Other Formats: MEDLINE
Links: Related Articles

+ BENEFIT

High-dose chemotherapy with autologous stem cell rescue for breast cancer: yesterday, today and tomorrow.

Brockstein BE, Williams SF

Department of Internal Medicine, University of Chicago, Illinois, USA.

Metastatic breast cancer remains incurable by conventional means and is the second leading cause of all cancer deaths in women in the United States. Laboratory and clinical studies have shown chemotherapy dose intensity may be important in breast cancer therapy, and therefore clinical trials have been investigating high-dose chemotherapy (HDC) with autologous stem cell rescue (ASCR) for the past decade. Initial Phase I trials in heavily pretreated patients demonstrated good response rates but short survival times. The next generation of trials used HDC as initial treatment for metastatic breast cancer and showed improved results. Most recently, patients receive HDC after "induction" chemotherapy to minimize tumor burden prior to HDC. Results from these most recent trials are encouraging, with complete remissions (CR) achievable in at least half of patients and long-term survivors noted. An ongoing randomized trial of HDC versus conventional chemotherapy should answer whether HDC is superior to conventional chemotherapy for metastatic breast cancer. Based on encouraging data from a preliminary trial, two ongoing randomized trials are comparing HDC versus conventional chemotherapy in high-risk primary breast cancer. Technological improvements, better supportive care and experience have all contributed to decrease the morbidity and mortality of this procedure. Additionally, hospitalizations have become shorter and costs may be decreasing. This review will discuss the issues pertinent to this modality in the past and present, including chemotherapy regimens, stem cell technology and related issues, outcomes, ongoing trials and future directions for consideration.

MeSH Terms:

- Antineoplastic Agents/administration & dosage*
- Antineoplastic Agents, Combined/administration & dosage*
- Breast Neoplasms/therapy
- Breast Neoplasms/drug therapy*
- Clinical Trials
- Combined Modality Therapy
- Female
- Hematopoietic Stem Cell Transplantation*
- Human

Substances:

- Antineoplastic Agents, Combined
- Antineoplastic Agents

High-Dose Chemotherapy with Autologous Stem Cell Rescue for Breast Cancer: Yesterday, Today and Tomorrow

Bruce E. Brockstein, Stephanie F. Williams

University of Chicago, Department of Internal Medicine, Chicago, Illinois, USA

Abstract. Metastatic breast cancer remains incurable by conventional means and is the second leading cause of all cancer deaths in women in the United States. Laboratory and clinical studies have shown chemotherapy dose intensity may be important in breast cancer therapy, and therefore clinical trials have been investigating high-dose chemotherapy (HDC) with autologous stem cell rescue (ASCR) for the past decade. Initial Phase I trials in heavily pretreated patients demonstrated good response rates but short survival times. The next generation of trials used HDC as initial treatment for metastatic breast cancer and showed improved results. Most recently, patients receive HDC after "induction" chemotherapy to minimize tumor burden prior to HDC. Results from these most recent trials are encouraging, with complete remissions (CR) achievable in at least half of patients and long-term survivors noted. An ongoing randomized trial of HDC versus conventional chemotherapy should answer whether HDC is superior to conventional chemotherapy for metastatic breast cancer. Based on encouraging data from a preliminary trial, two ongoing randomized trials are comparing HDC versus conventional chemotherapy in high-risk primary breast cancer.

Technological improvements, better supportive care and experience have all contributed to decrease the morbidity and mortality of this procedure. Additionally, hospitalizations have become shorter and costs may be decreasing.

This review will discuss the issues pertinent to this modality in the past and present, including chemotherapy regimens, stem cell technology and related issues, outcomes, ongoing trials and future directions for consideration. *Stem Cells 1996;14:79-89*

Introduction

Despite improvements in screening and detection, new active drugs to treat breast cancer, and improved supportive care, breast cancer mortality remains high, and it is estimated that 46,000 women will die from breast cancer in 1995 [1]. Breast cancer remains the second leading cause of all deaths in women 35-54 years old [1].

Metastatic breast cancer remains incurable with conventional chemotherapy, with less than 10% of patients alive five years after diagnosis. Multiple drugs used alone result in response rates of 20% or greater in previously untreated patients. These drugs include doxorubicin, cyclophosphamide, paclitaxel, the *Vinca* alkaloids (vinorelbine, vincristine and vinblastine), cisplatin, ifosfamide, 5-fluorouracil (5-FU), melphalan, methotrexate, mitomycin and thiotepa [2, 3]. Used in combination, up to 20% of previously untreated women can achieve a complete remission (CR) and an additional 40-50% a partial remission (PR) [4]. Unfortunately, the median duration of response with conventional chemotherapy is less than a year and median survival only about two years [4].

Clinical studies of dose intensity (total drug dose divided by time) have demonstrated its importance in breast cancer. Steep dose-response curves have been demonstrated in some breast cancer cell lines [5]. Retrospective [6, 7] and prospective [8] analyses of women treated with adjuvant chemotherapy have shown improved outcome for those patients receiving the greatest dose intensity. Likewise, retrospective and prospective analyses of women treated for advanced breast cancer have shown improved response rates in patients receiving higher dose intensity [3, 9-11]. These observations prompted investigators in the mid-1980s to

explore the use of high-dose chemotherapy (HDC) for the treatment of breast cancer. Bone marrow taken in large quantities from patients prior to chemotherapy was "transplanted" into these patients solely to ameliorate the severe life-threatening marrow suppression.

This review will discuss the issues pertinent to this modality in the past and present, including optimal chemotherapy regimens, stem cell technology and related issues, outcomes, ongoing trials and future directions for consideration.

History

Several investigators in the mid-1980s reported data on patients with a variety of refractory solid tumors who underwent HDC with bone marrow (BM) rescue [12-16]. Many of these patients treated on these Phase I trials had breast cancer. Data regarding some of these patients are presented in Table 1.

Notable from these early studies were the high response rates (CR 0%-38%, CR + PR 62%-94%) in patients with advanced, pretreated breast cancer. Unfortunately the duration of response was disappointingly low. Mortality was high, with interstitial pneumonitis, hepatic veno-occlusive disease and sepsis accounting for most of the deaths. Despite the disappointingly short period of response and the high mortality rate (9%-30%), the high response rates encouraged further study of this modality for the treatment of advanced breast cancer.

The next generation of studies focused on patients who were less heavily pretreated. Improved outcomes relative to heavily pretreated

patients were noted. Subsequent studies focused on treating minimally pretreated patients with "induction" chemotherapy followed by HDC. Theoretical benefits of this approach include: 1) a decrease in tumor burden prior to HDC in an attempt to increase CR rates (a requisite for long-term remission) and 2) selection of "chemosensitive" patients for HDC procedures, sparing toxicity to patients unlikely to respond to HDC. Important findings included: 1) the ability to convert patients to CR after previously achieving only a PR with conventional chemotherapy [17] and 2) long-term complete responses in a subset of patients. Treatment-related mortality remained high, however, and survival times were not clearly better than with conventional chemotherapy.

Chemotherapy Drugs for HDC

Optimal characteristics for a drug to be used in a dose-intensive fashion are: 1) demonstration of a steep dose-response curve both in vitro and in vivo (i.e., small increments in dose of the drug result in logarithmic tumor cell kill); 2) myelosuppression as its major acute toxicity, with other acute toxicities reversible; 3) lack of cross-resistance with previously administered drugs, at least in the dose range planned; and 4) minimal long-term toxicity. Several drugs, mostly alkylating agents, have emerged as suitable drugs. These drugs, their standard non-transplant doses, typical doses and major toxicities, are listed in Table 2.

As with conventional treatment for advanced breast cancer, drug combinations appear to be more active than single agents. Though many

Table 1. Results of selected high-dose chemotherapy regimens in women with advanced breast cancer treated in Phase I trials

Author	Agents	No. Patients	Complete Remission (%)	Complete Plus Partial Remission (%)	Median Response Duration (Mos.)	Mortality (%)
Peters [12]	Cy/CDDP/BCNU	9	33	89	3.5	27
Antman [13]	Cy/CDDP/BCNU	16	38	94	5*	22
Slease [14]	Cy/BCNU	10	20	80	2-7	30
Eder [15]	Cy/Thio/±Melph	8	0	75	2*	9
Moormeier [16]	Cy/Thio/±BCNU	13	8	62	3.5	22

*Median was reported for the entire trial only.
Cy = cyclophosphamide; CDDP = cisplatin; BCNU = carmustine; Thio = thiotepa; Melph = Melphalan

Table 2. Chemotherapy drugs used in HDC

Drug	Standard non-transplant dose (mg/m²)	Typical transplant dose (mg/m²)	Dose limiting toxicity
carmustine (BCNU)	50-100	300-600	interstitial pneumonitis/fibrosis
cyclophosphamide	500-1500	6000-7000	hemorrhagic cystitis; cardiac necrosis
carboplatin	400	800-1800	neurotoxicity; nephrotoxicity
cisplatin	50-100	120-180	neurotoxicity; nephrotoxicity
etoposide	100-500	750-1800	stomatitis
busulfan	1-8 mg/day	16 mg/kg	gastrointestinal; neurotoxicity
ifosfamide	1000-5000	6,000-20,000	hemorrhagic cystitis; neurotoxicity
mitoxantrone	10-15	20-90	cardiac; gastrointestinal
melphalan	40	120-180	mucositis; CNS toxicity
thiotepa	12-60	500-900	neurotoxicity; nephrotoxicity

combinations exist, the most commonly used include cyclophosphamide, cisplatin and BCNU [12], cyclophosphamide and thiotepa, and cyclophosphamide, thiotepa plus carboplatin. Recent trials have incorporated drugs such as etoposide, ifosfamide, mitoxantrone and Taxol®. A more exhaustive list of combinations used can be found in Table 3.

Stem Cell Rescue—Technology and Issues

In the doses currently used, HDC induces a state of bone marrow aplasia. In the absence of stem cell support, the prolonged aplasia could be fatal. Initial trials used bone marrow as a source of "stem cell rescue" (SCR). Prior to receiving high-dose chemotherapy, patients are taken to an operating room where, under general anesthesia, one to two liters of bone marrow are aspirated from the iliac crests bilaterally using multiple punctures. These cells are then cryopreserved with dimethylsulfoxide (DMSO) as the cryoprotectant. Approximately six to ten days after starting chemotherapy, these cells are rapidly thawed and transfused through a central venous catheter into the patient under careful

observation at the bedside. Limiting factors to this method have included: 1) the inability to use the bone marrow of patients with known marrow metastases; 2) marrow hypocellularity in patients having had extensive prior chemotherapy or radiation therapy; and 3) inadequate numbers of hematopoietic precursors in a given harvest with subsequent delay in engraftment. This led in the late 1980s to the successful investigation of "peripheral stem cell harvesting" (PSCH). Progenitor cells are separated or "leukapheresed" by a continuous flow cell separator from a venous access device in outpatients.

Using PSCH, it is possible not only to treat patients with tumor cells in their marrow and patients with low marrow cellularity, but also to acquire, by repetitive apheresis procedures, a predesignated number of stem cells likely to be adequate for hematopoietic recovery. Rapid reconstitution of bone marrow has been found to correlate well with the number of transfused colony forming units-granulocyte monocyte (CFU-GM) cells. Unfortunately, assessment of the CFU-GM number takes 10 to 14 days, and therefore more rapidly assessible surrogate markers must be used to determine the number of necessary daily leukapheresis procedures.

Table 3. Selected published data from HDC studies for patients with previously minimally treated metastatic disease

prev. tx/ chemo sensitive/ ? induction	Author	Year	Type Study	Center	Preparative Drugs	# Patients	CR rate (%)	PR rate (%)	CR & PR rate (%)	TTP (months)	Overall Survival (months from HDC)	Mortality rate (%)
-/-/-	Peters [38]	'88	Phase II	Duke	Cy, CDDP, BCNU	22	55	23	77	7.5	10	23%
-/+/+	Kennedy [39]	'91	II	Johns Hopkins	Cy, TT	24	46	54	100	13*	22*	0
-/+/+	Williams [40]	'92	II	U of Chgo	Cy, TT (±BCNU)	45	44	27	71	7.5**	13**	22**
+/+/+	Antman [41]	'92	II	Dana Farber	Cy, TT, Cb	29	45	41	86	6	23	3
+/+/±	Vaughn [42]	'92	II	Nebraska	Cy, TT, Hydrea	12	50	33	83	9	17 + (60%)	17
±/+/+	Fields [43]	'93	I/II	Tampa	Ifos, Cb, VP16	49	41	12	53	7.5	22	4
+/+/+	Crown [44]	'93	I/II	MSKCC	Cyx2→ Cy/Carbo/VP16	15	59	24	82	9	–	0
-/+/+	Somlo [45]	'93	I/II	City of Hope	Cy, VP16, CDDP	18	56	44	100	8	14	7
-/+/+	Somlo [46]	'94	I	City of Hope	Dox, Cy, VP16	14	–	–	–	9	22	0
±/±/±	Ghalie [47]	'94	I/II	Rush	Cy, CDDP, TT	39	36	31	67	–	–	15
±/+/+	Ayash [48]	'94	II	Dana Farber	Melph→ Cy, TT, Cb	20	35	55	90	15 (52%)	15 + (78%)	0
-/+/+	Dunphy [49]	'94	I/II	M D Anderson	*** (Cy, VP16, CDDP×2)	77	55	25	79	8	15	8

*time from induction; **for all patients, including 9 not receiving HDC; ***One-half of the patients had no stem cell reinfusion
Cy = cyclophosphamide; CDDP = cisplatin; TT = thiotepa; Cb = carboplatin; Hydrea = hydroxyurea; ifos = ifosfamide; VP16 = etoposide; dox = doxorubicin; melph = melphalan; tx = treatment; TTP = time to progression

Traditionally, the number of mononuclear cells (MNC) apheresed has been used to determine adequacy of apheresis, but the MNC number has been shown to correlate poorly to neutrophil and platelet recovery [18, 19]. More recently, the number of cells bearing the early stem cell antigen CD34 has been shown to correlate linearly with the CFU-GM number [18, 20], and several investigators have found a strong correlation between CD34 positive cell counts and the rapid recovery of neutrophils and platelets [18, 21, 22].

Mobilization Methods

Initial attempts to reconstitute hematopoiesis used peripheral stem cells (PSC) harvested from patients in an unstimulated steady state. It has been shown, however, that during the period of hematologic recovery from chemotherapy, progenitor cells are found in increased numbers in the peripheral blood. Leukapheresis during this period of recovery (optimally from about the time the white blood cell [WBC] count reaches 1000 or more from a hematologic nadir) results in the collection of greater numbers of precursor cells and more rapid neutrophil and platelet recovery [23]. Colony stimulating factors (CSFs) given prior to and during leukapheresis, may improve the rate of hematological recovery even further [23].

Microscopic Contamination of Stem Cell Products

Breast cancer cells have recently been shown to have the capacity to contaminate both BM and PSC collections and to possess clonogenic properties in vitro [24]. The use of chemotherapy and CSFs to mobilize PSC may increase the degree of contamination [25]. The clinical significance of contamination of the BM or PSC harvest product by small numbers of tumor cells is not clear. It has been demonstrated that in patients with early stage breast cancer, 4%-48% of patients will have immunohistochemically detectable breast cancer cells in their BM [26]. These patients do not all relapse, and several studies looking at outcome disagree as to whether these cells are correlated with worsened outcome [27-31]. Recently several publications have shown that the presence of tumor cells in stem cell harvests may mark for, or have a direct deleterious effect on outcome in leukemia [32], lymphoma [33], neuroblastoma [34] and breast cancer (Brockstein, submitted for publication).

Concern over the systemic spread of contaminating tumor cells has led several investigators to attempt to eradicate these cells with various forms of purging (negative selection). This includes the use of cytotoxic drugs, immunotoxins and monoclonal antibodies in combination with complement or magnetic microspheres [35]. Alternatively, selective reinfusion of progenitor CD34 stem cells (positive selection) is being investigated by others [36]. Currently, most HDC trials are conducted without stem cell purging.

Outcomes/Results

HDC for Metastatic Disease

Currently multiple academic centers, academic affiliates and recently, community hospitals are involved in HDC for breast cancer. Though early results are promising, HDC has not yet conclusively been shown to improve upon the survival results of standard dose chemotherapy. Unfortunately, the dissemination of this complicated, costly and potentially dangerous technology into widespread use outside of research settings may inhibit the appropriate evaluation of this modality.

The Autologous Blood and Marrow Transplantation Registry (ABMTR) is composed of many of the large institutions performing HDC with autologous stem cell rescue (ASCR). Compilation of data through this organization has allowed evaluation of HDC with ASCR in large numbers of patients. In 1992, over 900 patients underwent HDC with ASCR for breast cancer (550 for advanced disease). In 1994, the ABMTR reported a two-year probability of survival of 35% ± 4% in stage IV patients [37].

Table 3 lists data for selected published trials of HDC with ASCR for breast cancer [38-49]. Note that regardless of the preparative regimen, CR rates are consistently 35%-60% with overall response rates of 60%-100%. Median duration of response ranges from 6-15 months from the time of HDC with median overall survival from 10-22 months from the time of HDC.

Several points deserve mention in the interpretation of the data in Table 3. First, most of these recent studies have required patients to have demonstrated chemotherapy-responsive or at least stable disease. Therefore, response rates will generally be higher than for patients

not undergoing induction chemotherapy. Note too that survival times are generally reported from the time of HDC and, therefore, would be four to eight months longer if the time from diagnosis of metastatic disease were used.

Direct comparisons between HDC and conventional dose chemotherapy are lacking, although a randomized trial is in progress. A recent review of early published studies made indirect comparisons between reports of outcome with HDC and conventional chemotherapy. Response durations and overall survival rates were similar [50]. Caution must be used in drawing conclusions from such comparative analyses. Selection bias of eligibility criteria, aggressiveness of disease, and patient motivation and insurance status are a few factors which may invalidate such non-randomized comparisons.

Several investigators have examined outcome as a function of either response to induction chemotherapy or disease status (CR, PR, etc.) prior to HDC. In one large series, the three-year survival in patients in CR prior to HDC was 47% ± 12%. For patients in PR prior to HDC it was 18% ± 9% [51].

Other investigators have found different prognostic factors for improved outcome for HDC for breast cancer. *Dunphy et al.* found lack of disease in the liver or soft tissues to be associated with improved outcome, as were a disease-free interval greater than a year and a small number of metastatic disease sites. Notably, patients with prior adjuvant chemotherapy did worse, and response to induction chemotherapy was not a prognostic factor [49].

Initial reports in early studies demonstrated mortality rates from transplant of 9%-30% (Table 1). With improved patient selection, better supportive care and experience, mortality is presently under 5%.

HDC for High-Risk Stage II or III Disease

Patients with ≥10 involved lymph nodes at the time of diagnosis have an 80%-90% chance of disease recurrence over 10 years without adjuvant chemotherapy. With adjuvant chemotherapy, this number can be decreased, but most women will still die of their disease. Since high-dose chemotherapy can improve remission rates, and since the optimal setting for success may be in patients with minimal disease, HDC is being investigated as a more effective method of adjuvant chemotherapy.

Peters et al. reported on 85 stage II and III breast cancer patients with 10 or more involved lymph nodes. All patients received four cycles of cyclophosphamide, doxorubicin, and 5-fluorouracil (CAF) followed by high-dose cyclophosphamide, cisplatin and BCNU, followed by stem cell support with BM or BM + PSC with or without CSFs. Twelve percent of the patients died of therapy-related complications. The actuarial probability of relapse at 30 months was 19%. The event-free survival at 30 months was 72%. Comparison to historical controls showed a statistically significant improved outcome [52].

Toxicities

While the mortality from HDC has greatly decreased, acute and late toxicities remain troublesome.

Hematologic

Myelosuppression is, almost by definition, universal. Although red blood cells will always decrease, this limitation can be fairly safely overcome with packed red cell transfusions. Thrombocytopenia and neutropenia are much more menacing problems.

While platelet needs can usually be met initially with transfusion, repetitive transfusion often leads to alloimmunization and platelet refractoriness. In this setting gastrointestinal, genitourinary and central nervous system bleeding can be a source of morbidity and occasional mortality. The use of peripheral stem cells has led to earlier platelet engraftment (11-17 days) [18, 21, 53-56] which may result in fewer bleeding complications. Numerous CSFs have been used to attempt to ameliorate this toxicity, but unfortunately with much less in the way of beneficial effects on platelets as on neutrophils. The recent cloning of thrombopoietin [57] brings great hope toward minimization of the problem of persistent thrombocytopenia.

Neutropenia and leukopenia and the resultant bacterial and opportunistic infections have been a major source of morbidity and mortality in HDC patients. Prior to the use of CSFs, median time to neutrophil recovery (absolute neutrophil count [ANC] >500) was approximately 20 days [41, 53, 56]. The use of CSFs and the addition of peripheral blood progenitor cells (PBPC) have decreased it to approximately

13 da
cells
fusioi
engra
ity, ai
N
toxici
ventic
howev
transp
impor:

Nonhe
Pi
compl
cyclop
olar h
trophil:
and fil
indepe
receivii
or chro
of breai
carbon
tution
clinical
monary
He:
been a
clinical
rant pai
hepaton
chemotl:
may be
[58]. Lo
been use
ineffecti
Otho
toxicities
tericin, a
part of a
2) gastro
vomiting
and 4) ca
[60] and
syndrom
of breast
[52] and
Complic:
after HD(
has been
Whi:
surable c

13 days [18, 21, 54-56]. Selection of CD34+ cells and their expansion in vitro prior to reinfusion raises hopes of even quicker neutrophil engraftment, decreased morbidity and mortality, and decreased hospital stays and costs.

Myelosuppression is often the dose-limiting toxicity with HDC agents when given in conventional doses. Nonhematological toxicities, however, define dose-limiting toxicities in the transplant setting, and these toxicities are an important source of complications.

Nonhematologic Toxicity

Pulmonary toxicity is a major source of complications. Drug toxicity from BCNU, cyclophosphamide or busulfan, pulmonary alveolar hemorrhage related to recovery of neutrophils, volume overload, radiation pneumonitis and fibrosis, may complicate pneumonia or independently cause problems. In patients receiving BCNU, up to 31% [52] will have acute or chronic symptomatic toxicity with shortness of breath, cough, fever and a marked decrease in carbon monoxide diffusing capacity. Early institution of corticosteroids usually reverses the clinical symptoms, although measurable pulmonary function abnormalities may persist.

Hepatic veno-occlusive disease has also been a source of morbidity and mortality. This clinical syndrome marked by right upper quadrant pain, elevated bilirubin, weight gain and hepatomegaly is felt to be a direct toxicity of chemotherapy and/or radiation. Early diagnosis may be possible by doppler ultrasonography [58]. Low-dose heparin, though unproven, has been used in its treatment, but has been proven ineffective prophylactically [59].

Other important and frequently encountered toxicities include: 1) nephrotoxicity from amphotericin, aminoglycosides, and other drugs, or as part of a syndrome of multi-organ system failure; 2) gastrointestinal toxicity including mucositis, vomiting and diarrhea; 3) hemorrhagic cystitis; and 4) cardiac toxicity related to anthracyclines [60] and cyclophosphamide. The hemolytic uremic syndrome (HUS) has been reported in up to 8% of breast cancer patients recovering from HDC [52] and up to 10% of lymphoma patients [61]. Complications can also occur months to years after HDC. Myelodysplasia and/or acute leukemia has been reported in patients after HDC [62].

While neutropenia resolves in weeks, measurable defects, particularly in cell-mediated

immunity, are notable for about a year after HDC [63]. As a result, opportunistic infections are common in the first year after HDC. Two large series found 23%-34% of patients to have a manifestation of varicella zoster virus in the first several years after HDC [52, 64].

Thus nonhematologic toxicity can pose serious short-term problems as well as long-term sequelae.

Supportive Measures

In 1994, the American Society of Clinical Oncology recommended as "reasonable" the routine prophylactic use of CSFs after HDC [65]. Compared to patients treated without CSFs, patients receiving granulocyte colony stimulating factor (G-CSF) achieved an ANC >500 earlier than those not receiving CSFs [65-67].

The serotonin receptor antagonists ondansetron and granisetron have improved the tolerability of HDC by decreasing its emetigenicity [68]. Prophylactic antibiotics are frequently used to prevent infection. In particular, antibacterials such as ciprofloxacin and vancomycin, antifungals such as fluconazole, and antivirals such as acyclovir, may decrease the risk of infection associated with HDC. Standard "neutropenic precautions" including a low bacterial and fungal diet, minimization of invasive procedures, and mask-wearing, are routinely used. Patient rooms generally have high efficiency air filtration systems, and some centers treat patients in laminar flow rooms. Other more rigid preventive measures have not been shown to be helpful and may make for an even more isolating or depressing period for patients already separated from their family and friends and under tremendous stress. Regular intervention with a team of mental health professionals may also be beneficial.

Ongoing Randomized Trials

Preliminary data are promising for improved outcome in breast cancer patients undergoing HDC. Patient selection has, however, hampered direct comparison of HDC to conventional chemotherapy both for patients undergoing treatment of metastatic disease as well as patients receiving adjuvant therapy. It is hoped that large-scale randomized trials will definitively answer these questions.

In North America, the Philadelphia Bone Marrow Transplant Group is randomizing

patients with stage IV breast cancer to treatment with CAF × 6 cycles versus CAF × 6 cycles followed by cyclophosphamide, thiotepa and carboplatin. The CALGB together with some SWOG institutions are randomizing stage II and IIIA patients with ≥10 involved lymph nodes to four cycles of CAF followed by either high-dose cyclophosphamide, cisplatin, and BCNU with stem cell support or intermediate doses of these same drugs without stem cell support. Radiation is given post-transplant to both groups, and tamoxifen to receptor-positive patients. The ECOG and some SWOG centers are randomizing patients to CAF × 6 alone or followed by high-dose cyclophosphamide and thiotepa with stem cell support.

Other European trials are ongoing. Accrual to these trials is necessary to determine the appropriateness of this therapy.

Future Directions

That HDC for breast cancer has the potential to cure only a small fraction of patients mandates improvement in methods for eliminating systemic tumor. Our cost-conscious health care system will demand cost-effective treatment modalities. The morbidity and mortality, though decreasing, needs to decrease further. These three areas remain the focus of research in HDC for breast cancer.

Several approaches are targeted at improved tumor elimination. These include: 1) incorporation of new drugs into preparative regimens; 2) tandem, or multiple cycles of HDC followed by stem cell rescue [69]; 3) post-transplant immunomodulation aimed at inducing an anti-tumor effect [70]; and 4) bone marrow or PSC purging to eliminate contaminating tumor cells.

Improvements in stem cell technology and supportive care should decrease the cost of HDC for breast cancer [71] (recently estimated at $89,000 in 1985 dollars [52]). Improvements in CSF should lead to earlier engraftment. Stem cell expansion should decrease leukapheresis expenses and improve engraftment and thus decrease time spent in the hospital. The recent isolation and synthesis of thrombopoietin brings hope for fewer bleeding complications, shorter hospital stays and decreased expenses and risks related to platelet transfusions. Additionally, several centers are reporting results of outpatient

HDC which may further decrease both the resources needed for and the costs of HDC.

Finally, randomized clinical trials should determine if HDC improves on outcome. Regardless of the results of these trials, it is incumbent on researchers to improve outcome and decrease the cost and morbidity of this procedure.

References

1 Wingo PA, Tong T, Bolden S. Cancer statistics, 1995. Cancer 1995;45:8-30.

2 Henderson IC. Chemotherapy for metastatic disease. In: Harris JR, Hellman S, Henderson IC et al., eds. Breast Diseases. Philadelphia: J.B. Lippincott, 1991:604-665.

3 Hortobagyi GN. Overview of new treatments for breast cancer. Breast Cancer Res Treat 1992;21:3-13.

4 Mick R, Begg CB, Antman KH et al. Diverse prognosis in metastatic breast cancer: who should be offered alternative initial therapies? Breast Cancer Res Treat 1989;13:33-38.

5 Teicher BA, Cucci CA, Lee JB et al. Alkylating agents: in vitro studies of cross resistance patterns in human cell lines. Cancer Res 1986;46:4379-4383.

6 Hyrniuk W, Levine MN. Analysis of dose intensity for adjuvant chemotherapy trials in stage II breast cancer. J Clin Oncol 1986;4:1162-1170.

7 Bonnadonna G, Valagussa P. Dose-response effect of adjuvant chemotherapy in breast cancer. New Engl J Med 1981;304:10-15.

8 Wood WC, Budman DR, Korzun AH et al. Dose and dose intensity of adjuvant chemotherapy for stage II, node-positive breast cancer. New Engl J Med 1994;330:1253-1259.

9 Stewart THM, Retsky MW, Tsai SCJ et al. Dose response in the treatment of breast cancer. Lancet 1994;343:402-404.

10 Tannock IF, Boyd NF, DeBoer G et al. A randomized trial of two dose levels of cyclophosphamide, methotrexate and fluorouracil for patients with metastatic breast cancer. J Clin Oncol 1988;6:1377-1387.

11 Hyrniuk W, Bush H. The importance of dose intensity in chemotherapy of metastatic breast cancer. J Clin Oncol 1984;2:1281-1288.

12 Peters WP, Eder JP, Henner WP et al. High dose combination alkylating agents with autologous bone marrow support. A phase I trial. J Clin Oncol 1986;4:646-654.

13 Antman K, Eder JP, Elias A et al. High dose combination alkylating agent preparative regimen with autologous bone marrow support: the Dana Farber Institute/Beth Israel Hospital experience. Cancer Treat Rep 1987;71:119-125.

14 Slease RB, Benear JB, Selby GB et al. High-dose combination alkylating agent therapy with autologous bone marrow rescue for refractory solid tumors. J Clin Oncol 1988;6:1314-1320.

15 Eder JP, Antman K, Elias A. Cyclophosphamide and thiotepa with autologous bone marrow transplant in patients with solid tumors. J Natl Cancer Inst 1988;80:1221-1226.

16 Moormeier JA, Williams SF, Kaminer LS et al. High dose tri-alkylator chemotherapy with autologous stem cell rescue in patients with refractory malignancies. J Natl Cancer Inst 1990;82:29-34.

17 Williams SF, Mick R, Desser R et al. High dose consolidation chemotherapy with autologous stem cell rescue in stage IV breast cancer. J Clin Oncol 1989;7:1824-1830.

18 Ho AD, Gluck S, Germond C et al. Optimal timing of collection of blood progenitor cells following induction chemotherapy and granulocyte-macrophage colony stimulating factor for autologous transplantation in advanced breast cancer. Leukemia 1993;7:1738-1746.

19 Williams SF. Application of peripheral blood progenitors to dose intensive therapy of breast cancer. Breast Cancer Res Treat 1993;26(suppl 1):25-29.

20 Read EJ, O'Shaughnessy JA, Yu MY et al. Flow cytometric quantification of circulating hematopoietic progenitor cells in breast cancer patients on chemotherapy. Prog Clin Biol Res 1992;377:523-530.

21 Bensinger W, Singer J, Appelbaum F et al. Autologous transplantation with peripheral blood mononuclear cells collected after administration of recombinant granulocyte stimulating factor. Blood 1993;81:3158-3163.

22 Passos-Coelho JL, Braine HG, Davis JM et al. Predictive factors for peripheral-blood progenitor-cell collections using a single large-volume leukapheresis after cyclophosphamide and granulocyte-macrophage colony-stimulating factor mobilization. J Clin Oncol 1995;13:705-714.

23 Myers SE, Williams SF, Geller RB. Cyclophosphamide mobilization of peripheral blood stem cells for use in autologous transplant after high dose chemotherapy: clinical results in patients with contaminated or hypocellular bone marrow. J Hematother 1992;1:27-33.

24 Ross AA, Cooper BW, Lazarus HM et al. Detection and viability of tumor cells in peripheral blood stem cell collections from breast cancer patients using immunocytochemical and clonogenic assay techniques. Blood 1993;82:2605-2610.

25 Bruegger W, Bross KJ, Glatt M et al. Mobilization of tumor cells and hematopoietic progenitor cells into peripheral blood of patients with solid tumors. Blood 1994;83:636-640.

26 Osborne MP, Rosen PP. Detection and management of bone marrow micrometastases in breast cancer. Oncology 1994;8:25-31.

27 Mansi JL, Easton D, Berger U et al. Bone marrow micrometastases in primary breast cancer: prognostic significance after six years follow up. Eur J Cancer 1991;27:1552-1555.

28 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;9:1749-1756.

29 Dearnley DP, Ormerod OG, Sloane JP. Micrometastases in breast cancer: long-term follow-up of the first patient cohort. Eur J Cancer 1991;27:236-239.

30 Kamby C, Rasmussen DB, Kristensen V. Prognostic indicators of metastatic bone disease in human breast cancer. Cancer 1991;68:2045-2050.

31 Salvadori B, Squicciarini P, Rovini D et al. Use of monoclonal antibody MBr1 to detect micrometastases in bone marrow specimens of breast cancer patients. Eur J Cancer 1990;26:865-867.

32 Brenner MK, Rill DR, Moen RC et al. Gene-marking to trace origin of relapse after autologous-bone transplantation. Lancet 1993;341:85-86.

33 Sharpe JG, Joshi SS, Armitage JO et al. Significance of detection of occult non-Hodgkin's lymphoma in histologically uninvolved bone marrow by a culture technique. Blood 1992;79:1074-1080.

34 Rill DR, Santana VM, Roberts M et al. Direct demonstration that autologous bone marrow transplantation for solid tumors can return a multiplicity of tumorigenic cells. Blood 1994;84:380-383.

35 O'Briant KC, Shpall EJ, Houston LL et al. Elimination of clonogenic breast cancer cells from human bone marrow: a comparison of immunotoxin treatment with chemoimmunoseparation using 4-hydroxyperoxycyclophosphamide, monoclonal antibodies and magnetic microspheres. Cancer 1991;68:1272-1278.

36 Shpall EJ, Jones RB, Bearman SI et al. 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 1994;12:28-36.

37 Antman KS, Armitage JO, Horowitz MM et al. Autotransplants for breast cancer in North America. Proc ASCO 1994;67:69a.

38 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;6:1368-1376.

39 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;83:920-926.

40 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;10:1743-1747.

41 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;10:102-110.

42 Vaughn WP, Bierman PJ, Reed EC et al. High-dose hydroxyurea in autologous bone marrow transplantation: a promising "new" agent. Semin Oncol 1992;19:110-115.

43 Fields KK, Elfenbein GJ, Perkins JB et al. Two novel high-dose treatment regimens for metastatic breast cancer—ifosfamide, carboplatin, plus etoposide and mitoxantrone plus thiotepa: outcomes and toxicities. Semin Oncol 1993;20(suppl 6):59-66.

44 Crown J, Kirtz A, Vahadat L et al. Rapid administration of multiple cycles of high dose myelosuppressive chemotherapy in patients with metastatic breast cancer. J Clin Oncol 1993;11:1144-1149.

45 Somlo G, Doroschow JH, Foreman SJ et al. High-dose cisplatin, etoposide and cyclophosphamide with autologous stem cell reinfusion in patients with responsive metastatic or high-risk primary breast cancer. Cancer 1994;73:125-134.

46 Somlo G, Doroschow JH, Foreman SJ et al. High-dose doxorubicin, etoposide and cyclophosphamide with stem cell reinfusion in patients with metastatic or high dose risk primary breast cancer. Cancer 1994;73:1678-1685.

47 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;12:342-346.

48 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.

49 Dunphy FR, Spitzer G, 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;73:2157-2167.

50 Eddy DM. High-dose chemotherapy with autologous bone marrow transplantation for the treatment of metastatic breast cancer. J Clin Oncol 1992;10:657-670.

51 Grad G, Lane NL, Zimmerman T et al. High dose chemotherapy (HDC) and autologous stem cell support in metastatic breast cancer: the University of Chicago experience. Proc ASCO 1994;13:94a.

52 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;11:1132-1143.

53 Broun ER, Sledge W, Einhorn LH et al. High-dose carboplatin and mitoxantrone with autologous bone marrow support in the treatment of advanced breast cancer. J Clin Oncol 1993;16:9-13.

54 Williams SF, Zimmerman T, Grad G et al. Source of stem cell rescue: bone marrow versus peripheral blood progenitors. J Hematother 1993;2:521-523.

55 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;71:2515-2521.

56 Elias AD, Ayash L, Anderson K et al. Mobilization of peripheral blood progenitor cells by chemotherapy and GM-CSF for hematological support after high dose intensification for breast cancer. Blood 1992;79:3036-3044.

57 de Sauvage FJ, Hass PE, Spencer SD et al. Stimulation of megakaryocytopoiesis and thrombopoiesis by the c-Mpl ligand. Nature 1994;369:533-538.

58 McInnis S, Williams SF, Yachnin S et al. Correlation of hepatic ultrasound/doppler with liver biopsy findings in bone marrow transplant (BMT) patients with suspected veno-occlusive disease (VOD). Clin Res 1994;42:376a.

59 Marsa-Vila L, Gorin NC, Laporte JP et al. Prophylactic heparin does not prevent liver veno-occlusive disease following autologous bone marrow transplantation. Eur J Haematol 1991;47:346-354.

60 Lewkow LM, Hooker JL, Movahed A. Cardiac complications of intensive dose mitoxantrone and cyclophosphamide with autologous bone marrow transplantation in metastatic breast cancer. Int J Cardiol 1992;34:273-276.

61 Rabinowe SN, Soiffer RJ, Tarbell NJ et al. Hemolytic-uremic syndrome following bone marrow transplantation in adults for hematologic malignancies. Blood 1991;77:1837-1844.

62 Darrington DL, Vose JM, Anderson JR et al. Incidence and characterization of secondary myelodysplastic syndrome and acute myelogenous leukemia following high-dose chemoradiotherapy and autologous stem-cell transplantation for lymphoid malignancies. J Clin Oncol 1994;12:2527-2534.

63 Olsen GA. Altered immunologic reconstitution after high dose chemotherapy. Transplantation 1988;46:57-60.

64 Han CS, Miller W, Haike R et al. Varicella zoster infection after bone marrow transplantation: incidence, risk factors and complications. Bone Marrow Transplant 1994;13:277-283.

65 American Society of Clinical Oncology recommendations for the use of hematopoietic colony-stimulating factors: evidence-based, clinical practice guidelines. J Clin Oncol 1994;12:2471-2508.

66 Kennedy MJ, Davis J, Passos-Coehlo J et al. Administration of human recombinant granulocyte colony-stimulating factor (filgrastim) accelerates granulocyte recovery following high-dose chemotherapy and autologous marrow transplantation with 4-hydroxyperoxycyclophosphamide-purged marrow in women with metastatic breast cancer. Cancer Res 1993;53:5424-5428.

67 Neidhart J, Mangalik A, Kohler W et al. Granulocyte colony-stimulating factor stimulates recovery of granulocytes in patients receiving dose-intensive chemotherapy without bone marrow transplantation. J Clin Oncol 1989;7:1685-1692.

68 Jantunen IT, Muhonen TT, Kataga VV et al. 5-HT$_3$ receptor antagonist in the prophylaxis of acute vomiting induced by moderately hematogenic chemotherapy—a randomized study. Eur J Cancer 1993;29A:1669-1672.

69 Crown J, Vahgat L, Fennelly D et al. High-intensity chemotherapy with hematopoietic support in breast cancer. Ann NY Acad Sci 1993;698:377-388.

70 Kennedy MJ, Vogelzang S, Beverage RA et al. Phase I trial of intravenous cyclosporin to induce graft vs. host disease in women undergoing autologous bone marrow transplantation for breast cancer. J Clin Oncol 1993;11:478-484.

71 Peters WP, Rosner G, Ross M et al. Comparative effects of granulocyte-macrophage colony-stimulating factor (GM-CSF) in granulocyte colony-stimulating factor (G-CSF) on priming peripheral blood progenitor cells for use with autologous bone marrow after high-dose chemotherapy. Blood 1993;81:1709-1719.