Cancer Chemother Pharmacol (1998) 42 (Suppl): S60–S67

ORIGINAL ARTICLE

Martin S. Tallman · William J. Gradishar

High-dose chemotherapy and autologous stem cell transplantation as treatment for high-risk breast cancer

Abstract High-dose chemotherapy with autologous stem cell transplantation has emerged as a common treatment for patients with breast cancer who have a poor prognosis. The success of this approach appears to depend on the tumor burden and the sensitivity of the disease to chemotherapy because treatment techniques have been refined and treatment-related mortality has declined. Phase II studies in patients with stage II and III disease are encouraging and suggest that treatment with high-dose chemotherapy before the development of metastatic disease may provide an advantage in terms of relapse-free and overall survival. However, tumor cells may contaminate stem cell collections and contribute to relapse after transplantation. Therefore it may be important to separate and select purified CD34+ cells which are not contaminated. It has been suggested that selection bias contributes to the favorable preliminary results observed in phase II studies of high-risk patients. Such issues, together with patient and physician bias regarding the benefits of this strategy, emphasize the need to complete the prospective randomized trials now underway.

Key words Breast cancer · Autologous stem cell transplantation

Work presented at the 13th Bristol-Myers Squibb Nagoya International Cancer Treatment Symposium, "Strategic Cross Talk between Major Oncology Groups/Clinical Pharmacology in Cancer Chemotherapy," 17–18 October 1997, Nagoya, Japan

M. S. Tallman · W. J. Gradishar
Division of Hematology-Oncology, Department of Medicine, Northwestern University Medical School, Robert H. Lurie Cancer Center, Chicago, IL, USA

M. S. Tallman (✉)
Division of Hematology/Oncology, Northwestern University Medical School, Robert H. Lurie Cancer Center of Northwestern University, 233 East Erie Street Suite 700, Chicago, IL 60611, USA
e-mail: mtallman@casbah.acns.nwu.edu
Tel. 1 312 908 9412; Fax 1 312 908 4844

Introduction

The success of high-dose chemotherapy with stem cell transplantation in patients with hematologic malignancies has prompted its application to patients with chemotherapy-sensitive solid tumors including breast cancer. Accordingly, breast cancer is now the most common disease for which high-dose chemotherapy with autologous stem cell transplantation is carried out [2]. In 1995, 40% of patients undergoing autologous transplantation registered with the Autologous Bone Marrow Transplant Registry had breast cancer. Studies which have demonstrated the relation of dose intensity to response in patients with metastatic breast cancer and in the adjuvant setting have provided a sound rationale to explore this approach [27, 53]. As a result, a number of clinical trials involving relatively small numbers of patients conducted most often at single institutions have explored the role of high-dose chemotherapy with stem cell transplantation for patients with metastatic breast cancer [1, 3, 5, 6, 17, 19, 28, 29, 31, 38, 45, 49, 51, 52]. These trials have suggested that a small, but definite proportion of patients may enjoy a prolonged period of progression-free survival. However, the role of high-dose chemotherapy with autologous stem cell transplantation in the treatment of women with breast cancer has emerged as one of the most controversial areas in contemporary medical oncology [24]. Despite the lack of prospective randomized phase III clinical trials designed to determine the true survival benefit, significant patient and physician bias exists.

The observation that some patients with metastatic disease may derive meaningful clinical benefit as well as improvements in the techniques of administering high-dose chemotherapy have encouraged the use of this strategy for patients earlier in the natural history of the disease, ie, as consolidation in the adjuvant setting for patients at high risk of recurrence [7, 20, 22, 23, 25, 37, 41, 43, 46]. Under these circumstances, patients are likely to have microscopic disease which is sensitive to chemotherapy. However, this approach is intensive, costly, and may have long-term complications including the development of myelodyspla-

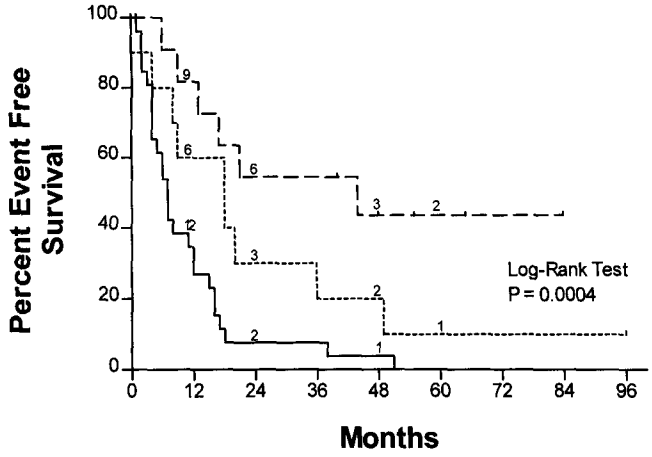

Fig. 1 Event-free survival for all patients according to whether (----------) or not (——————) they were free of disease at the time of transplantation or whether they had only bone disease (---------). Reproduced, with permission, from Tallman MS et al [45]

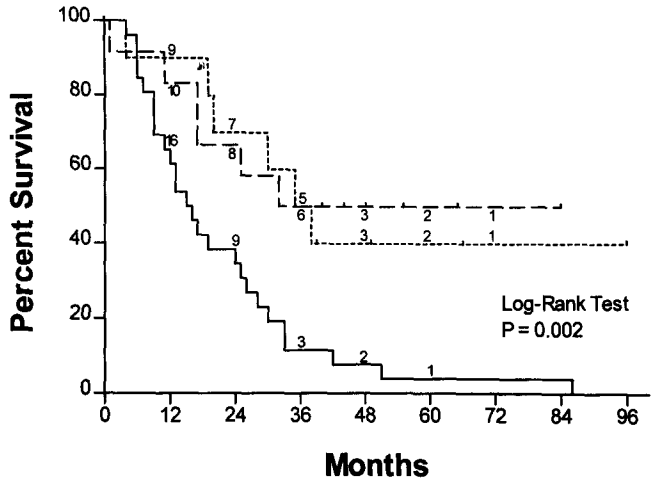

Fig. 2 Overall survival for all patients according to whether (----------) or not (——————) they were free of disease at the time of transplantation or whether they had only bone disease (---------). Reproduced, with permission, from Tallman MS et al [45].

Table 1 Selected trials of high-dose chemotherapy in patients with relapsed or refractory breast cancer (*CR* complete remission, *EFS* event-free survival, *OR* overall remission, *OS* overall survival, *PFS* progression-free survival)

Number of patients	CR (%)	OR (%)	Toxic Deaths (%)	PFS/EFS (%)	OS (%)	Reference
15	38	88	18	10	25	19
14	15	77	7	0	0	28
32	23	62	3	10	35	51
32	25	46	6	24	53	5
48	9[a]	33	4	17	25	45

[a] 3 of 34 evaluable patients (12 patients had no evidence of disease at the time of high-dose chemotherapy and 2 died early)

sia and secondary malignancies, as has been observed in patients with non-Hodgkin's lymphoma and Hodgkin's disease [16, 44]. Therefore several issues need to be addressed before this treatment is routinely recommended for all patients with early-stage breast cancer. First, what is the actual benefit derived from high-dose chemotherapy with autologous stem cell transplantation for patients with metastatic disease? Second, what benefit is observed when administering high-dose chemotherapy with stem cell transplantation for patients as a consolidation therapy in the adjuvant setting? Third, is this intensive approach superior to standard adjuvant chemotherapy in this setting? Fourth, can occult breast cancer cells in the bone marrow or peripheral blood harvested from patients undergoing high-dose chemotherapy with autologous stem cell transplantation be detected and, if so, are they clinically relevant?

High-dose chemotherapy with autologous stem cell transplantation for metastatic breast cancer

Patients with metastatic breast cancer are generally incurable. Despite combination chemotherapy, patients with metastatic breast cancer have a median response duration of approximately 12 months, a median overall survival of 2 years, and a probability of disease-free survival at 5 years of <5% [12, 15, 47]. A number of clinical trials have explored the role of high-dose chemotherapy with autologous stem cell transplantation in patients with advanced breast cancer [1, 3, 5, 6, 17, 19, 29, 30, 32, 38, 45, 49, 51, 52]. Initial studies were carried out in patients with relapsed or refractory disease who often had particularly poor prognostic factors such as younger age, estrogen receptor-negative disease, visceral disease, and prior therapy for metastases (Table 1). High-dose chemotherapy regimens have been developed using single or double alkylating agent chemotherapy, but other agents whose doses can be escalated without significant extramedullary toxicity, such as etoposide and mitoxantrone, have been included.

In the aggregate experience, although initial high response rates were reported, few patients survived disease-free for any length of time [5, 19, 28, 45, 51]. For example, 48 patients at Northwestern University with metastatic breast cancer received high-dose chemotherapy with cyclophosphamide and thiotepa, whether or not they had responded to pretransplant doxorubicin-based cytoreductive chemotherapy [45]. Those with nonprogressive disease posttransplantation received conventional doses of 5-fluorouracil and cisplatin to test the feasibility and efficacy of using posttransplantation chemotherapy to eradicate small numbers of cells, which potentially may have been reinfused with the transplanted stem cells. Despite this approach, only 17% of patients were alive and without disease at 4 years (Fig. 1) and the overall survival was 25% (Fig. 2). Patients free of disease at the time of high-dose chemotherapy had the most favorable outcome: 7 of the 48 patients survive disease-free and 5 of these 7 are among the 12 who had no evidence of disease at the time of high-dose chemotherapy.

Table 2 Selected trials of high-dose chemotherapy in patients with chemotherapy-sensitive metastatic breast cancer (*CR* complete remission, *EFS* event-free survival, *NA* not available, *OR* overall remission, *OS* overall survival, *PFS* progression-free survival)

Number of patients	CR (%)	Toxic Deaths (%)	PFS/EFS (%)	OS (%)	Reference
29	59	3	24	50	1
59	36	15	22	20[a]	52
24	37	0	10	33	29
19[b]	56	11	53	53	5
22	54	23	NA	40	37
20	35	0	52	80	3
15	53	13	0	20	31
26[c]	46	12	27	50	49
45	51	0	<20	<20	6
21[d]	5	0	30	68	17

[a] For all patients
[b] Ten patients had no evidence of disease, 2 early deaths
[c] Two patients had no evidence of disease at transplantation
[d] All patients received doxorubicin posttransplantation

The best results have been observed when this strategy is applied to patients with chemotherapy-sensitive disease either as initial therapy for metastatic disease or following the achievement of either complete or partial remission with pretransplantation conventional-dose, usually doxorubicin-based, chemotherapy [1, 3, 6, 17, 29, 31, 38, 49, 52] (Table 2). Under these circumstances, 35–55% of patients achieve a complete response and 20–30% survive without evidence of progression after 2–4 years of follow-up.

During the period from 1989 to 1995, several important trends arose [27] (Table 3). First, autologous transplants for breast cancer became increasingly common. Second, there was a complete shift in the source of hematopoietic stem cells from the bone marrow to the peripheral blood. Third, treatment-related mortality decreased from 22% to 5% and the majority of failures were attributable to resistant or progressive disease. Fourth, more patients were receiving high-dose chemotherapy for earlier-stage disease. In a multivariate analysis, prognostic factors which predict a more favorable outcome of metastatic disease include a single site of metastatic disease and the achievement of complete remission with pretransplantation induction chemotherapy [2, 4]. This observation is reminiscent of the improvement in outcome which occurred when patients with acute leukemia underwent allogeneic transplantation in first complete remission rather than when they had refractory disease [13]. Patients with metastatic disease who achieve complete remission with induction chemotherapy have a 3-year progression-free survival rate of approximately 30% [2]. Furthermore, the presence of hepatic or lung metastases or prior doxorubicin-based adjuvant chemotherapy appear to be particularly poor prognostic factors in that prolongation of progression-free survival is not observed in such patients [2, 18].

Trials of high-dose chemotherapy, particularly those including patients with metastatic disease, have been difficult to evaluate due to the small number of patients included in most studies, heterogeneity of the patient population, variability in response criteria, and relatively short follow-up. Most of the data regarding the efficacy of high-dose chemotherapy as a treatment for metastatic disease are derived from phase II trials. Generally, these results are compared to historical control patients treated with standard chemotherapy. Recently, Rahman and colleagues analyzed prospective data from 18 consecutive doxorubicin-containing protocols for the treatment of metastatic breast cancer [39]. A total of 1581 patients were enrolled in these studies. The data were analyzed to determine the outcome of patients who met the criteria for participating in high-dose chemotherapy trials. Of the 1581 patients enrolled, 645 were high-dose chemotherapy candidates and 936 were not candidates. Candidates for high-dose chemotherapy had a significantly better outcome: complete response rate 27% vs 7%; median overall survival 30% vs 17%; and survival at 5 years 21% vs 6%. These data highlight the possibility that emerging results from single-arm, phase II trials of high-dose chemotherapy for the treatment of metastatic breast cancer are due to selection bias [14, 22].

Only a single prospective randomized trial which compares high-dose chemotherapy with autologous stem cell transplantation to standard-dose chemotherapy for metastatic disease has been published [6]. This study showed that patients treated with high-dose chemotherapy had a

Table 3 Autotransplants for breast cancer registered with the ABMTR (*BM* bone marrow, *PBSC* peripheral blood stem cell)

Parameter	Year						
	1989	1990	1991	1992	1993	1994	1995 (first half)
No. of patients	272	342	683	1069	1189	1513	818
% autotransplants registered	16	16	25	33	33	39	40
Graft type							
%BM	81	79	58	42	30	19	10
%BM + %PBSC	5	7	22	33	30	25	18
%PBSC	14	14	20	25	40	56	72
100-day mortality	22	15	11	6	6	4	5
Stage prior to transplant (%)							
Stage I, III, IBC	7	16	23	34	31	39	49
Stage IV	93	83	77	65	68	60	50

Adapted, with permission, from Antman KH et al [2]

Table 4 Trials of high-dose chemotherapy in patients with early-stage high-risk breast cancer (*ck* cytokeratin, *DFS* disease-free survival, *EFS* event-free survival, *NA* not available, *OS* overall survival, *PFS* progression-free survival)

Reference	No. of patients	Toxic deaths (%)	EFS/PFS (%)	OS (%)	Median follow-up (months)	EFS/DFS historical control (%)
38	85	12	72	79	30	38–52
20	91	4	76	NA	24	NA
41	21	0		90	14	NA
ck+			67			
ck–			87			
23	67	2	57	70	49	41
43	92	<1			46	NA
Stage I			71	82		
Stage II			57	79		
46	40	0	72	89	35	NA
7	25	0	80	NA	20	NA
25	40	0	77	85	12	NA
22	39	3	71	85	24	57

statistically significant improvement in both disease-free and overall survival compared to those treated with standard-dose chemotherapy. However, the median response duration and overall survival of patients receiving the standard-dose treatment was short (median 34 weeks and 45 weeks, respectively). Furthermore, <20% of patients treated on the high-dose arm are alive and disease-free at 3 years. A high-priority prospective randomized trial currently being conducted by the Eastern Cooperative Oncology Group (ECOG), the Southwest Oncology Group (SWOG), and the North Central Cancer Treatment Group (NCCTG) which compares high-dose chemotherapy with cyclophosphamide, thiotepa, and carboplatin following 6 cycles of a doxorubicin-based chemotherapy regimen to conventional maintenance chemotherapy with cyclophosphamide, methotrexate, and 5-fluorouracil for 2 years in patients with metastatic breast cancer has just reached its accrual goal. Ancillary studies will compare the relative economic costs and quality of life.

High-dose chemotherapy and stem cell transplantation for high-risk breast cancer

Although a small subgroup of patients with metastatic breast cancer, for example those with limited tumor burden or chemotherapy-sensitive disease, appear to benefit from high-dose chemotherapy, the majority of patients progress because of resistant disease. Consequently, high-dose chemotherapy is being increasingly studied in the adjuvant setting for patients with early-stage, high-risk breast cancer. The first clinical trials with high-dose chemotherapy in patients with high-risk early stage breast cancer involved the subset of patients with ≥10 involved axillary lymph nodes because such patients have a minimal disease burden and are assumed to have chemotherapy-sensitive micrometastases. With the best conventional chemotherapy, such patients have a probability of remaining alive and free of disease at 10 years of 10–30% and a probability of survival of 24% [8, 11]. Initial studies of high-dose chemotherapy in patients with early-stage, high-risk breast cancer have focused on this subset of patients because of their particularly poor prognosis.

Although no prospective randomized trial comparing high-dose chemotherapy with autologous stem cell transplantation to standard adjuvant chemotherapy for patients with high-risk primary breast cancer has been completed, several phase II studies have been reported [7, 20, 22, 23, 25, 375, 41, 43, 46] (Table 4). Peters and colleagues first reported 85 patients treated with 6 cycles of adjuvant chemotherapy which included cyclophosphamide, doxorubicin, and 5-fluorouracil followed by a high-dose chemotherapy regimen which included cyclophosphamide, carboplatin, and BCNU [37]. The actuarial event-free survival was 72% with a median follow-up of 2.5 years. This cohort of patients was compared to an historical control population from 3 earlier adjuvant chemotherapy trials conducted by the Cancer and Leukemia Group B (CALGB) [9, 32, 48]. In the latter population, the event-free survival was 38–52% with 2.5 years of follow-up.

Two other studies testing this strategy in smaller numbers of patients have reported similarly favorable outcomes. Schultz and coinvestigators treated 21 patients with 2 cycles of induction chemotherapy including etoposide, ifosfamide, cisplatin, and epirubicin followed by high-dose chemotherapy which included etoposide, ifosfamide, carboplatin, and epirubicin [41]. After a median follow-up of 13.6 months (4–27 months), 17 of the 21 patients (81%) remained in complete remission and 4 had relapsed. Tomas and colleagues treated 40 patients with stage II or III breast cancer with >10 involved axillary lymph nodes with cyclophosphamide, thiotepa, and carboplatin followed by 6 cycles of anthracycline-based adjuvant chemotherapy [46]. The actuarial event-free survival was 72% at 3 years with a median follow-up of 35 months.

The largest number of patients evaluated prospectively is that reported by Somlo and colleagues [43]. In this study, 114 patients received high-dose chemotherapy including etoposide, cyclophosphamide, and either doxorubicin or cisplatin following standard-dose adjuvant chemotherapy. The estimated relapse-free survival for patients with stage II or IIIA disease is 71% and 57%, respectively, after a median follow-up of 46 months (range 23–93 months). The

Table 5 Prevalence of tumor cell contamination of peripheral blood and/or bone marrow (*BM* bone marrow, *GF* growth factor, *NA* not available, *PBSC* peripheral blood stem cell)

Mobilization method	Disease stage	PBSC (%)	BM (%)	*P* value	Reference
Chemotherapy and/or GF	III/IV	9/48 (19)	32/48 (67)	<0.005	40
Steady-state	IIIB/IV	1/23 (4)	4/27 (15)	NA	34
chemotherapy		2/28 (7)			
+ GF					
GF	II/IIIA with 10 positive nodes	2/57 (4)	30/83 (36)	NA	50
Steady-state	IIIB/IV	1/37 (3)	4/36 (11)	NA	35
chemotherapy		3/38 (8)	NA		
+ GF					
Chemotherapy		26/183 (14)	NA	NA	36
+ GF		26/267 (10)			

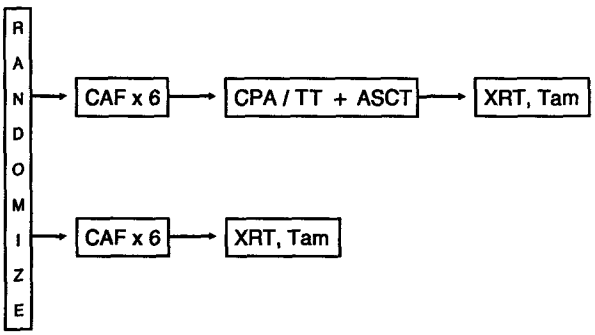

Fig. 3 Schema for Intergroup 0121 (ECOG protocol E2190). *CAF*, cyclophosphamide, doxorubicin, 5-fluorouracil; *CPA* cyclophosphamide; *TT* thiotepa; *ASCT* autologous stem cell transplant; *XRT* radiation; *TAM* tamoxifen

overall survival at 3.5 years is 82% and 79%, respectively. A prognostic factor analysis revealed that the risk of relapse was significantly lower in patients with progesterone receptor-positive disease and higher for patients with inflammatory breast cancer.

Investigators at the Instituto Nazionale di Tumori, Milan, treated 67 patients with sequential cycles of high-dose chemotherapy including cyclophosphamide as a first course followed by methotrexate, cisplatin, and vincristine as a second course and then high-dose melphalan with autologous stem cell rescue followed by locoregional radiation therapy [23]. The actuarial 5-year relapse-free survival was 56% with a median follow-up of 15 months. Finally, the Autologous Blood and Bone Marrow Transplant Registry reported 91 patients with high-risk stage II and III disease who received high-dose thiotepa and cyclophosphamide after standard-dose, doxorubicin-based, adjuvant chemotherapy [2]. The event-free survival was projected to be 75% at 2 years.

All of these recent studies have reported a treatment-related mortality rate of <5%, justifying the risks in this population. Although these preliminary studies are encouraging, it remains unclear whether this approach is definitely superior to conventional chemotherapy for all patients with high-risk disease involving ≥10 axillary lymph nodes or whether this approach would offer an advantage for patients with high-risk disease but <10 involved lymph nodes.

In August 1991, the ECOG, together with the SWOG and the CALGB initiated a randomized prospective trial for patients with stage II or III breast cancer with ≥10 involved axillary lymph nodes (Fig. 3). This National Cancer Institute high-priority clinical trial randomizes patients to either standard-dose adjuvant chemotherapy with 6 cycles of cyclophosphamide, doxorubicin, and 5-fluorouracil (CAF) followed by high-dose chemotherapy with cyclophosphamide and thiotepa or the identical adjuvant chemotherapy program alone. Subsequently, all patients receive locoregional radiation and estrogen receptor-positive patients receive tamoxifen for 5 years. All of the 536 patients needed have been accrued and 193 patients have received treatment with high-dose chemotherapy. This study also prospectively evaluates the incidence and degree of occult marrow contamination due to breast cancer by analyzing samples of marrow using a panel of monoclonal antibodies specific for breast cancer as well as evaluating changes in psychosocial function on the 2 treatment arms. A second trial for patients with stage II or III disease with ≥10 involved lymph nodes, conducted by the CALGB, randomizes patients to 4 cycles of standard-dose CAF chemotherapy followed by either high-dose cyclophosphamide, cisplatin, and carmustine or a lower dose of cyclophosphamide, cisplatin, and carmustine not requiring stem cell support. All patients then receive radiation therapy and tamoxifen. The completion of these 2 trials will help determine whether treatment with high-dose chemotherapy in this patient population results in substantially improved outcome and whether the natural history of the disease has been altered.

Detection of occult breast cancer cells and bone marrow and/or peripheral blood

Tumor cells may contaminate bone marrow and contribute to relapse among patients undergoing high-dose chemotherapy and autologous stem cell transplantation [10, 21, 30, 33–35, 40, 50]. Several studies have addressed the relative degree of tumor cell contamination of blood compared to bone marrow (Table 5) [33, 35, 40, 50]. Using a panel of IgG murine monoclonal antibodies directed against

breast or glandular epithelia, Ross and coinvestigators prospectively investigated the incidence and viability of breast cancer contamination of peripheral blood stem cells and bone marrow from patients with advanced breast cancer in a multiinstitutional study [40]. In this study, breast cancer cells detected by immunocytochemistry were less frequent in peripheral blood stem collections (9/48 or 19%) compared to bone marrow harvests (32/48 or 67%) ($P<0.005$). Immunocytochemical findings correlated well with in vitro clonogenic growth of the tumor cells. Vredenburgh and colleagues compared the degree of tumor cell contamination of progenitor cells harvested from the bone marrow compared to those harvested from the peripheral blood [50]. Tumor cells were detected using a panel of 4 murine monoclonal antibodies reactive with human breast cancer cells using an immunohistochemical technique. Thirty of 83 (36%) evaluable patients undergoing bone marrow harvesting had bone marrow tumor cell contamination compared to only 2 of the 57 patients (4%) undergoing harvesting of growth factor-mobilized peripheral stem cells. Furthermore, patients with tumor cell contamination of the bone marrow had shorter disease-free ($P = 0.04$) and overall survival ($P = 0.02$). There was no relationship between tumor cell contamination of the marrow and sites of relapse. In 2 other studies, the detection of occult breast cancer cells in stem cell collections was associated with a poor outcome [10, 21].

Several studies have compared the incidence of contamination of peripheral blood stem cell collections in patients mobilized with growth factor alone or with both chemotherapy and growth factor. Passos-Coelho and colleagues observed no difference [34], while in a preliminary report from a large multiinstitution study, Pecora et al observed a higher incidence of occult breast cancer cells in peripheral blood stem cell collections mobilized with growth factor alone [36]. These studies suggest that the separation and selection of $CD34^+$ cells which are not contaminated with tumor cells may be important [26, 42].

High-dose chemotherapy for patients with breast cancer is in widespread use. A small subset of patients with metastatic breast cancer may benefit; however, such benefit may reflect selection bias in phase II trials. More encouraging results have been observed in the high-risk adjuvant setting. The results from randomized trials are eagerly awaited. Peripheral blood stem cell harvests appear less contaminated with tumor cells than conventional bone marrow harvests. Whether this observation is clinically relevant requires further studies.

References

1. Antman K, Ayash L, Elias A, Wheeler C, Hunt M, Eder JP, Teicher BA, Critchlow J, Bibbo J, Schnipper LE (1992) A phase II study of high-dose cyclophosphamide, thiotepa, and carboplatin with autologous marrow support in women with measurable advanced breast cancer responding to standard-dose therapy. J Clin Oncol 10:102
2. Antman KH, Rowlings PA, Vaughan WP, Pelz CJ, Fay FW, Fields KK, Freytes CO, Gale RP, Hillner BE, Holland HK, Kennedy MJ, Klein JP, Lazarus HM, McCarthy PL Jr, Saez R, Spitzer G, Stadtmauer EA, Williams SF, Wolff S, Sobocinski KA, Armitage JO, Horowitz MM (1997) High-dose chemotherapy with autologous hematopoietic stem cell support for breast cancer in North America. J Clin Oncol 15:1870
3. Ayash LJ, Elias A, Wheeler C, Reich E, Schwartz G, Mazanet R, Tepler I, Warren D, Lynch C, Goniin R, Schnipper L, Frei E, Antman K (1994) Double dose-intensive chemotherapy with progenitor-cell support for metastatic breast cancer: a feasibility study. J Clin Oncol 12:37
4. Ayash LJ, Wheeler C, Fairclough D, Schwartz G, Reich E, Warren D, Schnipper L, Antman K, Frei E III, Elias A (1995) Prognostic factors for prolonged progression-free survival with high-dose chemotherapy with autologous stem-cell support for advanced breast cancer. J Clin Oncol 13:2043
5. Bensigner WI, Schiffman KS, Holmberg L, Appelbaum FR, Maziarz R, Montgomery P, Ellis E, Rivkin S, Weiden P, Lilleby K, Rowley S, Petersdorf S, Klarnet JP, Nichols W, Hertler A, McCroskey R, Weaver CH, Buckner CD (1997) High-dose busulfan, melphalan, thiotepa and peripheral blood stem cell infusion for the treatment of metastatic breast cancer. Bone Marrow Transplant 19:1183
6. Bezwoda WR, Seymour L, Dansey RD (1995) High-dose chemotherapy with hematopoietic rescue as primary treatment for metastatic breast cancer: a randomized trial. J Clin Oncol 13:2483
7. Bitran JD, Samuels B, Klein L, Schroeder L, Martinec J, Harris E (1996) Autologous bone marrow transplantation (ABMT) for women with stage II and IIIA high risk (greater than 10 involved nodes) breast cancer. Blood Cell and Bone Marrow Transplant Sixth Biennial, Sandoz-Keystone Symposium on Bone Marrow Transplantation. Keystone, Colorado, January 15-21:121 (abstract)
8. Bonadonna G, Valagussa P (1985) Adjuvant systemic therapy for resectable breast cancer. J Clin Oncol 3:259
9. Budman DR, Wood W, Henderson IC, Korzun AH, Cooper R, Younger J, Hart RD, Moore A, Ellerton J, Norton L, Feree C, Colangelo A, McIntyre OR (1992) Initial findings of CALGB 8541: a dose and dose intensity trial of cyclophosphamide (C), doxorubicin (A), and 5-fluorouracil (F) as adjuvant treatment of stage II, node + female breast cancer. Proc Am Soc Clin Oncol 11:51 (abstract)
10. Brockstein BE, Ross AA, Moss TJ, Khan DG, Hollingworth K, Williams SF (1996) Tumor cell contamination of bone marrow harvest products: clinical consequences in a cohort of advanced stage breast cancer patients. J Hematol Therapy 5:617
11. Buzdar AU, Kau S-W, Hortobagyi G, Ames FC, Holmes FA, Fraschini G, Hug V, Theriault RL, McNeese MD, Singletary SE (1992) Clinical course of patients with breast cancer with ten or more positive nodes who were treated with doxorubicin-containing adjuvant therapy. Cancer 69:448
12. Clark GM, Sledge GW Jr, Osborn CK, McGuire WL (1987) Survival from first recurrence: relative importance of prognostic factors in 1,015 breast cancer patients. J Clin Oncol 5:55
13. Clift RA, Buckner CD, Thomas ED (1987) The treatment of acute nonlymphoblastic leukemia by allogeneic bone marrow transplantation. Bone Marrow Transplant 2:243
14. Crump M, Goss PE, Prince M, Girouard C (1996) Outcome of extensive evaluation before adjuvant therapy in women with breast cancer and 10 or more positive axillary lymph nodes. J Clin Oncol 14:66
15. Cummings FJ, Lehman R, Horton J (1985) Comparison of CAF versus CMFP in metastatic breast cancer. Analysis of prognostic factors. J Clin Oncol 3:932
16. Darrington DL, Vose JM, Anderson JR, Bierman PJ, Bishop MR, Chan WC, Morris ME, Reed EC, Sanger WG, Tarantolo SR, Weisenberger DD, Kessinger A, Armitage JO (1994) Incidence and characterization of secondary myelodysplastic syndromes and acute myelogenous leukemia following high-dose chemotherapy and autologous stem-cell transplantation for lymphoid malignancies. J Clin Oncol 12:2527

17. de Magalhaes-Silverman M, Bloom E, Lembersky B, Lister J, Pincus S, Rybka W, Voloshin M, Wilson J, Ball E (1997) High-dose chemotherapy and autologous stem cell support followed by post-transplant doxorubicin as initial therapy for metastatic breast cancer. Clin Cancer Res 3:193
18. Dunphy FR, Spitzer G, Fornoff JE, Yau JC, Huan SD, Dicke KA (1994) Factors predicting long-term survival for metastatic breast cancer patients treated with high-dose chemotherapy and bone marrow support. Cancer 73:2157
19. Eder JP, Antman K, Peters W, Henner WD, Elias A, Shae T, Schryber S, Andersen J, Come S, Schnipper L, Frei E (1986) High-dose combination alkylating agent chemotherapy with autologous bone marrow support for metastatic breast cancer. J Clin Oncol 11:1592
20. Fay J, Jones S, Lynch J, Herzig R, Chistiansen N, Pineiro R, Collins R, Freeman B, Herzig G (1995) The treatment of primary breast cancer with intensive thiotepa (TPA) cyclophosphamide (CPA) and hematopoietic stem cell (HSC) transplantation- A phase II trial of the North American Marrow Transplant Group. Proc Am Soc Clin Oncol 14:117 (abstract)
21. Fields KK, Elfenbein GJ, Trudeau M, Perkins JB, Janssen WE, Moseinski LC (1996) Clinical significance of bone marrow metastases as detected by using the polymerase chain reaction in patients with breast cancer undergoing high-dose chemotherapy and autologous bone marrow transplantation. J Clin Oncol 14:1808
22. Garcia-Carbonero R, Hidalgo M, Paz-Ares L, Calzas J, Gomez H, Guerra JA, Hitt R, Hornedo J, Colomer R, Cortos-Funes H (1997) Patient selection in high-dose chemotherapy trials: relevance in high-risk breast cancer. J Clin Oncol 115:178
23. Gianni AM, Siena S, Bregni M, Di Nicola M, Orefice S, Cugumano F, Salvadori B, Luini A, Greco M, Zucali R, Rilke F, Zambetti M, Valagussa P, Bonadonna G (1997) Efficacy, toxicity and applicability of high-dose sequential chemotherapy as adjuvant treatment in operable breast cancer with 10 or more involved axillary nodes: five-year results. J Clin Oncol 15:2312
24. Gradishar WJ, Tallman MS, Abrams JS (1997) High-dose chemotherapy for breast cancer. Ann Intern Med 125:599
25. Haas R, Schmid H, Hahn U, Hobaus S, Goldschmidt H, Mureas S, Kaufman M, Wannenmacher M, Wallwiener D, Bestert G, Hunstein W (1997) Tandem high-dose therapy with ifosfamide, epirubicin, carboplatin, and peripheral blood stem support is an effective adjuvant treatment for high-risk primary breast cancer. Eur J Cancer 33:372
26. Hohaus S, Pforsich M, Murea S, Abdallah A, Lin Y-S, Funk L, Voso M, Kaul S, Schmid H, Wallwiener D, Haas R (1997) Immunomagnetic selection of $CD34^+$ peripheral blood stem cells for autografting in patients with breast cancer. Br J Haematol 97:881
27. Hyrniuk W, Bush H (1984) The importance of dose intensity in chemotherapy of metastatic breast cancer. J Clin Oncol 2:1281
28. Kaminer LS, Williams SF, Beschorner J, O'Brien S, Golick J, Bitran JD (1989) High-dose chemotherapy with autologous hematopoietic stem cell support in the treatment of refractory stage IV breast carcinoma. Bone Marrow Transplant 4:359
29. Kennedy MJ, Beveridge RA, Rowley SD, Gordon GB, Abeloff MD, Davidson NE (1991) High-dose chemotherapy with reinfusion of purged autologous bone marrow following dose-intensive induction as initial therapy for metastatic breast cancer. J Natl Cancer Inst 83:920
30. Kies MS, Gordon LI, Rosen ST, Kucuk O, Vriesendorp HM (1988) Autologous bone marrow transplantation in breast cancer: separation of clonogenic tumor cell colonies by gradient fractionation. Exp Hematol 16:190
31. Klumpp TR, Mangan KF, Glenn LD, MacDonald JS (1193) Phase II pilot study of high-dose busulfan and cyclophosphamide followed by autologous bone marrow or peripheral blood stem cell transplantation in patients with advanced chemosensitive breast cancer. Bone Marrow Transplant 11:337
32. Lichtman SM, Budman D, Bosworth H, Allen S, Schulman P, Weiselberg L, Weiss R, Lehrman R, Vinciguerra V (1991) Adjuvant therapy of stage II breast cancer treated with CMFVP, radiation therapy and VATH following lumpectomy. Am J Clin Oncol 14:317
33. Passos-Coelho J, Ross A, Davis JM, Huelskamp A, Clarke B, Noga SJ, Davidson N, Kennedy J (1994) Bone marrow micrometastases in chemotherapy-responsive advanced breast cancer: effect of ex-vivo purging with 4-hydroperoxy-cyclophosphamide. Cancer Res 54:2366
34. Passos-Coelho J, Ross A, Kahn D, Moss T, David J, Huelskamp AM, Noga SJ, Davidson NE, Kennedy MJ (1996) Similar breast cancer cell contamination of single-day peripheral blood progenitor cell collections obtained after priming with hematopoietic growth factor alone or after cyclophosphamide followed by growth factor. J Clin Oncol 14:2569
35. Passos-Coelho J, Ross A, Moss TJ, Davis JM, Huelskamp A, Noga S, Davidson N, Kennedy JM (1995) Absence of breast cancer cells in a single-day peripheral blood progenitor cell collection after priming with cyclophosphamide and granulocyte-macrophage colony-stimulating factor. Blood 85:1138
36. Pecora AL, Lazarus H, Cooper B, Copelan E, Hereig R, Meagher R, Kennedy J, Akard L, Jansen J, Isaacs R, Jennis A, Moss TJ (1996) The incidence of breast cancer cell contamination in peripheral blood stem cell collections in relation to the mobilization regimen. Blood 88 (suppl 1):408a
37. Peters WP, Ross M, Vredenburgh J, Meisenberg B, Marks LB, Winer E, Kurtzberg J, Bast RC, Jones R, Shpall E, Wu K, Rosner G, Gilber C, Mathias B, Coniglio D, Petros W, Henderson C, Norton L, Weiss RB, Budman D, Hurd D (1993) High-dose chemotherapy and autologous bone marrow support as consolidation after standard-dose adjuvant therapy for high-risk primary breast cancer. J Clin Oncol 11:132
38. Peters WP, Shpall E, Jones RB, Olsen GA, Bast RC, Gockerman JP, Moore JO (1988) High-dose combination alkylating agents with bone marrow support as initial treatment for metastatic breast cancer. J Clin Oncol 6:1368
39. Rahman ZU, Frye KD, Buzdar AU, Smith TL, Asmar L, Champlin RE, Hortobagyi GN (1997) 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 15:3171
40. Ross A, Cooper B, Lazarus H, Mackay W, Moss T, Ciobanu N, Tallman MS, Kennedy MJ, Davidson N, Sweet D, Winter C, Akard L, Jansen J, Copelan E, Meagher RC, Herzig R, Klumpp T, Kahn DG, Warner N (1993) Detection and viability of tumor cells in peripheral blood stem cell collections from breast cancer patients using immunocytochemical and clonogenic assay techniques. Blood 82:2605
41. Schulze R, Schulze M, Wischnik A, Ehnle S, Doukas K, Behr W, Ehret W, Schlimok G (1997) Tumor cell contamination of peripheral blood stem cell transplants and bone marrow in high-risk breast cancer patients. Bone Marrow Transplant 19:1223
42. Shpall E, Jones B, Bearman S, Franklin W, Archer P, Curiel T, Bitter M, Claman H, Stemmer S, Purdy M, Myers S, Hami L, Taffs S, Heimfeld S, Hallagan J, Berenson R (1994) Transplantation of enriched CD34-positive autologous marrow into breast cancer patients following high-dose chemotherapy: influence of CD34-positive peripheral-blood progenitors and growth factors on engraftment. J Clin Oncol 12:28
43. Somlo G, Doroshow JH, Forman SJ, Odom-Maryaon T, Lee J, Chow W, Hamasaki V, Leong L, Morgan R, Margolin K, Raschko J, Shibata S, Tetef M, Yen Y, Simpson J, Molina A (1997) High-dose chemotherapy and stem-cell rescue in the treatment of high-risk breast cancer: prognostic indicators of progression-free and overall survival. J Clin Oncol 15:2882
44. Stone RM, Neuberg D, Soiffer R, Takvorian T, Whelan M, Rabinowe S, Aster JC, Leavit P, Mauch P, Freedman AS, Nadler LM (1994) Myelodysplastic syndrome as a late complication following autologous bone marrow transplantation for non-Hodgkin's lymphoma. J Clin Oncol 12:2535

45. Tallman MS, Rademaker AW, Jahnke L, Brown SG, Bauman A, Magnan C, Kelly C, Rubin H, Gradishar WJ, Winter JN (1997) High-dose chemotherapy, autologous bone marrow or stem cell transplantation and post-transplant consolidation chemotherapy in patients with advanced breast cancer. Bone Marrow Transplant 20:721
46. Tomas JF, Perez-Carrion R, Escudero A, Lopez-Lorenzo JL, Lopez-Pascual J, Fernandez-Rañada JM (1997) Results of a pilot study of 40 patients using high-dose therapy with hematopoietic rescue after standard-dose adjuvant therapy for high-risk breast cancer. Bone Marrow Transplant 19:331
47. Tormey DC, Gelman R, Band PR, Sears M, Rosenthal SN, Dewys W, Perlia C, Rice MA (1982) Comparison of induction chemotherapy for metastatic breast cancer: an Eastern Cooperative Oncology Group trial. Cancer 50:1235
48. Tormey DC, Weinberg VE, Holland JF, Weiss RB, Glidewell OJ, Perloff M, Falkson G, Falkson HC, Henry PH, Leone LA, Rafla S, Ginsberg SJ, Silver RT, Blom J, Carey RW, Schein PS, Lesnick GJ (1983) A randomized trial of five and three drug chemotherapy and chemoimmunotherapy in women with operable node positive breast cancer. J Clin Oncol 1:138
49. Vaughan WP, Reed ED, Edwards B, Kessinger A (1994) High-dose cyclophosphamide, thiotepa and hydroxyurea with autologous hematopoietic stem cell rescue: an effective consolidation chemotherapy regimen for early metastatic breast cancer. Bone Marrow Transplant 13:619
50. Vredenburgh J, Silva O, Broadwater G, DeSombre K, Petros W, Peters W, Bast RC (1997) The significance of tumor contamination in the bone marrow from high-risk primary breast cancer patients treated with high-dose chemotherapy and hematopoietic support. Biol Blood Marrow Transplant 3:91
51. Wallerstein R, Spitzer G, Dunphy F, Huan S, Hortobagi G, Yau J (1990) A phase II study of mitoxantrone, etoposide, and thiotepa with autologous marrow support for patients with relapsed breast cancer. J Clin Oncol 8:1782
52. Williams SF, Gilewski T, Mick R, Bitran JD (1992) High-dose consolidation therapy with autologous stem cell rescue in stage IV breast cancer: follow-up report. J Clin Oncol 10:1743
53. Wood WC, Budman DR, Korzun AH, Cooper MR, Younger J, Hart RD, Moore A, Ellerton JA, Norton L, Ferree CR, Ballow AC, Frei E, Henderson IC (1994) Dose and dose intensity of adjuvant chemotherapy for stage II, node-positive breast carcinoma. N Engl J Med 330:1253