? BENEFIT

Am J Health Syst Pharm 1996 Mar 1;53(5):521-534

High-dose chemotherapy with stem-cell rescue for the treatment of breast cancer.

McCauley DL

Department of Pharmacy, State University of New York, Stony Brook 11794-7310, USA.

The use of high-dose chemotherapy with stem-cell rescue (HDC-SCR) in the treatment of breast cancer is reviewed. The rationale for HDC-SCR in breast cancer is based on the principles of dose response and dose intensity. After conventional-dose chemotherapy, hematopoietic progenitor cells are harvested from the bone marrow or peripheral blood. The patient then undergoes HDC-SCR. Peripheral-blood progenitor cells are becoming the preferred cells for hematopoietic rescue. Most clinical trails of HDC-SCR in metastatic breast cancer have resulted in high overall objective response rates (57-100%), with the highest rates occurring in patients with minimal residual disease or chemotherapy-sensitive disease at the time of high-dose treatment. Most protocols now include induction therapy before HDC-SCR; only patients who show sensitive disease proceed to high-dose therapy. In most studies published to date, the median duration of remission was less than one year from the time of high-dose therapy; however, 10-15% of patients achieved complete remissions lasting two or more years. Most patients relapse, however. Some studies have suggested value of HDC-SCR as consolidation therapy in the adjuvant setting for women at high risk of relapse. Short-term toxicities of HDC-SCR are manageable in experienced hands. Notable long-term adverse effects include leukemia, sterility, pulmonary toxicity, and hemolytic uremic syndrome. Unresolved issues include the utility of purging occult cancer cells from stem-cell-bearing specimens, the best preparative regimen, the implications of autologous graft versus-host disease, the use of sequential cycles of high-dose chemotherapy, cost-effectiveness, and effectiveness compared with standard therapy. HDC-SCR appears to be a valid option for selected patients with metastatic breast cancer, and in the adjuvant setting for patients at high risk of recurrence. The cost-benefit profile remains to be defined in randomized trials.

MeSH Terms:

- Antineoplastic Agents/therapeutic use*
- Antineoplastic Agents/adverse effects
- Antineoplastic Agents/administration & dosage*
- Breast Neoplasms/therapy*
- Breast Neoplasms/drug therapy
- Combined Modality Therapy
- Female
- Hematopoietic Stem Cell Transplantation*
- Human

Substances:

CLINICAL REVIEW

High-dose chemotherapy with stem-cell rescue for the treatment of breast cancer

DAYNA L. MCCAULEY

Abstract: The use of high-dose chemotherapy with stem-cell rescue (HDC–SCR) in the treatment of breast cancer is reviewed.

The rationale for HDC–SCR in breast cancer is based on the principles of dose response and dose intensity. After conventional-dose chemotherapy, hematopoietic progenitor cells are harvested from the bone marrow or peripheral blood. The patient then undergoes HDC–SCR. Peripheral-blood progenitor cells are becoming the preferred cells for hematopoietic rescue. Most clinical trials of HDC–SCR in metastatic breast cancer have resulted in high overall objective response rates (57–100%), with the highest rates occurring in patients with minimal residual disease or chemotherapy-sensitive disease at the time of high-dose treatment. Most protocols now include induction therapy before HDC–SCR; only patients who show sensitive disease proceed to high-dose therapy. In most studies published to date, the median duration of remission was less than one year from the time of high-dose therapy; however, 10–15% of patients achieved complete remissions lasting two or more years. Most patients relapse, however. Some studies have suggested value of HDC–SCR as consolidation therapy in the adjuvant setting for women at high risk of relapse. Short-term toxicities of HDC–SCR are manageable in experienced hands. Notable long-term adverse effects include leukemia, sterility, pulmonary toxicity, and hemolytic uremic syndrome. Unresolved issues include the utility of purging occult cancer cells from stem-cell-bearing specimens, the best preparative regimen, the implications of autologous graft-versus-host disease, the use of sequential cycles of high-dose chemotherapy, cost-effectiveness, and effectiveness compared with standard therapy.

HDC–SCR appears to be a valid option for selected patients with metastatic breast cancer, and in the adjuvant setting for patients at high risk of recurrence. The cost-benefit profile remains to be defined in randomized trials.

Index terms: Antineoplastic agents; Breast neoplasms; Clinical studies; Combined therapy; Dosage; Economics; Toxicity; Transplantation

Am J Health-Syst Pharm. 1996; 53:521-34

Breast cancer is a topic of intense interest today. One in every 10 women is expected to develop breast cancer during her lifetime.[1] Unprecedented amounts of local, state, and federal dollars are being allocated to breast cancer research. Factors possibly associated with an increased risk of breast cancer (e.g., estrogen replacement therapy, genetic factors) are routinely discussed in the media.[2,3] As health care costs continue to escalate, discussions about breast cancer can become highly charged. One of the most controversial issues is the appropriate role and timing of bone marrow transplantation (now referred to as high-dose chemotherapy with stem-cell rescue [HDC–SCR]) in the treatment of breast cancer; this topic is the subject of heated debate in the medical community and the insurance industry in this country.

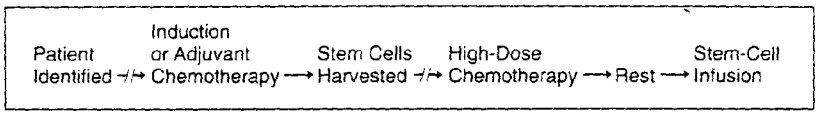
This article discusses the use of HDC–SCR in the treatment of breast cancer, the results of published clinical trials, and trials in progress. Financial considerations and unresolved issues are also considered. For details on the epidemiology, diagnosis, staging, treatment principles, and prognosis of breast cancer, the reader is referred elsewhere.[1,4]

DAYNA L. MCCAULEY, PHARM.D., is Specialist, Bone Marrow Transplantation, and Clinical Coordinator, Department of Pharmacy, Box 7310, State University of New York, Stony Brook, NY 11794-7310.

The reviews of Dr. Jonathan S. Harrison and Dr. Steven Sugarman are acknowledged.

This is **article 204-000-96-004-H01** in the **ASHP Continuing Education System**; it qualifies for 1.5 hours of continuing-education credit. See page 561 for learning objectives and test questions.

Figure 1. Sequence of events in high-dose chemotherapy with stem-cell rescue for the treatment of breast cancer. Interrupted arrows represent possible substantial time delays.



High-dose chemotherapy with stem-cell rescue

High-dose chemotherapy followed by hematopoietic progenitor-cell rescue is a method of providing escalating doses of cytotoxic drugs to treat a disease. Infusion of hematopoietic progenitor cells after myeloablative chemotherapy restores hematopoiesis, thus "rescuing" the patient from otherwise dose-limiting hematologic toxicity. This procedure, once broadly referred to as bone marrow transplantation (BMT), has been redefined, as bone marrow is no longer the sole source of hematopoietic progenitor cells. These cells are now obtained from either bone marrow or peripheral blood.

There are differences between bone marrow and peripheral-blood progenitor cells that deserve discussion. Bone marrow contains a mixture of true pluripotent (also known as totipotent) stem cells and early committed myeloid and lymphoid stem cells. Under normal conditions, these stem cells reside in the bone marrow in a quiescent state and do not circulate to any significant degree in the peripheral blood. The few marrow cells that circulate in the peripheral blood are usually not stem cells but late committed hematopoietic progenitor cells that go on to differentiate into the various hematopoietic cell lines. When bone marrow or peripheral blood is obtained from a patient for use after myeloablative chemotherapy, the goal is to obtain progenitor cells that can restore hematopoiesis. A specimen of pure pluripotent stem cells is most desirable. However, a surface marker unique to these cells has yet to be identified in humans. A recently identified cell-surface antigen known as CD34 is expressed on a mixture of early stem cells and more mature, lineage-committed precursor cells. CD34+ cells are capable of establishing and maintaining long-term hematopoiesis. Thus, cells marked with the CD34 antigen (i.e., a mixture of hematopoietic progenitor cells), and not pure stem cells, are currently the cells sought from a bone marrow or peripheral-blood specimen. The term "stem-cell rescue" is commonly, but somewhat inaccurately, used in clinical practice to describe hematopoietic rescue regardless of whether bone marrow or peripheral blood is used as the source. For simplicity, "stem-cell rescue" will be used throughout this article to describe rescue with hematopoietic progenitor cells from any source.

The basic sequence of events in HDC–SCR for breast cancer is shown in Figure 1. Once an appropriate candidate patient is identified, three to six cycles of conventional-dose chemotherapy are administered to document chemotherapy-responsive disease. After conventional-dose chemotherapy, hematopoietic progenitor cells are obtained from the patient's bone marrow, peripheral blood, or both. These cells may be stored for only a few days, or for several years, before use. The patient is subsequently admitted to the hospital for HDC–SCR. The high-dose chemotherapy regimens used with stem-cell infusions are referred to as conditioning or preparative regimens. Characteristics of drugs commonly used in preparative regimens before stem-cell infusion include: (1) inherent activity and a steep dose–response curve against the malignancy being treated, (2) dose-limiting hematopoietic toxicity, and (3) nonoverlapping nonhematologic toxicities among the drugs in question.[5] After the preparative regimen and a rest period of one to several days, stem cells are infused into the patient. Rest days allow the elimination of metabolites that could be cytotoxic to the infused progenitor cells. The number of days of rest is a function of the half-lives of the drugs administered.

Bone marrow is obtained under spinal or general anesthesia in an operating room under sterile conditions.[6] Marrow is obtained by multiple aspirations from the anterior or posterior iliac crests, which contain a mixture of pluripotent stem cells and early committed stem cells of both myeloid and lymphoid lineages. The bone marrow is then processed to remove fat and marrow spicules, frozen, and stored.[6] Occasionally, bone marrow is manipulated outside the body with chemical or immunologic agents in an effort to remove occult malignant cells before storage (this is referred to as purging)[6] or to select for colonies of CD34+ cells. At the time of stem-cell rescue, the autologous bone marrow is thawed and then infused into the patient (like a blood transfusion). The infused stem cells home in on the patient's bone marrow cavity, lodge there, and re-establish hematopoiesis.

Peripheral-blood progenitor cells (PBPCs) are obtained during apheresis, an outpatient procedure similar to dialysis.[7] Daily apheresis procedures of three to six hours' duration are performed until an adequate number of CD34+ cells have been obtained. Because the number of early hematopoietic cells ordinarily circulating in the peripheral blood is small, antineoplastic agents (e.g., cyclophosphamide) or hematopoietic growth factors (e.g., filgrastim, sargramostim) or both are commonly used as priming agents.[7-9] Under the influence of these agents, an adequate yield of early and

late hematopoietic progenitor cells can be obtained, often after only one or two long apheresis sessions. Once PBPCs have been obtained, they are processed, frozen, and stored like autologous bone marrow.

PBPCs are rapidly becoming the preferred cells for hematopoietic rescue in patients undergoing high-dose chemotherapy for solid tumors. These cells, alone or in combination with hematopoietic growth factors, shorten the time to hematopoietic recovery (engraftment) compared with autologous bone marrow.[10,11] Shortening the time to engraftment not only decreases the risk of infection and bleeding but can reduce the duration of hospitalization.[10,11] Another advantage is avoidance of potential complications from the general anesthesia required for obtaining bone marrow. Although PBPCs can be obtained in the outpatient setting, the overall cost is similar to that of obtaining bone marrow. The avoidance of hospital and operating room charges is largely offset by the need for expensive equipment and the high processing fees associated with outpatient apheresis. Although early studies of HDC–SCR for breast cancer treatment involved the use of autologous bone marrow, many investigators are now using PBPCs or a combination of PBPCs and bone marrow. Whether bone marrow, peripheral blood, or both sources of stem cells are used does not influence the response of the disease to this therapy.

Rationale

The fundamental rationale for HDC–SCR in the treatment of solid tumors, including breast cancer, is based on the principles of dose response and dose intensity. Dose response refers to the increase in logarithmic cell killing observed with higher doses of some antineoplastic drugs (e.g., alkylating agents) for some tumor cell lines in vitro.[12] For tumors showing a linear dose–response curve, higher doses of cytotoxic drugs should theoretically kill a higher percentage of tumor cells and ultimately improve the cure rate. Dose intensity refers to the amount of an antineoplastic agent administered per unit of time. Dose intensity could be decreased either by decreasing the dose or delaying treatment. Higher dose intensity is widely accepted as being associated with better responses and higher cure rates for some malignancies.

The design of clinical trials involving HDC–SCR for breast cancer is predicated on preclinical data,[12,13] retrospective reviews,[14,15] and prospective trials[16-18] supporting the position that dose intensity is important in the treatment of early and metastatic breast cancer. However, this position is not accepted by all breast cancer experts.[19-22] Opponents cite equally valid arguments and clinical trials refuting the thesis that breast cancer is a dose-responsive malignancy.[19,20]

Clinical applications

HDC–SCR for the treatment of breast cancer has its origins in two seminal Phase I studies published in the mid-1980s. Peters et al.[23] administered high-dose cyclophosphamide (1500–5625 mg/sq m), cisplatin (75–165 mg/sq m), and carmustine (150–600 mg/sq m), with or without melphalan (40–80 mg/sq m), to 29 patients with refractory or unresectable solid tumors (including 3 patients with metastatic breast cancer). Autologous bone marrow was then infused. Objective responses occurred in 84% of the patients, including one patient with breast cancer who had a complete response. Eder et al.[24] administered high-dose cyclophosphamide (6000 mg/sq m) and thiotepa (180–680 mg/sq m) to 23 patients with advanced, refractory solid tumors (2 patients also received melphalan 40 mg/sq m). After rescue with autologous bone marrow, objective responses were noted in 54% of the patients, including six of eight patients with metastatic breast cancer. Although the median duration of remission was short in both of these studies (5.2 and 2 months, respectively), they confirmed laboratory observations that very-high-dose chemotherapy could overcome inherent or acquired tumor resistance in vivo. In addition, these studies helped establish the maximum tolerated doses for antineoplastic agents used in preparative regimens today.

Metastatic breast cancer. Table 1 summarizes representative studies of HDC–SCR as first-line or second-line therapy for metastatic breast cancer.[25-37] Eligibility criteria varied, but the studies usually included young, premenopausal women who had normal renal, hepatic, cardiac, pulmonary, and hematopoietic function and who were free of concomitant medical illnesses. All but one study[36] excluded women with metastasis to the central nervous system or bone marrow, since the prognosis in such patients is dismal.[1] Most preparative regimens included combinations of alkylating agents (e.g., cyclosphosphamide with thiotepa and carboplatin or with cisplatin and carmustine), drugs that have demonstrated single-agent or synergistic activity against breast cancer.

Most trials of HDC–SCR in metastatic breast cancer have resulted in high overall objective response rates (57–100%).[10,25-37] The highest response rates were seen in patients with minimal residual disease or chemotherapy-sensitive disease at the time of high-dose chemotherapy. For example, higher responses were seen in patients who had not received adjuvant chemotherapy,[30] patients with minimal or no prior chemotherapy for metastatic disease,[25,26] patients in whom there had been a long period between diagnosis and first relapse,[34,35] and patients partially or completely responding to induction chemotherapy preceding high-dose chemotherapy.[27-30,33,34] Thus, most current protocols have evolved to include induction chemotherapy for several cycles before HDC–SCR (Figure 1). Only patients who demonstrate chemotherapy-sensitive disease (i.e., obtain a partial or complete response) proceed to high-dose therapy. Drugs and dosages used in induction

Table 1.
Summary of Clinical Trials of High-Dose Chemotherapy with Stem-Cell Rescue for Metastatic Breast Cancer

Ref.	No. Patients	Prior Chemotherapy for Metastatic Disease?	Induction Chemotherapy Administered?	High-Dose Chemotherapy Regimen	Overall Response Rate (%)[a]	Median Duration of Remission	Regimen-Related Mortality Rate (%)
25	17	Yes	No	Cyclophosphamide 1875 mg/sq m i.v. over 1 hr daily × 3 days (days −7, −6, and −5[b]), cisplatin 55 mg/sq m CIVI[c] daily × 3 days (days −7, −6, and −5), and carmustine 600 mg/sq m i.v. × 1 day (day −4) (administered at 5 mg/sq m/min)	88	5 mo	18
26	22	No	No	Cyclophosphamide 1875 mg/sq m i.v. over 1 hr daily × 3 days (days −6, −5, and −4), cisplatin 55 mg/sq m CIVI daily × 3 days (days −6, −5, and −4), and carmustine 600 mg/sq m i.v. × 1 day (day −3) (administered at 5 mg/sq m/min)	77	9 mo in pts. with complete response only	22
27	27	No	Yes	Cyclophosphamide 2.5 g/sq m i.v. daily × 3 days (days −6, −4, and −2), and thiotepa 225 mg/sq m i.v. daily × 3 days (days −6, −4, and −2)	86 in 22 pts. proceeding to HDC[d]	6 mo from HDC	15 overall; 18 for HDC pts. only
28	58	No	Yes	Cyclophosphamide 1.5–1.75 g/sq m i.v. over 1 hr daily × 3 days, etoposide 250–400 mg/sq m i.v. daily × 3 days, and cisplatin 40–60 mg/sq m i.v. over 2 hr daily × 3 days; cycle repeated at approximately 1 mo	85 in all pts.	57 wk from induction	9
29	30	No	Yes	Cyclophosphamide 1.5 g/sq m/day CIVI daily × 4 days and thiotepa 200 mg/sq m/day CIVI daily × 4 days	80	13 mo from induction	0
30	59	No	Yes	Cyclophosphamide 7.5 g/sq m total and thiotepa 675 mg/sq m total, with or without carmustine 450 mg/sq m total (administration schedule not specified)	71 in pts. proceeding to HDC	7.5 mo from HDC	30 overall; 22 for HDC pts. only
31	6	No	Yes	Carboplatin 500 mg/sq m i.v. over 15 min daily × 3 days (days −7, −5, and −3) and mitoxantrone 40–50 mg/sq m i.v. over 4 hr × 1 day (day −7)	40 (no complete responses)	NA[e]	30
32	39	Yes in 25 pts.	No	Cyclophosphamide 60 mg/kg/day i.v. daily × 2 days (days −3 and −2), thiotepa 225–300 mg/sq m i.v. daily × 3 days (days −11, −10, and −9), and cisplatin 50–100 mg/sq m i.v. × 2 days (days −11 and −3)	67	8 mo for pts. in complete remission; 4 mo for pts. in partial remission	15
33	29	Yes	Yes	Cyclophosphamide 1.5 g/sq m CIVI daily × 4 days (days −7, −6, −5, and −4), thiotepa 125 mg/sq m CIVI daily × 4 days (days −7, −6, −5, and −4), and carboplatin 200 mg/sq m CIVI daily × 4 days (days −7, −6, −5, and −4)	100	10 mo from induction; 19 mo from HDC in patients with complete response	3
34	18	Yes	Yes	Cyclophosphamide 100 mg/kg i.v. × 1 day (day −3), etoposide 30 mg/kg/day i.v. × 2 days (days −12 and −5), and cisplatin 50–150 mg/sq m i.v. × 2 days (days −12 and −5)	NA	20% estimated PFS[f] rate at 2 yr; 7 of 10 pts. with complete response 4–32 mo after HDC	7
35	20	Unknown	Yes	Cycle 1: melphalan 140–180 mg/sq m i.v. × 1 day (administered in two doses 12 hr apart); cycle 2 (median of 25 days later): cyclophosphamide 6 g/sq m, carboplatin 800 mg/sq m, and thiotepa 500 mg/sq m (all administered CIVI over 96 hr on days −7 to −3)	90	52% PFS rate at 15 mo	0

Continued on next page

Table 1 (*continued*)

Ref.	No. Patients	Prior Chemotherapy for Metastatic Disease?	Induction Chemotherapy Administered?	High-Dose Chemotherapy Regimen	Overall Response Rate (%)[a]	Median Duration of Remission	Regimen-Related Mortality Rate (%)
36	26	Yes	Yes	Cyclophosphamide 1.5 g/sq m/day CIVI daily × 4 days (days −7 to −3), thiotepa 150 mg/sq m/day CIVI daily × 4 days (days −7 to −3), and hydroxyurea 1500 mg/sq m/dose p.o. q 6 hr × 12 doses total (days −3, −2, and −1)	NA	27% estimated PFS rate at 2 yr	12
37	14	Yes	No	Melphalan 130 mg/sq m i.v. × 1 (day −5), cyclophosphamide 50 mg/kg/day i.v. × 3 days (days −4, −3, and −2), and carboplatin 400 mg/sq m/day CIVI daily × 3 days (days −4, −3, and −2)	57	2.9 mo	9

[a]Complete plus partial responses.
[b]Days before stem-cell infusion (day 0).
[c]CIVI continuous intravenous infusion.
[d]HDC = high-dose chemotherapy.
[e]NA = not applicable.
[f]PFS = progression-free survival.

regimens vary, but most include doxorubicin, the single most active agent in the treatment of breast cancer. In all studies, the median duration of remission was short (less than one year from the time of high-dose therapy).[10,25-37] However, 10–15% of patients had complete remissions lasting two or more years.[25-30,33,34] These patients were generally patients who were in complete remission after induction chemotherapy at the time of HDC–SCR. In addition, there have been many reports of patients who were converted from a partial response during induction chemotherapy to a complete response after HDC–SCR,[27,29,30,33,35] and several of these patients attained prolonged complete remissions.

Most of the patients in these trials relapsed. The most common site of relapse was the site of prior bulky disease.[10,25-30,38] Consequently, many clinicians now irradiate sites of prior bulky disease after HDC–SCR in an attempt to help attain or maintain a complete remission.[29,32-35,37,38] Other attempts to minimize the possibility of relapse include giving patients with estrogen-receptor-positive disease tamoxifen after HDC–SCR.[29,32-34,37]

A few authors have attempted to identify patient factors associated with improved survival after HDC–SCR for metastatic breast cancer. In a univariate analysis of 80 patients, an absence of liver involvement, an absence of a soft-tissue-site relapse, a small number of metastatic sites, and a disease-free interval of longer than one year from the time of diagnosis to the time of relapse were factors associated with improved survival.[39] When a multivariate analysis was applied for the same patients, hepatic metastases, soft-tissue disease, and prior adjuvant chemotherapy were negative predictors of overall survival.[39] Other factors associated with improved outcome included no prior chemotherapy,[25,30] inflammatory breast cancer,[25] a long interval from the time of adjuvant therapy to the time of relapse,[34,35] and estrogen-receptor-positive tumors.[33,34] Most of these studies were too small to allow definitive conclusions about risk factors associated with a good or a poor prognosis.

HDC–SCR induces high overall response rates in patients with metastatic breast cancer. However, the key question in today's health care climate is whether this strategy provides a survival benefit relative to conventional chemotherapy. In an attempt to answer this question, Eddy[20] conducted a comprehensive review of the literature published before October 1991 evaluating standard therapy and HDC–SCR for metastatic breast cancer. The weighted averages for complete and overall response rates for all patients treated with HDC–SCR were 36% and 70%, respectively. These averages were superior to the weighted averages for complete and overall response rates of 8% and 39%, respectively, for patients given conventional chemotherapy. In contrast, when overall survival data were evaluated, there was no additional survival benefit for patients who had undergone HDC–SCR. The weighted-average survival times for patients undergoing HDC–SCR and patients given conventional chemotherapy were 16 and 16.6 months, respectively. From these and other results, Eddy concluded that HDC–SCR is not superior to conventional chemotherapy for metastatic breast cancer, and is substantially more toxic.

Since Eddy's review paper appeared, one randomized trial of HDC–SCR for the primary treatment of metastatic breast cancer has been published.[40] Ninety women 50 years of age or younger with previously untreated metastatic breast cancer (hormonal therapy

was allowed) were randomly assigned to receive either two cycles of high-dose chemotherapy (cyclophosphamide 2.4 g/sq m, mitoxantrone 35–45 mg/sq m, and etoposide 2.5 g/sq m) followed by stem-cell support or six to eight cycles of conventional chemotherapy (cyclophosphamide 600 mg/sq m, mitoxantrone 12 mg/sq m, and vincristine sulfate 1.4 mg/sq m). The two groups were similar with respect to mean age, performance status, menopausal status, estrogen-receptor status, and any prior adjuvant chemotherapy. As in the nonrandomized trials, the complete and overall response rates were significantly higher in the HDC–SCR group (51% and 95%, respectively) than in the standard chemotherapy group (4% and 53%, respectively). However, in contrast to the findings of Eddy,[20] both the median duration of response and the median survival time were significantly longer in the HDC–SCR patients (80 and 90 weeks, respectively) than in the conventional chemotherapy group (34 and 45 weeks). Although toxicities were more severe in the HDC–SCR group, there were no treatment-related deaths in either group. This was the first published randomized trial to suggest that HDC–SCR may be superior to conventional chemotherapy as a first-line treatment of metastatic breast cancer.

At least two randomized Phase III trials comparing HDC–SCR and conventional chemotherapy for metastatic breast cancer have been completed or are under way in the United States. One study (Intergroup 0127) was closed to new subjects in 1994. Patients responding to induction chemotherapy were randomly assigned to receive nine or more cycles of induction chemotherapy or HDC–SCR under the STAMP (Solid Tumor Autologous Marrow Program)-V protocol (cyclophosphamide 1500 mg/sq m/day, thiotepa 125 mg/sq m/day, and carboplatin 200 mg/sq m/day, all given by continuous i.v. infusion for four days). All patients had to have undergone at least one prior regimen of chemotherapy for metastatic disease, and patients with estrogen-receptor-positive tumors had to have failed to respond to hormonal therapy. The primary endpoint of this trial is to determine if HDC–SCR improves survival compared with standard therapy. The analysis will involve stratifying patients by extent of disease, site and number of metastases, and induction regimen.

In another randomized Phase III trial (Southwest Oncology Group 9412), women with metastatic breast cancer are first undergoing four to six cycles of induction chemotherapy (with standard dosages of cyclophosphamide, doxorubicin, and fluorouracil [or methotrexate substituted for doxorubicin if the patient has previously been treated with doxorubicin]). Responding patients then receive either two years of maintenance therapy with CMF (cyclophosphamide 100 mg/sq m orally daily on days 1–14, methotrexate 40 mg/sq m i.v. on days 1 and 8, fluorouracil 600 mg/sq m i.v. on days 1 and 8; cycle repeated every 28 days) or HDC–SCR under the STAMP-V protocol. Overall survival rates, toxicity, economic costs, and quality of life will be compared between the two groups. By July 1995, 333 patients had been enrolled in this study; the goal is 549 patients.

These two trials, and other randomized trials, should provide definitive answers to questions about whether HDC–SCR confers a survival benefit relative to standard therapy.

Adjuvant treatment for patients at high risk of relapse. Patients with large primary tumors or tumor invasion of four or more lymph nodes at the time of diagnosis are at high risk of relapse.[1] For example, the risk of recurrence within five years is 65–80% for women who have primary lesions measuring ≥5 cm and axillary lymph nodes positive for malignancy.[1] In contrast, the five-year risk of recurrence for women with primary lesions of <2 cm and negative axillary lymph nodes is only 8–13%. High rates of objective responses to HDC–SCR as first-line therapy for early metastatic breast cancer,[26-30] plus the documented dose–response association for chemotherapy in the adjuvant setting,[15,17,18] prompted the evaluation of HDC–SCR as adjuvant therapy for breast cancer. However, because morbidity and mortality rates can be high with HDC–SCR (Table 1), only patients at high risk of relapse after standard adjuvant therapy have been evaluated. A growing number of studies have evaluated HDC–SCR as consolidation therapy for women with primary breast cancer who are at high risk of relapse.[31,34,37,41-46]

Studies with the largest number of patients are summarized in Table 2.[34,41-43,46,47] In several[41-43] but not all[44] of the studies, the definition of high risk included stage II or III disease and 10 or more axillary lymph nodes positive for cancer. The majority of the studies combined a program of standard-dose adjuvant chemotherapy (usually with a doxorubicin-containing regimen), HDC–SCR, and local radiation therapy and tamoxifen if the patient's tumor was estrogen-receptor positive. The radiation therapy and tamoxifen were used in hopes of providing further protection against relapse.

Peters et al.[41] conducted the most informative trial of HDC–SCR in this high-risk patient population to date. Eighty-five women with stage II or III disease and 10 or more positive axillary lymph nodes underwent standard-dose adjuvant therapy with four cycles of cyclophosphamide, doxorubicin, and fluorouracil followed by HDC–SCR (see Table 2 for the preparative regimen). The patients then received chest-wall and lymph-node irradiation, followed by tamoxifen therapy if their tumors were estrogen-receptor positive. A progression-free survival rate of 72% was reported at a median follow-up time of 2.5 years. The results were recently updated to a median follow-up time of five years; the survival rate remained virtually unchanged.[47] Comparison with other large trials in comparable high-risk patients given conventional adjuvant chemotherapy

Table 2.
Summary of Clinical Trials of High-Dose Chemotherapy with Stem-Cell Rescue as Consolidation Therapy for Patients with Primary Breast Cancer at High Risk of Relapse

Ref.	No. Patients	High-Dose Chemotherapy Regimen[a]	Progression-Free Response Rate (%) and Median Duration of Follow-up	Regimen-Related Mortality Rate (%)
34	11	Cisplatin 50–150 mg/sq m on days –12 and –5,[b] etoposide 30 mg/kg on days –12 and –5, and cyclophosphamide 100 mg/kg on day –3	64 (16+ mo)	7
41, 47	85	Cyclophosphamide 1875 mg/sq m daily x 3 days, cisplatin 55 mg/sq m daily x 3 days, and carmustine 600 mg/sq m x 1 day	72 (2.5 yr), 71 (5 yr)	12
42	47	Cyclophosphamide 1500 mg/sq m daily x 4 days, thiotepa 125 mg/sq m daily x 4 days, and carboplatin 200 mg/sq m daily x 4 days	87 (412 days)	2
43	91	Cyclophosphamide 5625 mg/sq m, cisplatin 165 mg/sq m, and carmustine 450 mg/sq m	91 (772 days)	0
46	19	Cyclophosphamide 1500 mg/sq m daily x 4 days, thiotepa 125 mg/sq m daily x 4 days, and carboplatin 200 mg/sq m daily x 4 days	79 (4 mo)	0

[a]All the studies included several courses of standard-dose adjuvant chemotherapy before the high-dose chemotherapy, followed by irradiation of the original site of bulky disease, and tamoxifen for estrogen-receptor positive tumors after consolidation with high-dose chemotherapy. All doses were given intravenously.
[b]Days before stem-cell infusion (day 0).

reveals a substantial progression-free survival advantage for HDC–SCR (71% versus 28–34%).[47]

These encouraging results prompted the launching of two high-priority multicenter Phase III trials, Eastern Cooperative Oncology Group (ECOG) 2190 and Cancer and Leukemia Group B (CALGB) 9082, comparing standard adjuvant chemotherapy with standard adjuvant chemotherapy followed by consolidation with HDC–SCR in patients with primary breast cancer with a high risk of recurrence (appendix). By July 1995, 287 women had been enrolled in ECOG 2190; the goal is 429 patients. In the larger of the two trials, CALGB 9082, the targeted sample size was recently expanded to 774 patients. As of August 1995, 544 patients had been enrolled. More than five years will have to pass after the end of enrollment for these two trials before meaningful conclusions about efficacy can be drawn. Until then, it will not be known whether the potential survival benefit of HDC–SCR outweighs the risk of long-term toxicity in patients at high risk of recurrence.

Toxic effects

Short-term toxicities. Because hematopoietic toxicity is overcome in a patient by stem-cell infusions, nonhematologic toxicities specific to the agents used become the dose-limiting effects (Table 3). Early death caused by regimen-related toxicity can be a major issue; rates range from 0% to 30% in the trials published to date.[10,25-37] However, clinical experience with these agents and improvements in administration techniques (i.e., fractionated or continuous i.v. infusion rather than bolus-dose administration) have reduced treatment-related mortality.[33,35] Another advance that has markedly changed the toxicity profile of these preparative regimens is the use of PBPCs and hematopoietic growth factors. Shorter time to engraftment (a median of 10–11 days instead of 17–20 days) has reduced the severe bleeding and mucosal and skin toxicities associated with these regimens in earlier studies.[10,48] Early neutrophil recovery is associated with rapid healing of mucous membranes and reduced gastrointestinal toxicity. Few patients develop difficulty swallowing that precludes oral intake or requires parenteral nutrition for support. Early neutrophil recovery, in combination with prophylactic or empirical antimicrobial therapy, has also significantly reduced the frequency of documented bacteremia.[49]

Table 3.
Nonhematologic Toxicities Associated with Agents Commonly Used in High-Dose Chemotherapy for Breast Cancer

Agent	Nonhematologic Toxicity
Cyclophosphamide	Hemorrhagic cystitis, interstitial pneumonitis, cardiomyopathy, congestive heart failure
Thiotepa	Mucositis, erythematous rash, central nervous system toxicity (dizziness, seizures)
Cisplatin	Renal insufficiency, renal failure, ototoxicity, peripheral neurotoxicity
Melphalan	Mucositis, renal insufficiency, erythematous rash
Carboplatin	Hepatic enzyme elevations, renal insufficiency
Carmustine	Interstitial pneumonitis, veno-occlusive disease of the liver

All preparative drug regimens cause moderate to severe nausea and vomiting. Antiemetic strategies should include agents appropriate for use with highly emetogenic regimens. Hemorrhagic cystitis resulting

from cyclophosphamide therapy can be prevented or minimized with aggressive hydration, bladder irrigation, and the urinary-tract protectant mesna.[50,51] Renal insufficiency induced by cisplatin occurs in up to 30% of patients,[23,26] but it is reversible within two weeks in almost all cases. Aggressive hydration and diuresis can minimize cisplatin-induced renal dysfunction.[23,26] Hepatic toxicity is most commonly manifested by asymptomatic elevations in hepatic enzymes. Occasionally, veno-occlusive disease of the liver can occur. Veno-occlusive disease is a potentially life-threatening complication arising from small thromboses within hepatic venules. Although this problem appears to be more common in patients undergoing carmustine-containing regimens, the overall frequency is less than 5% when PBPCs and hematopoietic growth factors are used. The cornerstone of treatment for established veno-occlusive disease is supportive care, although continuous i.v. infusion of alteplase has been used with some success.[52] Pharmacologic strategies to prevent veno-occlusive disease include prostaglandin E_1,[53] pentoxifylline,[54,55] and continuously infused heparin[56]; however, pentoxifylline has been shown to be ineffective in randomized, controlled clinical trials.[54,55] Although rare in patients undergoing HDC–SCR for breast cancer, veno-occlusive disease can occasionally cause fulminant hepatic failure and death.

Cardiotoxicity, manifested by electrical conduction abnormalities or cardiomyopathy, is most commonly associated with regimens containing high-dose cyclophosphamide. If cardiomyopathy or congestive heart failure develops, standard treatment with diuretics, inotropic agents, or angiotensin-converting-enzyme inhibitors is used.

Long-term toxicities. The most feared long-term toxicity associated with HDC–SCR is drug-induced leukemia. Alkylating agents are notorious for inducing secondary leukemia after curative therapy for other malignancies.[57-59] The risk of secondary leukemia approaches 10% 10 years after therapy. To date, secondary leukemia has not been widely reported in patients with breast cancer who underwent HDC–SCR; this reflects the fact that most patients have had metastatic disease and thus have been unlikely to enjoy long-term disease-free survival. However, as the number of patients undergoing consolidation therapy (therapy given soon after induction of remission) with HDC–SCR in the adjuvant setting increases, reports of secondary leukemia may increase. Drug-induced ovarian failure (sterility) is another consequence of treatment with high doses of alkylating agents.[60,61] Although most women with breast cancer are beyond reproductive age, more and more women are being diagnosed at an early age. These women are the patients most likely to be referred for aggressive, potentially curative therapy with HDC–SCR.

Pulmonary toxicity is another long-term problem associated with preparative regimens used in the treatment of breast cancer. Decreases in pulmonary function have been noted in patients receiving regimens containing cyclophosphamide, thiotepa, melphalan, and carmustine.[62] Of these agents, carmustine is thought to be the primary offending agent,[62] although combinations of carmustine and cyclophosphamide may be synergistic with respect to adverse pulmonary effects.[63] Carmustine causes a syndrome of latent pulmonary toxicity manifested by dyspnea, coughing, fever, hypoxemia, and a deterioration of pulmonary function.[23,26,63] This condition, also known as interstitial pneumonitis, occurs a mean of 48 days after high-dose therapy[63] in up to 40% of patients.[23,26,63] Treatment with corticosteroids (10–40 mg of prednisone per day for months to years) will control symptoms in the majority of patients. Occasionally, progressive pulmonary failure and death occur.[63]

Hemolytic uremic syndrome may be a late complication after treatment with cyclophosphamide, cisplatin, and carmustine.[41] This syndrome, which occurs in less than 10% of patients, is characterized by sudden-onset thrombocytopenia, anemia with hemolysis, altered mental status, hypertension, impaired renal function, and respiratory insufficiency. Corticosteroids or plasmapheresis may be helpful.[41]

Economic considerations

The economic impact of HDC–SCR in the United States is a major facet of the debate over the value of this therapy for breast cancer. At original cost estimates, provided in the 1980s when this treatment modality was in its infancy, of up to $100,000 per case for an uncomplicated course of treatment,[64,65] the total cost to the health care system is potentially staggering. The financial cost, coupled with the unresolved debate over therapeutic effectiveness, has resulted in unusual reimbursement dilemmas.

A study by Peters and Rogers[66] explored insurance approval of HDC–SCR for breast cancer. Seventy-seven percent of 533 patients with breast cancer enrolled in grant-supported, peer-reviewed clinical trials at Duke University Medical Center between 1989 and 1992 were approved by their health insurance companies to undergo HDC–SCR; the remainder were not. The most common reason cited for denial of coverage was that the therapy was "experimental" or "investigational." More than 187 insurance companies were represented. There appeared to be no association between patient clinical status, trial design, or insurance carrier and approval. For example, patients with metastatic breast cancer were about as likely to receive insurance approval (84%) as patients with high-risk primary disease (76%). In addition, it made no difference whether patients were responsive or unresponsive to induction chemotherapy or were enrolled in a Phase I or Phase II trial. Within the same insurance company, some re-

quests were approved and some denied for patients enrolled in identical protocols. The authors concluded that insurance approval of HDC–SCR appeared "arbitrary and capricious."

Health insurance policies commonly include clauses that deny coverage for experimental or investigational therapies, and such clauses are the basis for the majority of denials of coverage for HDC–SCR for breast cancer. However, insurance approvals for this therapy are becoming more frequent, largely because of increasing public pressure and high-profile litigation. Many patients, including about half of the patients in the Peters and Rogers study who were originally denied coverage, have been able to obtain payment for their therapies after suing their insurance companies.[66,67] In September 1994, the Office of Personnel Management mandated that health insurers of federal employees must reimburse for HDC–SCR without increasing employee premiums.[65] Similarly, the state of Massachusetts passed a law in 1994 requiring health insurers to pay for claims submitted when BMT is used in treating patients with breast cancer.[68] Blue Cross and Blue Shield of California, and other Blue Cross carriers nationally, have agreed to pay for HDC–SCR in breast cancer patients participating in randomized controlled clinical trials funded by the National Cancer Institute.[69] This is the first time insurance companies have agreed to participate in funding any ongoing national clinical trial.

Estimating the cost-effectiveness of HDC–SCR in the treatment of breast cancer is problematic. The original cost estimate of about $100,000 for an uncomplicated case has been decreasing with advances in supportive care that facilitate outpatient treatment.[49,70,71] Consequently, published predictions of cost-effectiveness may not be valid.

Hillner et al.[72] estimated the cost-effectiveness of HDC–SCR in the treatment of metastatic breast cancer. They used response and recurrence rates from published clinical trials for standard therapy and cost data from their own institution for only six uncomplicated courses of HDC–SCR. They assumed an average length of stay of 40 days for patients undergoing HDC–SCR and average costs (not charges) of $66,200. These authors concluded that HDC–SCR, relative to standard therapy, has a significant clinical benefit but at a cost that may be "untenable." However, several advances in supportive care have substantially changed the reliability of the assumptions made by Hillner et al. For example, the use of PBPCs in conjunction with hematopoietic growth factors has reduced the time to engraftment by 8–10 days.[10,48] Reduced time to engraftment and the use of broad-spectrum prophylactic antimicrobials have decreased the duration of neutropenia, infectious complications, and duration of hospitalization.[49,70,71] Indeed, at experienced facilities, this improvement in supportive care has resulted in the successful management of patients undergoing HDC–SCR in the ambulatory care setting.[70,71]

An assessment of the overall cost-effectiveness of HDC–SCR for breast cancer depends on several factors, including the patient's age, the stage of the disease at the time of treatment, comparative costs of standard therapy, and any survival advantage gained by HDC–SCR. If a therapy is very expensive but results in a significant survival advantage, such that patients remain free of disease for many years (a proposed benefit of HDC–SCR as adjuvant therapy for patients at high risk of relapse), then it may indeed be cost-effective. The ongoing national randomized trials will provide answers to questions regarding not only therapeutic effectiveness but also quality of life, resource utilization, and cost-effectiveness.

Other unresolved issues

Role of bone marrow purging. Purging is a procedure in which a hematopoietic stem-cell-containing specimen is manipulated outside the body to remove occult malignant cells. Several methods are used for purging, including exposure to chemicals (e.g., 4-hydroperoxycyclophosphamide), incubation with monoclonal antibodies, and positive selection for hematopoietic progenitor cells (CD34+ cells).[73] Purging is commonly done when autologous bone marrow is used with high-dose chemotherapy to treat patients with acute leukemia.[6,74] However, the utility of purging stem-cell-bearing specimens is unclear for breast cancer patients. Most clinical trials of HDC–SCR in breast cancer patients to date have excluded patients with known bone marrow metastases and have involved unpurged marrow or peripheral-blood specimens. The rationale for not routinely purging the marrow of these patients is a presumed low likelihood of malignancy contaminating the stem-cell-containing specimen in the absence of clinical evidence for metastatic involvement of the bone marrow (e.g., normal findings for complete blood count or bone marrow biopsy).

At first glance, this approach of disregarding the potential for stem-cell contamination appears reasonable. Unlike leukemia, breast cancer is not a primary hematologic malignancy. Thus, there should be little reason to routinely suspect bone marrow involvement. However, there is increasing evidence that bone marrow contamination by breast cancer epithelial cells is more common than was initially thought and undetectable by standard clinical methods. For example, using a specific breast cancer monoclonal antibody assay, Redding et al.[75] detected bone marrow micrometastases in 28% of bone marrow specimens obtained from women undergoing initial treatment of primary breast cancer. Standard tests failed to detect the bone marrow metastases. Micrometastatic involvement of the bone marrow was documented even in patients with very early breast cancer (e.g., small primary lesions or axillary lymph node-negative disease). These findings have been corroborated by other investigators.[76-79]

Bone marrow micrometastases may be a predictor of early relapse. In 49 patients with early breast cancer (stage I or II), the rate of recurrence at two years was 33% and 3% for patients with and without evidence of bone marrow micrometastases at the time of initial evaluation, respectively.[80]

The clinical implications of this information are unclear. Most patients undergoing autologous stem-cell infusion for metastatic breast cancer have recurrences at a site of prior bulky disease.[25-38] Therefore, whether the stem-cell inoculum is contaminated may be irrelevant. Nonetheless, there is evidence that a few patients without prior evidence of bone or bone marrow involvement have relapsed with diffuse bony metastases after receiving autologous bone marrow.[29,38] This pattern of relapse is suggestive of contamination from the infused bone marrow. The relevance of bone marrow micrometastases may increase as the use of HDC–SCR is expanded to include adjuvant therapy in patients at high risk of relapse. In the future, these patients may be routinely screened for occult malignant cells. If such cancer is present, the specimens would be purged before infusion. Alternatively, the need to purge stem-cell infusions may become obsolete as the use of PBPCs increases. Contamination of peripheral blood with micrometastatic breast cancer cells is less common than contamination of bone marrow.[78,79] Until more study is completed, the exact role and most effective method of purging will remain undefined.

What is the best preparative regimen? Comparative studies to determine the most effective preparative regimen have yet to be performed. Commonly used preparative regimens follow traditional principles.[5] All regimens include more than one drug administered at dosages at or near the upper limit of safety based on nonhematologic toxicities (these strategies are designed to overcome inherent tumor resistance and to decrease the development of further resistance), have inherent activity against breast cancer cells in vivo or in vitro, and incorporate drugs with nonoverlapping nonhematologic toxicities. Cisplatin, an agent used in the studies by Peters et al.,[23,26,41] is an exception. Hematologic toxicity is not dose limiting for cisplatin, but the drug has inherent activity in breast cancer.

The first preparative regimen widely used with hematopoietic progenitor cell support in the treatment of breast cancer was carmustine, cisplatin, and cyclophosphamide with or without melphalan.[23,25,26] Death from toxic effects occurred in 14–24% of patients in early studies[23,25] but now occurs in less than 12% of patients if PBPCs and hematopoietic growth factors are used.[41,47] Melphalan has been dropped from this regimen because life-threatening mucositis and renal insufficiency precluded significant dose escalation.

Other widely used preparative regimens are designed to minimize the pulmonary toxicity and renal toxicity of carmustine-containing and cisplatin-containing regimens, respectively. These regimens include cyclophosphamide and thiotepa with or without carboplatin.[27,29,33] Death due to toxicity has been reported in fewer than 15% of the patients treated with these agents. Administering these agents as a continuous i.v. infusion over 96 hours has reduced the rate of toxicity-related death to less than 5%.[33] Low treatment-related mortality and avoidance of latent pulmonary toxicity are two advantages of the STAMP-V regimen used in some of the national randomized trials.

More recent regimens incorporate such agents as hydroxyurea,[36] mitoxantrone,[5,40] or etoposide.[5,34,40] These new regimens are designed to enhance the inherent antitumor effects of existing regimens.

Inpatient versus outpatient therapy. The treatment of patients with HDC–SCR for breast cancer and other solid tumors is rapidly moving from the inpatient to the outpatient setting. The time to engraftment and the frequency of infectious complications have been reduced by the use of hematopoietic growth factors, PBPCs, and oral prophylactic antimicrobials and antifungals.[10,48,49] These advances have made it possible to treat complex cases on an outpatient basis, something that would have been unthinkable just a few years ago.

Outpatient management of women with breast cancer undergoing HDC–SCR was pioneered at Duke University Medical Center.[71,72] In early 1992, a pilot program began in which the site of most care for these patients was transferred to an outpatient facility. Patients are first admitted for five days to the hospital, where the preparative drugs (carmustine, cyclophosphamide, and cisplatin) are administered. This hospitalization is required because intensive hydration is necessary to minimize toxicity. After the high-dose chemotherapy, patients are discharged to a local hotel and an adjacent outpatient facility open seven days a week. Patients go to the outpatient facility daily for supportive care, including evaluation by a physician, hydration, administration of antiemetics and blood products, and, if necessary, once-daily i.v. administration of antimicrobials. To date, a total of 240 patients have been treated in this program. The average duration of hospitalization has been reduced from at least 22 days to 7 days for patients with primary or metastatic breast cancer given identical chemotherapy.[71] Forty-six percent of patients never require readmission to the hospital; 14% require readmission for less than 24 hours.[71] The program has reduced total charges associated with HDC–SCR by more than $50,000 per patient at this institution.[70]

Outpatient management of patients undergoing HDC–SCR should be provided only in sophisticated settings with appropriate support. Peters et al.[70] recommended that the following be available for high-quality care in an outpatient setting: a dedicated clinic, a blood bank, and the availability of medical, nursing, and

support personnel seven days a week. Other key elements include sophisticated computer support to facilitate the transfer of patient information and the participation of a family member or significant other to help ensure the patient's compliance.

Autologous graft-versus-host disease. Graft-versus-host disease (GVHD) is an immunologically mediated rejection episode whereby immunocompetent T lymphocytes in the graft (i.e., donor bone marrow) recognize host histocompatibility antigens as foreign. GVHD is the most common and serious complication following allogeneic BMT for the treatment of acute leukemia and other primary hematologic disorders.[81-83] However, at least in patients with acute leukemia, GVHD also confers a beneficial effect. Residual host leukemia cells are also recognized as foreign and are eradicated in a phenomenon known as the graft-versus-leukemia effect.[81-83] The graft-versus-leukemia effect is thought to be the reason why patients with acute myelogenous leukemia undergoing allogeneic BMT have a significantly lower rate of relapse than similar patients undergoing autologous BMT.[81-83]

Graft-versus-host reactions are usually not elicited by infusions of autologous bone marrow or PBPCs. Because these cells are obtained from the host, the host and the graft are immunologically identical. Research is under way to discover therapies that can induce an autologous graft-versus-host reaction, with the intent of enhancing antitumor efficacy.[84,85] Two agents, cyclosporine and recombinant interferon gamma, have been used in breast cancer patients undergoing HDC-SCR. Although the exact mechanism of action is unknown, these agents are thought to up-regulate the expression of histocompatibility antigens on breast cancer cells and increase recognition of these antigens by T lymphocytes. In preliminary studies, cyclosporine (1.0–3.75 mg/kg/day i.v. for 28 days) with or without interferon gamma (0.025 mg/sq m subcutaneously every other day during days 7–28) has been shown to induce a syndrome resembling GVHD in patients with breast cancer after HDC-SCR.[84,85] Although such results are provocative, the implications remain unclear.

Sequential treatment cycles. There are two ways to increase dose intensity: (1) increasing the dosage of each drug within a treatment cycle and (2) increasing the number of treatment cycles. Because current preparative regimens involve drugs at or near maximum tolerated dosages, increasing these dosages is not feasible for most patients. Thus, the use of sequential cycles of high-dose chemotherapy is being evaluated as a means of dose intensification.

Theoretically, sequential cycles may be more appropriate than a single cycle for solid tumors because of slow tumor-doubling time, poor vascularity, and multiple mechanisms of acquired resistance.[35] The first high-dose cycles should reduce the tumor burden, recruit quiescent cells into division, and improve the blood supply to the remaining tumor cells. Subsequent high-dose cycles would be administered in the hope of eradicating residual disease.[5,35]

Dunphy et al.[28] evaluated sequential cycles of high-dose CEP (cyclosphosphamide 1.5–1.75 g/sq m, etoposide 250–400 mg/sq m, and cisplatin 40–60 mg/sq m) in 58 patients with metastatic breast cancer in first relapse. Poor prognostic features included estrogen-receptor-negative or hormone-refractory tumors, young age (mean, 42 years), and more than one site of metastasis (63% of patients). The patients underwent four cycles of induction chemotherapy with standard-dose doxorubicin-containing regimens. Patients with a complete or partial response, or stable disease after induction therapy, underwent two cycles of CEP with or without bone marrow infusions. The time between cycles was only long enough to ensure hematologic recovery. Eighty-four percent of the patients responded to induction chemotherapy and went on to sequential high-dose therapy. After two cycles of CEP, the overall response rate remained at 85%; however, the number of patients in complete remission increased from 34% after induction to 55% after high-dose therapy. The median rate of progression-free survival two years after induction was estimated at 25%. The authors cited a 5–10% two-year survival rate for comparable poor-prognosis patients undergoing standard-dose therapy. Treatment-related death occurred in 9% of the patients. Other authors have reported similarly high rates of response to sequential high doses of alternating non-cross-resistant agents (e.g., high-dose melphalan followed by high-dose cyclophosphamide, carboplatin, and thiotepa).[5,35,86] For now, though, the data are too limited for us to know whether sequential high-dose therapies improve upon the response rates or durations of response achieved with one cycle of high-dose therapy.

Summary

The past 10 years have witnessed important advances in the treatment of breast cancer. Improved supportive strategies and refinement of HDC-SCR technology have resulted in the advent of a potentially curative therapy for an increasingly prevalent malignancy. However, with the health care industry facing severe financial cutbacks, it will be crucial to identify which patients are most likely to benefit from this expensive therapy.

Results of uncontrolled trials of HDC-SCR in women with heavily pretreated or refractory metastatic breast cancer indicate that, although high objective response rates can be obtained, they are usually brief. In this patient population the risks of therapy probably do not outweigh the potential benefits. In contrast, data from one small randomized trial suggest that a high objective response rate, as well as improved survival, may be obtained when HDC-SCR is used as first-line therapy for women with metastatic breast cancer. Two large

randomized trials will help confirm whether HDC–SCR provides a survival advantage, an economic benefit, or increased quality of life when used as in the treatment of metastatic breast cancer.

Applying HDC–SCR in the adjuvant setting for patients at high risk of relapse may represent a major advance. Preliminary evidence suggests that patients at high risk of relapse remain in remission significantly longer after HDC–SCR than comparable patients given standard therapy. Two high-priority randomized trials are under way to compare the efficacies of HDC–SCR and standard therapy in these high-risk patients.

Meaningful conclusions about the role, optimal timing, and economics of HDC–SCR for breast cancer must await the results of randomized clinical trials. Further complicating the picture is the slower-than-expected recruitment of study subjects; recruitment is lagging because insurance coverage for off-protocol treatment has been increasing.[65,87] It is in the best interests of us all to ensure that recruitment continues.

Conclusion

High-dose chemotherapy with stem-cell rescue appears to be a valid option for women with breast cancer—especially patients with chemotherapy-sensitive metastatic disease receiving the treatment on a first-line basis or patients at high risk for relapse who undergo it as consolidation therapy. However, whether the cost and risks of this approach will be ultimately justified remains to be seen.

References

1. Harris JR, Morrow M, Bonadonna G. Cancer of the breast. In: Cancer: principles and practice of oncology. 4th ed. DeVita VT, Hellman S, Rosenberg SA, eds. Philadelphia: Lippincott; 1993:1264-332.
2. Colditz GA, Hankinson SE, Hunter DJ et al. The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. *N Engl J Med.* 1995; 332:1589-93.
3. Weber BL. Susceptibility genes for breast cancer. *N Engl J Med.* 1994; 331:1523-4.
4. McGuire TR. Breast cancer. In: Pharmacotherapy: a pathophysiologic approach. DiPiro JT, Talbert RL, Hayes PE et al., eds. 2nd ed. Norwalk, CT: Appleton & Lange; 1993:1930-45.
5. Spitzer G, Adkins D, Dunphy F et al. Design of preparative regimens for stem cell transplantation in breast cancer. *Breast Cancer Res Treat.* 1993; 26:S3-9.
6. Jones R, Burnett AK. How to harvest bone marrow for transplantation. *J Clin Pathol.* 1992; 45:1053-7.
7. Kessinger A. Utilization of peripheral blood stem cells in autotransplantation. *Hematol Oncol Clin North Am.* 1993; 7:535-45.
8. Haas R, Ho AD, Bredthauer U et al. Successful autologous transplantation of blood stem cells mobilized with recombinant human granulocyte-macrophage colony-stimulating factor. *Exp Hematol.* 1990; 18:94-8.
9. To LB, Sheppard KM, Haylock DN et al. Single high doses of cyclophosphamide enable the collection of high numbers of hematopoietic stem cells from the peripheral blood. *Exp Hematol.* 1990; 18:442-7.
10. Kritz A, Crown JP, Motzer RJ et al. Beneficial impact of peripheral blood progenitor cells in patients with metastatic breast cancer treated with high-dose chemotherapy plus granulocyte-macrophage colony-stimulating factor. *Cancer.* 1993; 71:2515-21.
11. Peters WP, Rosner G, Ross M et al. Comparative effects of granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF) on priming peripheral blood progenitor cells for use with autologous bone marrow after high-dose chemotherapy. *Blood.* 1993; 81:1709-19.
12. Frei E, Canellos GP. Dose: a critical factor in cancer chemotherapy. *Am J Med.* 1980; 69:585-93.
13. Frei E, Antman K, Teicher B et al. Bone marrow autotransplantation for solid tumors—prospects. *J Clin Oncol.* 1989; 7:515-26.
14. Hryniuk W, Bush H. The importance of dose intensity in chemotherapy of metastatic breast cancer. *J Clin Oncol.* 1984; 2:1281-8.
15. Hryniuk W, Levine MN. Analysis of dose intensity for adjuvant chemotherapy trials in stage II breast cancer. *J Clin Oncol.* 1986; 4:1162-70.
16. Tannock IF, Boyd NF, DeBoer G et al. A randomized trial of two dose levels of cyclophosphamide, methotrexate and fluorouracil chemotherapy for patients with metastatic breast cancer. *J Clin Oncol.* 1988; 6:1377-87.
17. Bonadonna G, Valagussa P. Dose–response effect of adjuvant chemotherapy in breast cancer. *N Engl J Med.* 1981; 304:10-5.
18. Bonadonna G, Valagussa P, Moliterni A et al. Adjuvant cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer—the results of 20 years of follow-up. *N Engl J Med.* 1995; 332:901-6.
19. Henderson IC, Hayes DF, Gelman R. Dose–response in the treatment of breast cancer: a critical review. *J Clin Oncol.* 1988; 6:1501-15.
20. Eddy DM. High-dose chemotherapy with autologous bone marrow transplantation for the treatment of metastatic breast cancer. *J Clin Oncol.* 1992; 10:657-70.
21. Canellos GP. The dose dilemma. *J Clin Oncol.* 1988; 6:1363-4. Editorial.
22. Hryniuk WM. More is better. *J Clin Oncol.* 1988; 6:1365-7. Editorial.
23. Peters WP, Eder JP, Henner S et al. High-dose combination alkylating agents with autologous bone marrow support: a Phase I study. *J Clin Oncol.* 1986; 4:646-54.
24. Eder JP, Antman K, Elias A et al. Cyclophosphamide and thiotepa with autologous bone marrow transplantation in patients with solid tumors. *J Natl Cancer Inst.* 1988; 80:1221-6.
25. Eder JP, Antman K, Peters W et al. High-dose combination alkylating agent chemotherapy with autologous bone marrow support for metastatic breast cancer. *J Clin Oncol.* 1986; 4:1592-7.
26. Peters WP, Shpall EJ, Jones RB et al. High-dose combination alkylating agents with bone marrow support as initial treatment for metastatic breast cancer. *J Clin Oncol.* 1988; 6:1368-76.
27. Williams SF, Mick R, Desser R et al. High-dose consolidation therapy with autologous stem cell rescue in stage IV breast cancer. *J Clin Oncol.* 1989; 7:1824-30.
28. Dunphy FR, Spitzer G, Buzdar AU et al. Treatment of estrogen receptor-negative or hormonally refractory breast cancer with double high-dose chemotherapy intensification and bone marrow support. *J Clin Oncol.* 1990; 8:1207-16.
29. Kennedy MJ, Beveridge RA, Rowley SD et al. High-dose chemotherapy with reinfusion of purged autologous bone marrow following dose-intense induction as initial therapy for metastatic breast cancer. *J Natl Cancer Inst.* 1991; 83:920-6.
30. Williams SF, Gilewski T, Mick R et al. High-dose consolidation therapy with autologous stem-cell rescue in stage IV breast cancer: follow-up report. *J Clin Oncol.* 1992; 10:1743-7.
31. Broun ER, Sledge GW, Einhorn LH et al. High-dose carboplatin and mitoxantrone with autologous bone marrow support in the treatment of advanced breast cancer. *Am J Clin Oncol.* 1993; 16:9-13.
32. Ghalie R, Richman CM, Adler SS et al. Treatment of metastatic breast cancer with a split-course high-dose chemotherapy regimen and autologous bone marrow transplantation. *J Clin*

Oncol. 1994; 12:342-6.
33. Antman K, Ayash L, Elias A et al. 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.* 1992; 10:102-10.
34. Somlo G, Doroshow JH, Forman S. High-dose cisplatin, etoposide, and cyclosphosphamide with autologous stem cell reinfusion in patients with responsive metastatic or high-risk primary breast cancer. *Cancer.* 1994; 73:125-34.
35. Ayash LJ, Elias A, Wheeler C et al. Double dose-intensive chemotherapy with autologous marrow and peripheral-blood progenitor-cell support for metastatic breast cancer: a feasibility study. *J Clin Oncol.* 1994; 12:37-44.
36. Vaughn WP, Reed ED, Edwards B et al. 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.* 1994; 13:619-24.
37. Kotesek D, Sage RE, Dale DM et al. Dose intensive therapy with autologous blood stem cell transplantation in breast cancer. *Aust N Z J Med.* 1994; 24:288-95.
38. Mundt AJ, Sibley GS, Williams S et al. Patterns of failure of complete responders following high-dose chemotherapy and autologous bone marrow transplantation for metastatic breast cancer: implications for the use of adjuvant radiation therapy. *Int J Radiat Oncol Biol Phys.* 1994; 30:151-60.
39. Dunphy FR, Spitzer G, Rossiter-Fornoff JE et al. Factors predicting long-term survival for metastatic breast cancer patients treated with high-dose chemotherapy and bone marrow support. *Cancer.* 1994; 73:2157-67.
40. Bezwoda WR, Seymour L, Dansey RD. High-dose chemotherapy with hematopoietic rescue as primary treatment for metastatic breast cancer: a randomized trial. *J Clin Oncol.* 1995; 13:2483-9.
41. Peters WP, Ross M, Vredenburgh JJ et al. High-dose chemotherapy and autologous bone marrow support as consolidation after standard-dose adjuvant therapy for high-risk primary breast cancer. *J Clin Oncol.* 1993; 11:1132-43.
42. Holland HK, Klein L, Geller RB et al. High-dose chemotherapy (HDC) with cyclophosphamide, thiotepa and carboplatin & autologous bone marrow transplant (AuBMT) for patients with stage II'III breast cancer and 10 or greater lymph nodes: two year follow-up report. *Proc Am Soc Clin Oncol.* 1995; 14:112. Abstract.
43. Fay J, Jones S, Lynch J et al. 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.* 1995; 14:104. Abstract.
44. Bearman SI, Overmoyer BA, Bolwell BG et al. High-dose chemotherapy with autologous peripheral blood progenitor cells (PBPC) for stage II/III breast cancer in patients with 4–9 involved axillary lymph nodes. *Proc Am Soc Clin Oncol.* 1995; 14:133. Abstract.
45. Garcia-Conde J, Solano C, Lluch A et al. High-dose (HD) chemotherapy (CT) and autologous stem cell transplantation (ASCT) in breast cancer. *Proc Am Soc Clin Oncol.* 1995; 14:319. Abstract.
46. Raftopoulos H, Vahdat L, Garrett TJ et al. High-dose chemotherapy with autologous stem cell rescue in patients with high risk and metastatic breast cancer: the Columbia University experience. *Proc Am Soc Clin Oncol.* 1995; 14:329. Abstract.
47. Peters WP, Berry D, Vredenburgh JJ et al. Five year follow-up of high-dose combination alkylating agents with ABMT as consolidation after standard-dose CAF for primary breast cancer involving ≥ 10 axillary lymph nodes (DUKE/CALGB 8782). *Proc Am Soc Clin Oncol.* 1995; 14:317. Abstract.
48. Peters WP, Rosner G, Ross M et al. Comparative effects of granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating (G-CSF) on priming peripheral blood progenitor cells for use with autologous bone marrow after high-dose chemotherapy. *Blood.* 1993; 81:1709-19.
49. Gilbert C, Meisenberg B, Vredenburgh JJ et al. Sequential prophylactic oral and empiric once-daily parenteral antibiotics for neutropenia and fever after high-dose chemotherapy and autologous bone marrow support. *J Clin Oncol.* 1994; 12:1005-11.
50. Shepherd JD, Pringle LE, Barnett MJ et al. Mesna versus hyperhydration for the prevention of cyclophosphamide-induced hemorrhagic cystitis in bone marrow transplantation. *J Clin Oncol.* 1991; 9:2016-20.
51. Vose JM, Reed EC, Pippert GC et al. Mesna compared with continuous bladder irrigation as uroprotectant during high-dose chemotherapy and transplantation: a randomized trial. *J Clin Oncol.* 1993; 11:1306-10.
52. Bearman SI, Shuhart MC, Hinds MS et al. Recombinant human tissue plasminogen activator for the treatment of established severe veno-occlusive disease of the liver after bone marrow transplantation. *Blood.* 1992; 80:2458-62.
53. Gluckman E, Jolivet I, Scrobohaci ML et al. Use of prostaglandin E1 for prevention of liver veno-occlusive disease in leukaemic patients treated by allogeneic bone marrow transplantation. *Br J Haematol.* 1990; 74:277-81.
54. Clift RA, Bianco JA, Appelbaum FR et al. A randomized controlled trial of pentoxifylline for the prevention of regimen-related toxicities in patients undergoing allogeneic marrow transplantation. *Blood.* 1993; 82:2025-30.
55. Attal M, Huguet F, Rubie H et al. Prevention of regimen-related toxicities after bone marrow transplantation by pentoxifylline: a prospective, randomized trial. *Blood.* 1993; 82:732-6.
56. Bearman SI, Hinds MS, Wolford JL et al. A pilot study of continuous infusion heparin for the prevention of hepatic veno-occlusive disease after bone marrow transplantation. *Bone Marrow Transplant.* 1993; 5:407-11.
57. Pedersen-Bjergaard J, Larsen SO. Incidence of acute nonlymphocytic leukemia, preleukemia, and acute myeloproliferative syndrome up to 10 years after treatment for Hodgkin's disease. *N Engl J Med.* 1982; 307:965-71.
58. Greene MH, Boice JD, Greer BE et al. Acute nonlymphocytic leukemia after therapy with alkylating agents for ovarian cancer. *N Engl J Med.* 1982; 307:1416-21.
59. Casciato DA, Scott JL. Acute leukemia following prolonged cytotoxic agent therapy. *Medicine.* 1979; 58:32-45.
60. Sobrinho LG, Levine RA, DeConti RC. Amenorrhea in patients with Hodgkin's disease treated with antineoplastic agents. *Am J Obstet Gynecol.* 1971; 109:135-9.
61. Myers SE, Schilsky RL. Prospects for fertility after cancer. *Semin Oncol.* 1992; 19:597-604.
62. Tiersten A, Raptis G, Yao TJ et al. Significant alterations in pulmonary function tests (PFT) in patients undergoing high dose chemotherapy (HDC) for breast cancer. *Proc Am Soc Clin Oncol.* 1995; 14:313. Abstract.
63. Todd NW, Peters WP, Ost AH et al. Pulmonary drug toxicity in patients with primary breast cancer treated with high-dose combination chemotherapy and autologous bone marrow transplantation. *Am Rev Respir Dis.* 1993; 147:1264-70.
64. Spitzer TR, Swain SM, Lippman ME et al. Reimbursement for solid tumor autologous bone marrow transplantation trials: a strategy for ensuring continuation of a promising therapy. *Cancer Invest.* 1991; 9:93-7.
65. U.S. government supports reimbursement for controversial cancer therapy. *Univ Hosp Consort Technol Alert.* 1995; Feb 2.
66. Peters WP, Rogers MC. Variation in approval by insurance companies of coverage for autologous bone marrow transplantation for breast cancer. *N Engl J Med.* 1994; 330:473-7.
67. Wynstra NA. Breast cancer: selected legal issues. *Cancer.* 1994; 74:491-511.
68. Mahaney FX. Bone marrow transplant for breast cancer: some insurers pay, some insurers don't. *J Natl Cancer Inst.* 1994; 86:420-1. News.
69. One of the Blues to selectively reimburse for bone marrow transplantation. *Univ Hosp Consort Technol Alert.* 1995; Apr 4.

70. Peters WP, Ross M, Vredenburgh JJ et al. The use of intensive clinic support to permit outpatient autologous bone marrow transplantation for breast cancer. *Semin Oncol.* 1994; 21(4, suppl 7):25-31.
71. Ross M, Dukelow K, Gilbert C et al. Outpatient bone marrow transplantation: two year update. *Proc Am Soc Clin Oncol.* 1995; 14:316. Abstract.
72. Hillner BE, Smith TJ, Desch CE. Efficacy and cost-effectiveness of autologous bone marrow transplantation in metastatic breast cancer: estimates using decision analysis while awaiting clinical trial results. *JAMA.* 1992; 267:2055-61.
73. Shpall EJ, Stemmer SM, Bearman SI et al. New strategies in marrow purging for breast cancer patients receiving high-dose chemotherapy with autologous bone marrow transplantation. *Breast Cancer Res Treat.* 1993; 26:S19-23.
74. Yeager AM, Kaizer H, Santos GW et al. Autologous bone marrow transplantation in patients with acute nonlymphocytic leukemia, using ex vivo marrow treatment with 4-hydroperoxycyclophosphamide. *N Engl J Med.* 1986; 315:141-7.
75. Redding WH, Coombes RC, Monaghan P et al. Detection of micrometastases in patients with primary breast cancer. *Lancet.* 1983; 2:1271-4.
76. Cote RJ, Rosen PP, Hakes TB et al. Monoclonal antibodies detect occult breast carcinoma metastases in the bone marrow of patients with early stage breast cancer. *Am J Surg Pathol.* 1988; 12:333-40.
77. Diel IJ, Kaufmann M, Solomayer EF et al. Micrometastatic tumor cells in bone marrow versus nodal status in breast cancer—impact on prognosis in patients with primary breast cancer. *Proc Am Soc Clin Oncol.* 1995; 14:110. Abstract.
78. Vredenburgh J, Silva O, deSombre K et al. The significance of bone marrow micrometastases for patients treated with high-dose chemotherapy and hematopoietic support. *Proc Am Soc Clin Oncol.* 1995; 14:110. Abstract.
79. Passos-Coelho JL, Ross AA, Moss TJ et al. Low incidence of breast cancer (BC) contamination of a single peripheral blood progenitor cell (PBPC) collection after priming with hematopoietic cytokine alone or cytokine and cyclophosphamide (CY). *Proc Am Soc Clin Oncol.* 1995; 14:110. Abstract.
80. Cote RJ, Rosen PP, Lesser ML et al. Prediction of early relapse in patients with operable breast cancer by detection of occult bone marrow micrometastases. *J Clin Oncol.* 1991; 9:1749-56.
81. Ferrara JLM, Deeg HJ. Graft-versus-host disease. *N Engl J Med.* 1991; 324:667-74.
82. Pietryga D. Prevention and treatment of acute graft-vs.-host disease. *Am J Pediatr Hematol Oncol.* 1993; 15:28-48.
83. Christiansen NP. Allogeneic bone marrow transplantation for the treatment of acute leukemias. *Hematol Oncol Clin North Am.* 1993; 7:177-200.
84. Kennedy MJ, Vogelsang GB, Beveridge RA et al. Phase I trial of intravenous cyclosporine to induce graft-versus-host disease in women undergoing autologous bone marrow transplantation for breast cancer. *J Clin Oncol.* 1993; 11:478-84.
85. Kennedy MJ, Vogelsang GB, Jones RJ et al. Phase I trial of interferon gamma to potentiate cyclosporine-induced graft-versus-host disease in women undergoing autologous bone marrow transplantation for breast cancer. *J Clin Oncol.* 1994; 12:249-57.
86. Fennelly D, Vahdat L, Schneider J et al. High-intensity chemotherapy with peripheral blood progenitor cell support. *Semin Oncol.* 1994; 21(suppl 2):21-5.
87. NCI survey explores the M.D.'s perspective on ABMT trials. *J Natl Cancer Inst.* 1995; 87:1510-1. News.

Appendix—Phase III Trials Comparing Standard Adjuvant Chemotherapy with Standard Adjuvant Chemotherapy followed by High-Dose Chemotherapy with Stem-Cell Rescue

Eastern Cooperative Oncology Group (ECOG) 2190

1. Women are eligible if they are ≤60 years old, have undergone primary surgical treatment for their breast cancer, and have ≥10 positive axillary lymph nodes, good performance status, normal organ function, and no evidence of metastatic disease. Patients are stratified by age, estrogen-receptor status, and menopausal status.
2. All patients receive cyclophosphamide 100 mg/sq m orally daily for 14 days, doxorubicin hydrochloride 30 mg/sq m i.v. on days 1 and 8, and fluorouracil 500 mg/sq m i.v. on days 1 and 8, with the cycle repeated every 28 days for total of six cycles.
3. Patients are randomly assigned one of the following subsequent treatments:
   a. Optional hematopoietic progenitor-cell harvest, then radiation and tamoxifen therapy.
   b. Hematopoietic progenitor-cell harvest; then cyclophosphamide 1500 mg/sq m/day and thiotepa 200 mg sq m/day, each given as a continuous i.v. infusion for four days; then progenitor-cell infusion (autologous bone marrow, peripheral-blood progenitor cells [PBPCs], or both) and hematopoietic growth factors; then radiation and tamoxifen therapy.

Cancer and Leukemic Group B (CALGB) 9082

1. Women are eligible if they are ≤50 years old, have undergone primary surgical treatment for their breast cancer, and have stage II or IIIA disease, ≥10 positive axillary lymph nodes, good performance status, normal organ function, documentation of financial coverage, and no evidence of metastatic disease. Patients are stratified by stage of disease, estrogen-receptor status, and menopausal status.
2. All patients receive CAF (cyclophosphamide 600 mg/sq m i.v. on day 1, doxorubicin hydrochloride 60 mg/sq m i.v. on day 1, and fluorouracil 600 mg/sq m i.v. on days 1 and 8); the CAF regimen is repeated every 28 days for a total of three cycles.
3. Patients are randomly assigned one of the following subsequent treatments:
   a. CAF for one cycle; then cyclophosphamide 900 mg /sq m i.v., cisplatin 90 mg/sq m given as a continuous i.v. infusion over three days, and carmustine 90 mg/sq m i.v.; then radiation and tamoxifen therapy.
   b. Bone marrow harvest; then CAF for one cycle; then filgrastim-primed PBPC harvest; then cyclophosphamide 5625 mg/sq m i.v., cisplatin 165 mg/sq m given as a continuous i.v. infusion over three days, carmustine 600 mg/sq m i.v. given over two hours, bone marrow and PBPC infusion, and filgrastim therapy; then radiation and tamoxifen therapy.