–65)	45 (22–66)
Status of BC at Tx										
No evidence of disease (adjuvant)	3	19	52	100	175	282	420	523	645	463
Inflammatory BC	12	12	29	59	77	121	147	188	159	117
Metastatic BC	29	60	78	137	207	226	408	396	470	284
Source of HSC										
Marrow	38	88	138	112	49	19	11	10	16	6
Blood	10	10	32	191	508	749	1203	1378	1575	1030
Marrow and blood	6	15	28	41	18	14	11	12	9	5
Treatment-related mortality within 100 days from ASCT (%)	3	7	4	3	5	1	2	2	1	1

ASCT = autologous stem cell transplantation; BC = breast cancer; Tx = transplant; HSC = hematopoietic stem cells.

Table 2 Autotransplants for stage II and III BC in Europe 1990–1999

High-risk primary BC	
Number of patients registered	2683
Median age (range)	46 (18–70)
Number of positive axillary nodes:	
<10	408
$\geqslant 10$	627
$\geqslant 20$	130
ER status	
Positive	381
Negative	476
Source of HSC	
Marrow	89
Blood	2549
Marrow and blood	28
Conditioning regimen	
CTCb or variant	470
HDS	274
C-PAM-M	146
I-Cb-E	49
Others	258
Toxic death rate at day 100	1%
Inflammatory breast cancer	
Number of patients registered	921
Median age (range)	45 (19–65)
Source of HSC	
Marrow	81
Blood	786
Marrow and blood	22
Type of conditioning regimen	
CTCb (or variant)	102
C-PAM-M	131
Others	122
Toxic death rate at day 100	2%

ER = estrogen receptor; HSC = hematopoietic stem cells; C = cyclophosphamide; T = thiotepa; Cb = carboplatin; HDS = high-dose sequential chemotherapy; PAM = melphalan; M = mitoxantrone; I = ifosphamide; E = etoposide.

II/III BC, and 29 in stage IV patients, have been reported among EBMT centers. Interestingly, BCNU-containing regimens were not a therapeutic option in Europe.

High-risk primary breast cancer

Relevant patient characteristics are reported in Table 2. Among 1165 patients with fully available data, 35% had <10 positive axillary nodes, and 54% had $\geqslant 10$ positive nodes. A proportion of cases had been treated for very high-risk BC, that is, $\geqslant 20$ positive nodes ($n = 130$; 11%). Kaplan–Meier estimates of OS and PFS of the whole cohort of adjuvant patients and subgroups with different lymph node involvement are reported in Figure 1. Median PFS for the whole high-risk group and those with $\geqslant 10$ positive nodes were 74 and 69 months (Figure 1 a and b), respectively; for patients receiving HDC with less than 10 positive nodes, median PFS was not reached (Figure 1b). In patients with $\geqslant 20$ positive nodes at surgery, survival rates significantly dropped (median DFS = 37 months) (Figure 1c). No statistically significant difference was observed in OS and PFS regarding estrogen-receptor (ER) status (data not shown).

Table 3 Autotransplants for MBC in Europe 1990–1999

Number of patients registered	2295
Median age (range)	45 (18–69)
ER status	
Positive	475
Negative	405
Status of BC at graft:	
CR	635
PR	562
SD	477
SR	519
Front line	102
Conditioning regimen	
CTCb or variant	392
C-PAM-M	237
I-Cb-E	127
T-PAM	99
Others	343
Toxic death rate at day 100	3%
Interval between diagnosis and transplant	
<12 mo	625
$\geqslant 12$ mo	1670

MBC = metastatic breast cancer; ER = estrogen receptor; CR = complete response; PR = partial response; SD = stable disease; SR = sensitive relapse; C = cyclophosphamide: T = Thiotepa; Cb = carboplatin; PAM = melphalan; M = mitoxantrone; I = ifosphamide; E = etoposide; mo = months.

Inflammatory breast cancer

The EBMT BC Registry includes 921 patients with non-metastatic IBC treated with HDC, which corresponds to a rather elevated percentage of 25% of all stage II/III patients when compared to the ABMTR survey. Although there is no definitive explanation for these data, the tendency toward ASCT for this disease has been rather high in Europe. In fact, several studies in France have specifically investigated the role of HDC in IBC. Patient characteristics and survival rates are shown in Table 2 and Figure 1d. Median time to progression after transplant was 40 months.

Metastatic breast carcinoma

Characteristics of women who received HSC with ASCT for MBC are listed in Table 3. A total of 28% of all patients were given HDC as consolidation after achieving a complete response (CR) with conventional treatments. Overall and PFS of the whole cohort of patients are reported in Figure 2a; median OS and PFS were 31 and 13 months, respectively. Patients receiving HDC with ASCT in first CR had a significantly better PFS compared to those receiving this therapy in partial response, stable disease or progression (median 25 *vs* 13 months, Fig. 2b). Poorer outcomes were associated with ER-negative tumors (31 *vs* 43% OS at 5 years) (Figure 2c) and a shorter interval between diagnosis and transplant (data not shown).

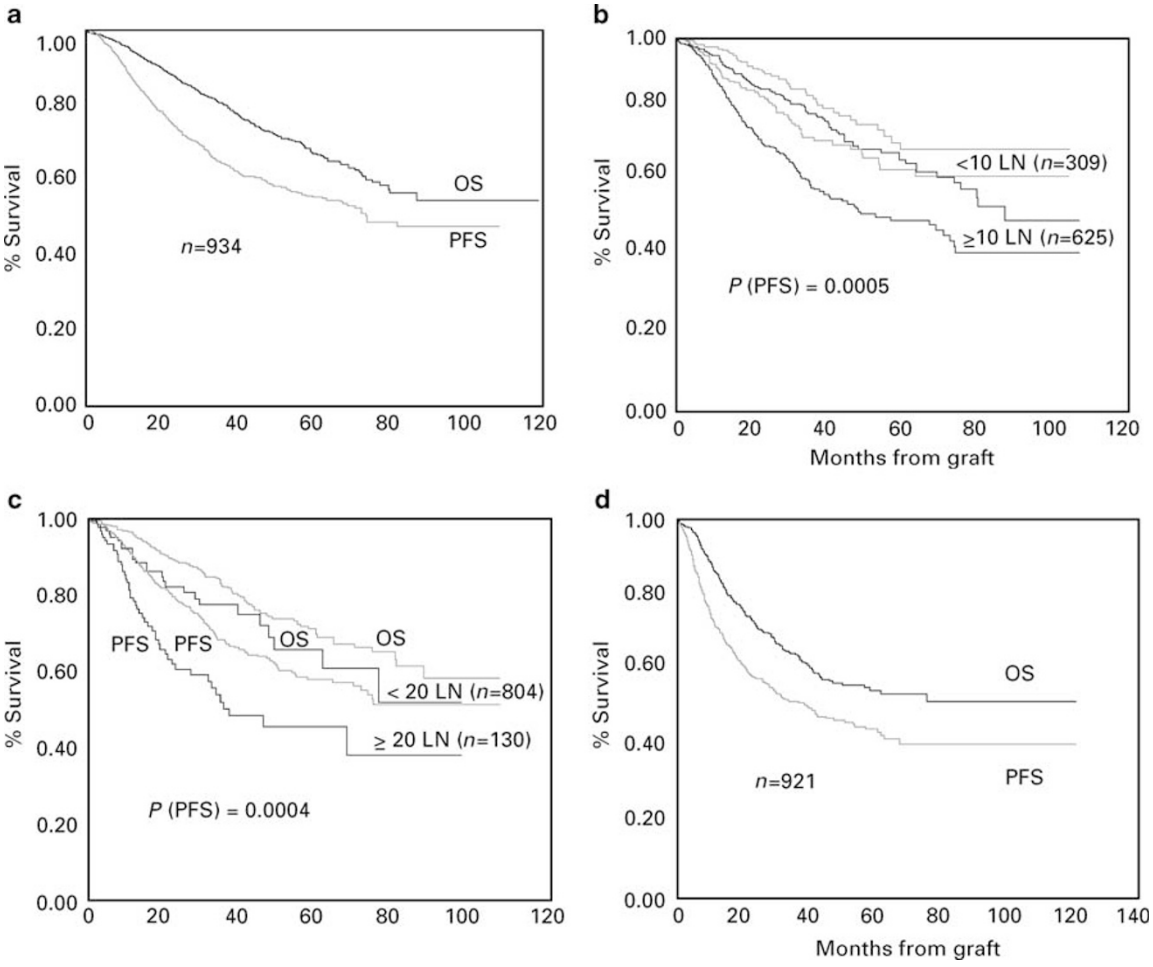

Figure 1 Kaplan–Meier estimates of OS and PFS of patients with high-risk primary breast cancer (**a**: whole cohort; **b** and **c**: by lymph node involvement) and inflammatory breast cancer (**d**).

Discussion

As a result of high expectations for the role of HDC as a treatment for BC, the number of transplants performed in Europe consistently increased from 1990 to 1998. In more recent years, the number of procedures has diminished due to premature reports from randomized trials that did not show the expected survival advantage in favor of HDC. Highs and lows in the enthusiasm for HDC in BC has been largely unreasonable since no definitive conclusions can be drawn despite a huge number of studies reported throughout the last two decades.[16,17] This has cast a pall over the entire field and has resulted in both a low accrual of early prospective trials (irrational exuberance phase) and a moratorium on new studies (reticence phase).

The EBMT Registry data confirm that HDC with ASCT today is a safe procedure. Mortality rate within 100 days from transplantation has significantly reduced during the last decade, possibly related to the use of blood cells as source of HSC and a widespread better knowledge of the whole procedure. Moreover, the overall low mortality rate might also be related to the use of preparative regimens with a low toxicity profile, that is, the cyclophosphamide/ BCNU/ cisplatin (STAMP I) regimen, which is associated with a high treatment-related mortality,[14] is only anecdotally reported in European surveys.[10] It is worth noting that the switch from BM to PB as the source of stem cells occurred rapidly in mid-1990s and the reinfusion of BM plus PB stem cells has been utilized in a minority of patients in Europe (ie 12% in 1993, 0.25% in 1995) compared to the higher rate reported in the North American Registry.[23] This might be related to legal issues, which were more stringent in the US, or possibly to a earlier confidence of European physicians on the durability of hematopoiesis following autografting of PB cells.[24]

The clinical results of our retrospective analysis should be viewed considering that patients receiving HDC differ from the general population of women with BC. Thus, differences observed between patients receiving transplantation and those who received SDC in historical data bases may result from selection biases. This underscores the importance of comparing HDC and SDC in comparable subjects within large randomized trials. Unfortunately, the outcomes of the phase III studies so far reported had been quite variable, this partially depending on their heterogeneity and the lack of sufficient numbers of patients to assess interventions with adequate statistical power.[15] In addition, they have been reported in some cases without

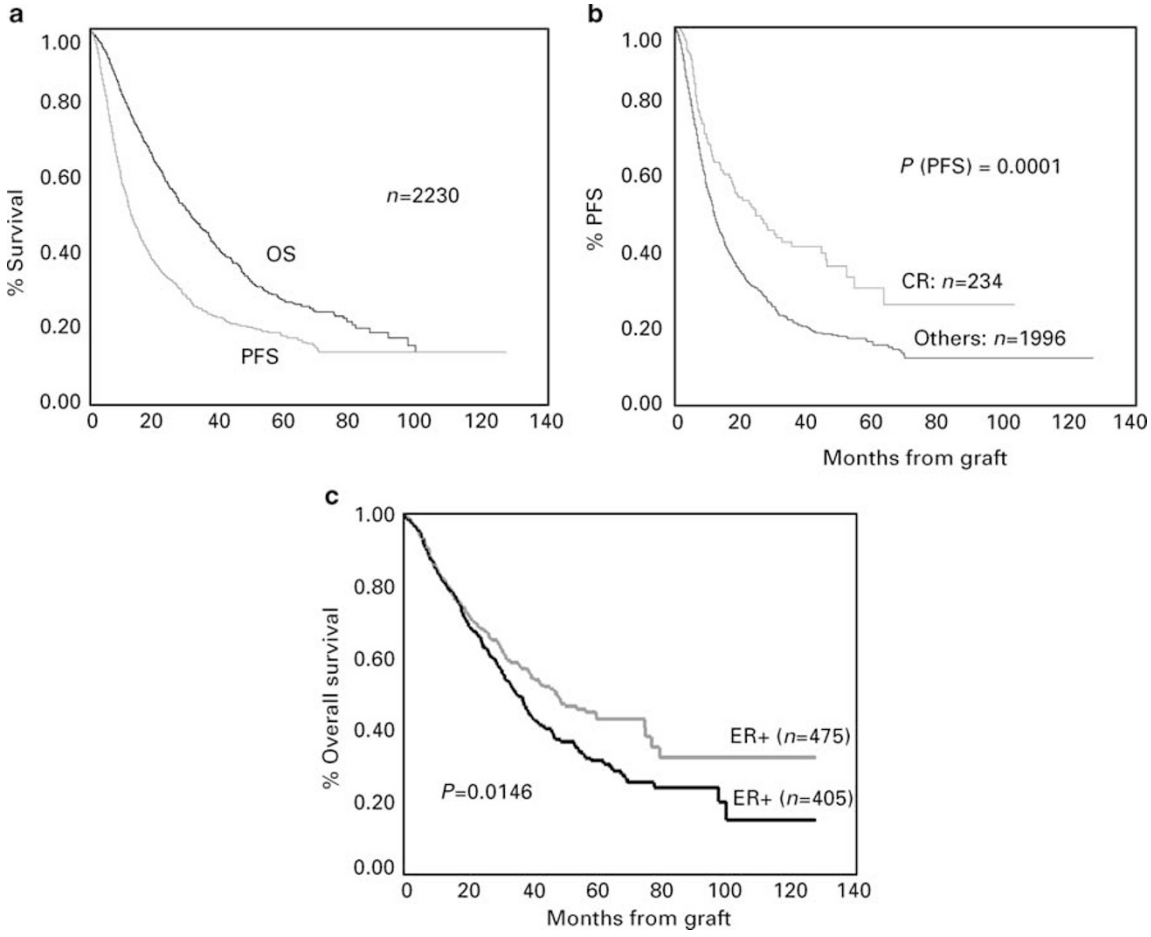

Figure 2 Kaplan–Meier estimates of OS and PFS for metastatic breast cancer. (**a**) whole cohort patients; (**b**) by responsiveness to chemotherapy; (**c**) by ER status.

sufficient follow-up.[11,25] Our retrospective analysis, including almost 6000 patients reported in the EBMT Registry, may be useful in complementing data from these randomized trials. It allows the following clinical considerations.

In the 934 evaluable patients with high-risk primary BC, defined by extensive axillary node involvement, our data confirm that survival is related to the number of positive nodes at surgery, but not to the ER status. Results presented here cannot be compared with previous reports of SDC and the controversy about the efficacy of HDC for high-risk BC remains unsettled. The available results of six large phase 3 studies,[13–15,26–28] only one having been published in a peer-reviewed journal,[13] are still too preliminary, while in two studies the control arms were not conventional therapies.[13,14]

In the 921 patients with IBC, our data suggest an apparent advantage in DFS rates from the inclusion of HDC in the multidisciplinary management of this disease.[29–31] Randomized trials in this subgroup of patients are necessary to evaluate the potential benefits of such a strategy.

In the large cohort of 2230 patients with MBC, women receiving HDC as consolidation therapy after achieving CR had the best prognosis, with one out of four patients being disease-free at 5 years. This result confirms the data from the ABMTR[18,23,32] and suggests that HDC with ASCT may cure a subset of patients with MBC.[33] Despite these encouraging results, available data from randomized trials reported to date are contradictory. It is noteworthy that three trials, [11,12,34] which addressed the value of consolidation with HDC *vs* SDC in chemosensitive patients, were undersized as to the number of patients transplanted in CR. This aspect seems critical in interpreting their results, as patients in CR are those who are likely to benefit most from HDC. In our analysis time to relapse and ER-positive disease were associated with a better outcome as previously reported.[32]

Based on the results of this analysis, we recommend that continued investigation of high-dose strategies is still necessary. The information presented here, as well as the maturing of data from large controlled studies should guide future trials aimed at identifying subsets of patients who are more likely to benefit from HDC. Further improvement of HDC with ASCT is likely to come, in the near future, by integrating HDC with novel treatment strategies with different and potentially complementary mechanisms of action.

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References

1 Winer EC, Morrow M, Osborne CK, Harris JR. Malignant tumors of the breast. In: DeVita Jr VT, Hellman S, Rosenberg SA (eds). *Cancer: Principles and Practice of Oncology*. Lippincott-Raven: Philadelphia, PA, 2001, pp. 1651–1716.

2 Greenberg PA, Hortobagyi GN, Smith TL *et al*. Long-term follow-up of patients with CR following combination chemotherapy for metastatic breast cancer. *J Clin Oncol* 1996; **14**: 2197–2205.

3 Skipper HE. Dose intensity *versus* total dose of chemotherapy: an experimental basis. In: De Vita VT, Hellman S, Rosenberg SA (eds). *Important Advances in Oncology*. Lippincott-Raven: Philadelphia, PA, 1990, pp. 43–64.

4 Lazarus HM. Hematopoietic progenitor cell transplantation in breast cancer: current status and future directions. *Cancer Invest* 1998; **16**: 102–126.

5 Crown J. High-dose chemotherapy of metastatic breast cancer: the end of the beginning? *Br J Cancer* 1997; **75**: 467–479.

6 Gianni AM, Siena S, Bregni M *et al*. Granulocyte-macrophage colony-stimulating factor to harvest circulating haemopoietic stem cells for autotransplantation. *Lancet* 1989; **2**: 580–585.

7 Siena S, Bregni M, Brando B *et al*. Circulation of CD34+ hematopoietic stem cells in the peripheral blood of high-dose cyclophosphamide-treated patients: enhancement by intravenous recombinant human granulocyte–macrophage colony-stimulating factor. *Blood* 1989; **74**: 1905–1914.

8 Schmitz N, Linch DC, Dreger P *et al*. Randomized trial of filgrastim-mobilized peripheral blood progenitor cell transplantation *versus* autologous bone-marrow transplantation in lymphoma patients. *Lancet* 1996; **347**: 353–357.

9 Siena S, Schiavo R, Pedrazzoli P, Carlo-Stella C. Therapeutic relevance of CD34 cell dose in blood cell transplantation for cancer therapy. *J Clin Oncol* 2000; **18**: 1360–1377.

10 Neymark N, Rosti G: Patient management strategies and transplantation techniques in European stem cell transplantation centers offering breast cancer patients high-dose chemotherapy with peripheral blood stem cell support: a joint report from the EORTC and EBMT. *Haematologica* 2000; **85**: 733–744.

11 Stadtmauer EA, O'Neill A, Goldstein LJ *et al*. Conventional-dose chemotherapy compared with high-dose chemotherapy plus autologous hematopoietic stem-cell transplantation for metastatic breast cancer. *N Engl J Med* 2000; **342**: 1069–1076.

12 Crump M, Gluck S, Stewart D *et al*. A randomized trial of high-dose chemotherapy (HDC) with autologous peripheral blood stem cell support (ASCT) compared to standard therapy in women with metastatic breast cancer: a National Cancer Institute of Canada (NCIC) Clinical Trials Group Study. *J Clin Oncol* 2001; **20**: 21a (Abstr).

13 Bergh J, Wiklund T, Erikstein B *et al*. Tailored fluorouracil, epirubicin, and cyclophosphamide compared with marrow-supported high-dose chemotherapy as adjuvant treatment for high-risk breast cancer: a randomised trial. Scandinavian Breast Group 9401 study. *Lancet* 2000; **356**: 1384–1391.

14 Peters W, Rosner G, Vrendeburgh J *et al*. Updated results of a prospective, randomized comparison of two doses of combination alkylating agents as consolidation after CAF in high-risk primary breast cancer involving ten or more axillary lymph nodes: CALBG 9082/SWOG 9114/NCIC Ma. 13. *J Clin Oncol* 2001; **20**: 21a (Abstr).

15 Gianni A, Bonadonna G. Five-year results of the randomized clinical trial comparing standard versus high-dose myeloablative chemotherapy in the adjuvant treatment of breast cancer with >3 positive nodes. *J Clin Oncol* 2001; **20**: 21a (Abstr).

16 Gianni L: High-dose chemotherapy for breast cancer: any use for it. *Ann Oncol* 2002; **13**: 650–652.

17 Pedrazzoli P, Siena S. Clinical results in 2001 show high dose therapy and hematopoietic progenitor cell transplantation as a therapeutic option for breast cancer. *Haematologica* 2001; **86**: 900–907.

18 Berry DA, Broadwater G, Klein JP *et al*. High-dose *versus* standard chemotherapy in metastatic breast cancer: comparison of cancer and leukemia group B trials with data from the autologous blood and marrow transplant registry. *J Clin Oncol* 2002; **20**: 743–750.

19 Gratwohl A, Hermans J. Bone marrow transplantation activity in Europe 1992: report from the European Group for Bone Marrow Transplantation (EBMT). *Bone Marrow Transplant* 1994; **13**: 5–10.

20 Gratwohl A, Passweg J, Baldomero H, Urbano-Hispizua A. European Group for Blood and Marrow Transplantation (EBMT), hematopoietic stem cell transplantation activity in Europe 1999. *Bone Marrow Transplant* 2001; **27**: 899–916.

21 Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958; **53**: 457–481.

22 Cox DR. Regression models and life tablets. *J R Stat Soc B* 1972; **3**: 187–202.

23 Antman KH, Rowlings PA, Vaughn 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.

24 Siena S, Bregni M, Di Nicola M *et al*. Durability of hematopoiesis following autografting with peripheral blood hematopoietic progenitors. *Ann Oncol* 1994; **5**: 935–941.

25 Stadtmauer EA, O'Neill A, Goldstein LJ *et al*. Conventional-dose chemotherapy with high-dose chemotherapy plus autologous stem cell transplantation for metastatic breast cancer: 5-year update of the Philadelphia trial. *J Clin Oncol* 2002; **21**: 43a (Abstr).

26 Rodenhuis S, Bontenbal M, Beex L *et al*. Randomized phase III study of high-dose chemotherapy with cyclophosphamide, thiotepa and carboplatin in operable breast cancer with 4 or more axillary lymph nodes. *J Clin Oncol* 2000; **19**: 74a (Abstr).

27 Crown JP, Lind M, Gould A *et al*. High dose chemotherapy with autograft (PBP) support is not superior cyclophosphamide, methotrexare and FU following doxorubicin induction in patients with breast cancer and 4 or more involved axillary lymph nodes: the anglo-celtic I study. *J Clin Oncol* 2002; **21**: 42a (Abstr).

28 Zander AR, Kruger W, Kroger N *et al*. High-dose chemotherapy with autologous hematopoietic stem-cell support (HSCS) *vs*. standard dose chemotherapy in breast cancer patients with 10 or more positive lymph nodes: first result of a randomized trial. *J Clin Oncol* 2002; **21**: 415a (Abstr).

29 Jaiyesimi IA, Buzdar AU, Hortobagyi G. Inflammatory breast cancer: a review. *J Clin Oncol* 1992; **10**: 1014–1024.

30 Thomas F, Arriagada R, Spielmann M *et al*. Pattern of failure in patients with inflammatory breast cancer treated by alternating radiotherapy and chemotherapy. *Cancer* 1995; **76**: 2286–2290.

31 Viens P, Penault-Llorca F, Jacquemier J *et al*. High-dose chemotherapy and haematopoietic stem cell transplantation for inflammatory breast cancer: pathologic response and outcome. *Bone Marrow Transplant* 1998; **21**: 249–254.

32 Rowlings PA, Williams SF, Antman KH *et al*. Factors correlated with progression-free survival after high-dose chemotherapy and hematopoietic stem cell transplantation for metastatic breast cancer. *JAMA* 1999; **282**: 1335–1343.

33 Hortobagyi GN. Can we cure limited metastatic breast cancer? *J Clin Oncol* 2002; **20**: 620–623.

34 Lotz JP, Cure H, Janvier M *et al*. High dose chemotherapy with hematopoietic stem cell transplantation for metastatic breast cancer: results of the French protocol PEGASE 04. *J Clin Oncol* 1999; **18**: 43a (Abstr).