AU: Please provide an abstract

2. INTRODUCTION

The infusion of autologous hematopoietic stem cells allows the administration of higher than normal doses of marrow toxic chemotherapeutic agents. Further escalation of drug doses with stem cell support is ultimately limited by non-hematopoietic toxicities, primarily to the mucous membranes, lungs and liver. The source of stem cells for support following the administration of high-dose chemotherapy (HDC) was originally from bone marrow (BM) which essentially limited this technology to transplant referral centers. However, the emergence of peripheral blood stem cells (PBSC) over the past decade, as the preferred source of hematopoietic stem cells, has made HDC with stem cell support widely available. Peripheral
Blood stem cells can be collected following the administration of chemotherapy and a growth factor or a growth factor alone in an outpatient or blood bank setting by apheresis(1) and cryopreservation technology is relatively simple and widely available.(2)

Although there is controversy about the relative merits of HDC with PBSC support compared to lower-dose chemotherapy treatments with or without the administration of growth factors most published randomized trials have shown superiority for HDC. Selected randomized prospective clinical trials, summarized in table 1, have demonstrated better event-free (EFS) or overall survival (OS) following HDC with stem cell support compared to conventional dose therapy for patients with: Hodgkin’s disease who have relapsed with or without resistant disease(3), aggressive non-Hodgkin’s lymphoma (NHL) as initial therapy(4), aggressive NHL as consolidation in first complete remission (CR)(5), NHL with responding disease who have relapsed after achieving a remission(6), newly diagnosed aggressive non-Hodgkin’s lymphoma (NHL) as initial therapy(4), aggressive NHL as consolidation in first complete remission (CR)(5), NHL with responding disease who have relapsed after achieving a remission(6), newly diagnosed multiple myeloma(8) acute myeloid leukemia (AML) in first remission.(9) No randomized trial has shown HDC with stem cell support to be inferior to conventional dose chemotherapy but some studies have shown equivalency or differences in favor of HDC that were not statistically significant, possibly due to small numbers of patients evaluated.(10,11)

Over the past two decades numerous phase II studies have evaluated HDC supported by autologous hematopoietic stem cells in a variety of chemo-sensitive malignant diseases including malignant lymphoma, AML, chronic myeloid leukemia, multiple myeloma, breast cancer, ovarian cancer, neuroblastoma, Ewing’s sarcoma, germ cell tumors, brain tumors and lung cancer. Review of results of autologous transplants for all these diseases is beyond the scope of this review but have been reviewed elsewhere.(12-14)

The purpose of this manuscript is to present the results of clinical trials of HDC with PBSC support performed in community cancer centers under the supervision of practicing oncologists. Diseases treated are breast cancer, malignant lymphoma, multiple myeloma and ovarian cancer where oncologists participating in these studies believe that HDC with PBSC support is “standard of care”. Data presented here were derived from protocols developed since 1989 by the Clinical Trials Division of Response Oncology Inc.(ROI) involving over 4,000 patients treated with HDC and PBSC support. Approximately 1200 patients/year are evaluated and 650 are treated with HDC and PBSC support in 50 centers by 400 medical oncologists in the ROI network. The list of participating centers is included at the end of this manuscript. This is predominantly an outpatient program with all drugs being administered, PBSC collected and infused in an outpatient department with patients being admitted only for clearly defined complications requiring hospitalization.

### 3. MOBILIZATION AND HARVESTING OF PBSC

Initially, PBSC were harvested after chemotherapy alone, usually high doses of cyclophosphamide (Cy) and infused after HDC.(15,16) Following the availability of recombinant growth factors, granulocyte-colony stimulating factor (G-CSF) or granulocyte macrophage-colony stimulating factor (GM-CSF) were added to high doses of Cy with or without other drugs such as etoposide and cisplatin.(15) With the use of chemotherapy and G-CSF or GM-CSF adequate quantities of PBSC, as measured by the number of CD34+ cells, can be collected in 1-3 aphereses in the majority of patients.(17-19) The administration of G-CSF or GM-CSF alone, without chemotherapy, for mobilization of PBSC is associated with lower, but generally adequate, CD34+ cell yields, has lower morbidity, no hospitalization and apheresis can be scheduled for weekday performance making this the method of choice for blood banks.(1,20,21)

Several studies, summarized in table 2, have been carried out to define yields of PBSC following different regimens. In all these studies CD34+ cell number was used as a measure of hematopoietic PBSC content of the apheresis product.(22) In these studies the minimum CD34+ cell dose necessary for proceeding to HDC was assumed to be ≥2.5 x 106/kg and the optimal dose was ≥5.0 x 106 CD34+ cells/kg.(23,24,20,25,1,22) For comparisons between regimens, effectiveness of a mobilization regimen

<table>
<thead>
<tr>
<th>Disease</th>
<th>Phase</th>
<th>Years</th>
<th>HDC</th>
<th>CC</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodgkin’s</td>
<td>Relapse</td>
<td>3</td>
<td>53%</td>
<td>10%</td>
<td>3</td>
</tr>
<tr>
<td>NHL</td>
<td>First Response</td>
<td>4.5</td>
<td>76%</td>
<td>49%</td>
<td>4</td>
</tr>
<tr>
<td>NHL</td>
<td>First Relapse</td>
<td>5</td>
<td>46%</td>
<td>12%</td>
<td>6</td>
</tr>
<tr>
<td>NHL</td>
<td>First Remission</td>
<td>5</td>
<td>59%</td>
<td>39%</td>
<td>5</td>
</tr>
<tr>
<td>Myeloma</td>
<td>Early Phase</td>
<td>5</td>
<td>28%</td>
<td>10%</td>
<td>9</td>
</tr>
<tr>
<td>AML</td>
<td>First Remission</td>
<td>5</td>
<td>48%</td>
<td>30%</td>
<td>9</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>Metastatic</td>
<td>2</td>
<td>42%</td>
<td>4%</td>
<td>7</td>
</tr>
</tbody>
</table>

**Table 1.** Randomized trials demonstrating superiority of high dose chemotherapy with hematopoietic stem cell support compared to conventional chemotherapy

* *= overall survival; Ref. = reference; HDC = high dose chemotherapy; CC = conventional chemotherapy; NHL = non-Hodgkin's lymphoma; AML = acute myeloid leukemia
Autologous peripheral blood stem cell transplantation

4. MOBILIZATION OF PBSC WITH G-CSF ALONE

Peripheral blood stem cells can be mobilized with growth factors alone without chemotherapy. The optimal growth factor or combination of growth factors for mobilization of PBSC has yet to be defined. However, the most commonly used growth factor for mobilization of PBSC is G-CSF administered in doses of 5-10 µg/kg with initiation of collections on day 5. In order to optimize usage different doses and schedules of G-CSF are still being evaluated.

The effects of escalating doses of G-CSF on yields of CD34+ stem cells were evaluated in 90 patients with metastatic breast cancer and the results are summarized in Table 2. Fifty-five patients were randomized to receive G-CSF 10, 20, 30 or 40 µg/kg/day with more CD34+ cells/kg/apheresis being harvested after the 3 highest dose levels. Thirty-five additional patients were randomized to receive 10 or 30 µg/kg of G-CSF. The median number of CD34+ cells collected after 10 µg/kg (n=31) was 0.7 x 106/kg/apheresis (range 0.1-4.4) compared to 1.2 (range 0.1-6.8) after 30 µg/kg (n=32) (p=0.04). Among patients randomized to 10 versus 30 µg/kg, more achieved ≥5.0 x 106 CD34+ cells/kg and less aphereses were required to achieve ≥2.5 x 106 CD34+ cells/kg after the higher dose (p=0.04). In multivariate analyses patients receiving 10 µg/kg (n=31) had lower yields of CD34+ cells (p=0.026) and had a 3.3 fold increase in the probability of not achieving ≥5.0 x 106 CD34+ cells/kg as compared to patients receiving 20-40 µg/kg (n=59). Patients who had received radiation had a 2.9 fold probability of not achieving ≥2.5 x 106 CD34+ cells/kg. These data suggested that, in patients with good marrow reserves, doses of G-CSF above 10 µg/kg/day mobilized more CD34+ cells with fewer aphereses and may be useful when high numbers of CD34+ cells are desired. However, as a generality, increasing the dose of G-CSF did not improve CD34+ yields in heavily pretreated patients. As shown in Table 2 the highest dose of G-CSF mobilized fewer CD34+ cells/kg/apheresis than any of the chemotherapy regimens evaluated.

5. MOBILIZATION OF PBSC WITH CHEMOTHERAPY AND A GROWTH FACTOR

A variety of chemotherapy and growth factor regimens for mobilization of PBSC have been evaluated and results of studies carried out in an outpatient setting by physicians affiliated with the Clinical Trials Division of ROI are reviewed below and in table 2.

6. MOBILIZATION OF PBSC WITH CYCLOPHOSPHAMIDE, ETOPOSIDE (CE) AND G-CSF

Four hundred ninety seven patients with a variety of malignant diseases received Cy (4 g/m2), etoposide (600 mg/m2) and G-CSF (6 µg/kg/day) for mobilization and collection of a target CD34+ cell harvest ≥2.5 x 106/kg. Results of this study are summarized in table 2. A median of 14.71 x 106 CD34+ cells/kg (range, 0.08-137.55) was harvested with a median of 2 (range, 1-11) aphereses. Ninety-one percent of patients yielded ≥2.5 x 106 CD34+ cells/kg. Patients with stage II-III breast cancer, with pre-treatment platelet counts ≥150 x 109/L and patients who had received ≥1 prior chemotherapy regimen had improved CD34+ cell yields. However, the majority of patients with adverse risk factors yielded ≥2.5 x 106 CD34+ cells/kg. These observations confirm previous reports that the intensity of prior therapy adversely affects the quantity of CD34+ cells harvested. Pre- and post-treatment variables did not predict with any certainty the small fraction of patients who failed to yield ≥2.5 x 106 CD34+ cells/kg with multiple aphereses.

7. EVALUATION OF 2 VERSUS 4 G/M2 OF CYCLOPHOSPHAMIDE IN THE CE REGIMEN

The purpose of this study was to develop a less toxic outpatient chemotherapy regimen for mobilizing PBSC in patients with non-metastatic breast cancer and the results of this study are summarized in table 2(26). Three hundred and eighteen patients with newly diagnosed stage II-III breast cancer who had received conventional-dose adjuvant chemotherapy were randomized to receive intermediate-dose Cy (2 g/m2), etoposide (600 mg/m2) and G-CSF 6 µg/kg/day (ID-Cy, N=162) or high-dose Cy (4...
g/m2) and the same doses of etoposide and G-CSF (HD-Cy, N=156) followed by the collection of PBSC. Patients who received the highest dose of Cy also received mesna for prevention of hemorrhagic cystitis. Three hundred seventeen of 318 patients had apheresis performed. The median numbers of CD34+ cells collected in a median of 2 aphereses following ID-Cy and HD-Cy were 19.9 and 22.2 x 10^6/kg, respectively (p=0.04). The fractions of patients achieving CD34+ cell harvests ≥2.5 or ≥5.0 x 10^6/kg were not different between the two regimens. More patients receiving HD-Cy had grade 3-4 nausea (p=0.001), vomiting (p=0.03) and mucositis (p=0.04). The fractions of patients having a neutrophil nadir <0.5 x 10^9/L following ID-Cy and HD-Cy were .83 and .95, respectively (p=0.001). The fractions of patients having a platelet nadir <25 x 10^9/L following ID-Cy and HD-Cy were .13 and .51, respectively (p=0.001). More patients in the HD-Cy group received platelet (p=0.001) and red blood cell (p=0.001) transfusions and were admitted to the hospital more frequently (p=0.03) than patients receiving ID-Cy. It was concluded that a regimen of Cy 2 g/m2 with etoposide and G-CSF without mesna was effective for mobilization of PBSC with low morbidity and resource utilization in patients with limited prior chemotherapy exposure.

8. COMPARISON OF CE TO CEP FOR MOBILIZATION OF PBSC

The purpose of this study was to evaluate the effects of dose intensity on CD34+ cell yields. Eighty-one patients with malignant lymphoma were randomized to receive Cy (4 g/m2), etoposide (600 mg/m2) and G-CSF (6 μg/kg/day) (CE, N=41) or the same drugs with cisplatin (105 mg/m2) (CEP, N=40) followed by collection of PBSC.(19) Results of this study are summarized in table 2. Seventy-eight of 81 patients (96%) had apheresis performed and 70 (86%) received HDC with PBSC support. The median number of CD34+ cells collected following CE was 19.77 compared to 9.39 x 10^6/kg following CEP (p=0.09). More patients receiving CEP had grade 3-4 gastrointestinal (p=0.03) and neurologic toxicities (p=0.05), had significant delays in recovery of neutrophils (p=0.0001) and platelets (p=0.009) and received more red blood cell (p=0.03) and platelet (p=0.08) transfusions than patients receiving CE. There were no significant differences in treatment-related deaths, relapse or EFS between patients receiving CE or CEP when all 81 patients or the 70 patients receiving HDC were evaluated. It was concluded that the addition of cisplatin to CE did not improve CD34+ cell yields, was associated with higher morbidity and resource utilization and was not associated with improvement in outcomes.

9. EVALUATION OF CYCLOPHOSPHAMIDE, PACLITAXEL AND G-CSF FOR MOBILIZATION OF PBSC

Pacitaxel is an effective agent for the treatment of patients with breast and ovarian cancer. The purpose of this study was to determine if paclitaxel could be utilized for mobilization of PBSC. One hundred forty-one patients with metastatic breast (n=115) or advanced ovarian cancer (n=26) received paclitaxel 170 mg/m2 and Cy, 2 g/m2 (n=42) or paclitaxel 200 mg/m2 and Cy, 3 g/m2 (n=99) and G-CSF (6 μg/kg/day) followed by collection of PBSC by apheresis.(18) Results of this study are summarized in table 2. The 2 dose levels of paclitaxel and Cy tested were well tolerated. The median yield of CD34+ cells from all patients was 6.53 x 10^6/kg (range, 0.11-51.76) collected with a median of 2 aphereses (range, 1-8). A target CD34+ cell yield ≥2.5 x 10^6/kg was achieved in 85% of patients. The mean daily collection of CD34+ cells was 5.46 x 10^6/kg for patients receiving 200 mg/m2 of paclitaxel and 3 g/m2 of Cy as compared to 2.77 for patients receiving the lower doses (p=0.0005). Increasing the dose of paclitaxel and Cy did not significantly increase the fraction of patients achieving a target CD34+ cell harvest ≥2.5 x 10^6/kg (87% vs. 81%, p=0.367) but did increase the fraction achieving ≥5.0 x 10^6 CD34+ cells/kg (73% vs. 45%, p=0.002). The mean daily collection of CD34+ cells for patients who had received only 1 prior chemotherapy regimen was 6.59 x 10^6/kg as compared to 3.47 for patients who had received more than 1 prior chemotherapy regimen (p<0.0001). Prior radiation therapy (p=0.003) and patient performance status (p=0.047) were adverse risk factors for achieving a target CD34+ cell yield ≥2.5 x 10^6/kg.

It was concluded from this study that paclitaxel could be incorporated into a strategy of treatment of patients with breast cancer which involved induction, mobilization of PBSC and HDC.

10. EVALUATION OF CYCLOPHOSPHAMIDE, DOCETAXEL AND G-CSF FOR MOBILIZATION OF PBSC

Docetaxel is an active agent for the treatment of patients with breast cancer. The purpose of this study was to develop a regimen of docetaxel, Cy and G-CSF for mobilization of PBSC in patients with metastatic breast cancer (N=66). A phase I trial of Cy 2, 3 or 4 g/m2 with docetaxel 100 mg/m2, in consecutive cohorts of 4 patients each, did not reveal any dose-limiting toxicities and subsequent patients were randomized to receive 3 or 4 g/m2 of Cy.(27) Patients receiving Cy 4 g/m2 also received mesna for protection against hemorrhagic cystitis. Results of this study are summarized in table 2. The median yield of CD34+ cells from all patients was 11.06 x 10^6/kg (range, 0.03-84.77) from a median of 2 aphereses (range, 1-7); 6.52 x 10^6 CD34+ cells/kg/apheresis (range, 0.01-52.07). Target CD34+ cell harvests ≥2.5 and ≥5.0 x 10^6/kg were achieved in 89% and 79%, respectively. There were no statistically significant differences in CD34+ cell yields or target CD34+ cell harvests following 3 or 4 g/m2 of Cy. Patients with only one prior chemotherapy regimen yielded a median of 12.82 x 10^6 CD34+ cells/kg/apheresis compared to 5.85 for those receiving ≥2 regimens (p=0.03). It was concluded that the combination of docetaxel, 100 mg/m2 and Cy 3 g/m2 without mesna could be administered with acceptable toxicity with collection of adequate quantities of PBSC from the majority of patients with metastatic breast cancer.
11. PATIENTS WHO HAVE LOW CD34+ CELL YIELDS WITH FIRST ATTEMPTS

A small but significant fraction of patients have low CD34+ cell yields with initial mobilization attempts and management of such patients is problematic. Two hundred fifty of 2,157 patients (12%) with breast cancer, lymphoma and multiple myeloma failed to harvest ≥2.5 x 10^6 CD34+ cells/kg in a median of 4 aphereses (range, 1-11).(28) Repeat mobilization attempts were made with chemotherapy and G-CSF (N=61) or G-CSF alone (N=58) in patients who failed initial mobilization with chemotherapy and G-CSF (N=92) or G-CSF alone (N=27). A median of 0.27 x 10^6 CD34+ cells/kg/apheresis was collected following second mobilization compared to 0.16 with initial harvests (p=0.0001). Forty-eight percent achieved a target CD34+ cell harvest ≥2.5 x 10^6/kg when collections from first and second mobilizations were combined. Fifteen of 17 patients (88%) with ≥1.5 x 10^6 CD34+ cells/kg harvested following first mobilization had ≥2.5 x 10^6 CD34+ cells/kg collected when first and second harvests were combined compared to 42 of 102 (41%) achieving <1.5 x 10^6 CD34+ cells/kg with first PBSC harvests (p=0.0001). Second mobilizations with chemotherapy and G-CSF or G-CSF alone resulted in similar CD34+ cell yields. Toxicities of second mobilizations were comparable to first mobilizations. It was concluded that second mobilization attempts in patients who fail to achieve ≥2.5 x 10^6 CD34+ cells/kg on initial mobilization were successful in 48% of patients. G-CSF alone was as effective as chemotherapy plus G-CSF in mobilizing CD34+ cells and was associated with less morbidity. The data also suggested that doses of G-CSF ≥10 µg/kg/day were more effective than 10 µg/kg/day.

12. CONCLUSIONS CONCERNING STUDIES OF PBSC MOBILIZATION

It is evident that PBSC can be harvested after the administration of a growth factor or a combination of growth factors without chemotherapy(20,29,30,21) or following the administration of a variety of chemotherapeutic agents and a growth factor.(31,32,24,33,1,22,17,18) More CD34+ cells can be collected following chemotherapy and a growth factor than following a growth factor alone. However, the potential advantages to administering a growth factor alone include less toxicity and ease of scheduling of apheresis. It is not clear that any chemotherapy regimen is more optimal than another and at the present time it would seem prudent to utilize chemotherapeutic agents for mobilization of PBSC that are appropriate for the disease being treated.

Approximately 5% of patients will fail to achieve adequate doses of CD34+ cells despite second and third mobilization regimens. These patients cannot be identified with any certainty prior to initial mobilization. Such patients would be ideal candidates for future ex-vivo cell expansion studies or for evaluation of new growth factors. However, at the present time ex-vivo cell expansion is not feasible in patients who do not mobilize adequate quantities of CD34+ cells. Whether or not newer growth factors will be effective in this patient population will be of interest.

13. CURRENT STATUS OF PURGING OF BM OR PBSC

The success of HDC with PBSC support is limited mainly by disease recurrence, which ranges from 30-90%. Relapses following HDC are predominantly due to the failure to eradicate residual disease in the patient but are possibly contributed to by infusion of malignant cells contained in the graft.(34) The current status of purging of autologous grafts has recently been reviewed.(35,36)

14. PURGING OF GRAFTS IN PATIENTS WITH NON-HODGKIN'S LYMPHOMA

There have been no randomized trials comparing unpurged to purged grafts in patients with NHL. However, recently the European Bone Marrow Transplant Group published an analysis of 448 patients with NHL receiving purged or unpurged BM following several HD treatment regimens.(37) Purging was performed utilizing a variety of negative techniques, i.e., monoclonal antibodies with complement, immunomagnetic beads or cytotoxic drugs to remove putative tumor cells from the graft. These analyses demonstrated no decrease in relapses or improvement in OS or EFS for patients receiving purged BM. It can be concluded from these analyses that the infusion of occult tumor cells either had no impact on outcomes of patients with NHL or that the purging techniques used were ineffective.

Gribben, et al reported that patients with low-grade NHL who had BM purged with monoclonal antibodies and complement to BCL-2 negativity prior to autologous BM transplantation had a 20% probability of relapse as compared to >85% for patients who did not have BM purged to BCL-2 negativity.(38) All patients had PCR-detectable lymphoma cells in the BM before purging was performed. These observations could be interpreted as direct evidence that the infusion of BCL-2 positive BM caused relapses. However, it is just as likely that patients who are purged to BCL-2 negativity have less endogenous tumor which may be more sensitive to chemo-radiotherapy compared to patients whose BM were not purged to BCL-2 negativity.

In summary, current data would suggest that the benefit of purging of BM or PBSC in patients with low-grade or any other histologic types of NHL has not yet been documented.

15. PURGING OF GRAFTS IN PATIENTS WITH MULTIPLE MYELOMA

Most studies of autologous transplantation for patients with multiple myeloma have utilized unpurged BM or PBSC,(39,40) including the only randomized trial demonstrating superiority of autologous transplantation...
16. PURGING OF GRAFTS IN PATIENTS WITH BREAST CANCER

The role of infused tumor cells in causing relapse after HDC for breast cancer is unresolved. In order to address this issue an evaluation of occult tumor contamination of PBSC, using a sensitive immunocytochemistry (ICC) test in conjunction with BIS Laboratories, was carried out.(43) The purpose of this study was to evaluate the frequency of detecting occult tumor cells in PBSC harvests and to determine the impact of infusing such cells on relapses after HDC. Peripheral blood stem cell harvests from 223 patients with breast cancer were examined by ICC and infused after HDC without consideration of test results. Fifty-three of 581 harvests (9%); 8% from stage II-III and 10% from stage IV patients, were positive by ICC (p=0.68). Forty-one of 223 patients (18%), 17/122 (14%) with stage II-III and 24/101 (24%) with stage IV disease, had positive harvests (p=0.06). Eleven % of patients who had 1-2 harvests tested positive as compared to 32% of patients who had ≥3 PBSC harvests tested (p=0.001). These data suggest that the number of patients with positive ICC tests can be increased by increasing the number of cells tested or increasing the number of apheresis products tested. Implicit in this observation is the likelihood that all patients will have positive tests if enough PBSC products are analyzed.

The probabilities of relapse at 24 months for 97 patients with stage II-III disease infused with ICC negative and the 17 with ICC positive PBSC were .19 and .13, respectively (p=0.48). Probabilities of relapse for the 2 groups of patients, updated to April 1, 1998, are shown in figure 1. The probabilities of relapse at 18 months for patients achieving a CR or a CR in non-bone sites and improvement in bone lesions were .55 for the ICC negative group (n=30) and .45 for the ICC positive group (n=11) (p=0.60). It was concluded that occult tumor cells were detected by ICC in PBSC harvests from a relatively small fraction of women with breast cancer, but were not associated with a significant increase in the probability of early relapse or progression when infused after HDC.

Positive selection of BM or PBSC, using the Ceprate device, has been utilized to purge autologous grafts in patients with breast cancer with a 1-2 log reduction of tumor cells.(44) A randomized trial of unselected versus CD34+ cell selected BM was performed in patients with metastatic breast cancer receiving HDC showing a 31% EFS for both groups.(44) Thus, there was no effect on survival of CD34+cell selection in patients with metastatic breast cancer.

17. CONCLUSIONS CONCERNING PURGING OF PBSC

Despite intense efforts in the laboratory to develop techniques to remove tumor cells from BM or PBSC grafts there have been few randomized clinical trials performed and the only one reported in a definitive form showed no effect on EFS.(44) There are several possible reasons for this but the major one is the large number of patients that are required to document the efficacy of purging, predominantly due to the high relapse rate from endogenous tumor in most clinical situations. As long as treatment failures occur because of failure to eradicate disease in the patient, purging studies will be difficult to perform. However, until data is available documenting a
of both platelet and neutrophil recovery is the CD34+ cell counts within 2 weeks. The single most powerful mediator and platelets with virtually all patients recovering blood. With the use of PBSC larger quantities of stem cells can be extensively transfusion support and antibiotic therapy. (45) marrow, having prolonged pancytopenia requiring 4 weeks of pancytopenia with a small but significant fraction of patients, depending on the quality of the

FOLLOWING INFUSION OF PBSC

18. NEUTROPHIL AND PLATELET RECOVERY FOLLOWING INFUSION OF PBSC

Autologous BM infusion after HDC resulted in 3-4 weeks of pancytopenia with a small but significant fraction of patients, depending on the quality of the marrow, having prolonged pancytopenia requiring extensive transfusion support and antibiotic therapy. (45) With the use of PBSC larger quantities of stem cells can be collected resulting in more rapid recovery of neutrophils and platelets with virtually all patients recovering blood counts within 2 weeks. The single most powerful mediator of both platelet and neutrophil recovery is the CD34+ cell content of the PBSC product. (22) An evaluation of over 600 patients has shown that the optimal cell dose for rapid and complete engraftment of all patients is ≥5 x 10^6 CD34+ cells/kg. (22) Patients will spend <7 days with neutrophils <0.5 and platelets <20 x 10^9/L following infusion of ≥5.0 x 10^6 CD34+ cells/kg. figure 2 shows the mean neutrophil and platelet counts following high-dose CTCb and PBSC infusion of ≥5.0 x 10^6 CD34+ cells/kg in patients with breast cancer. This short period of pancytopenia has significantly lowered the cost of administering HDC by allowing much of the treatment to take place in an outpatient setting. Neutropenia is no longer a reason to admit patients to the hospital if patients are carefully monitored in an outpatient setting and receive prophylactic antibiotics and platelet transfusions.

19. EFFECTS OF INFUSION OF PBSC WITH A LOW CD34+ CELL DOSE

There are clinical situations where infusion of PBSC with relatively low CD34+ cell numbers is a reasonable therapeutic choice. In order to evaluate outcomes in this situation, engraftment kinetics after HDC were determined in patients receiving autologous PBSC infusions with a low CD34+ cell content. (28) Forty-eight patients were infused with <2.5 x 10^6 CD34+ cells/kg; 36 because of poor harvests and 12 because they electively received only a fraction of their harvested cells. A median of 2.12 x 10^6 CD34+ cells/kg (range, 1.17-2.48) were infused following 1 of 7 different HDC regimens. All patients achieved absolute neutrophil counts ≥0.5 x 10^9/L at a median of day 11 (range, 9-16). Forty-seven patients achieved platelet counts ≥20 x 10^9/L at a median of day 14 (range, 8-250). Nine of 47 (19%) had platelet recovery after day 21, 4/47 (9%) after day 100 and one died on day 240 without platelet recovery. Twenty-six patients (54%) died of progressive disease in 51-762 days; 22 (46%) are alive at a median of 450 days (range, 94-1844), 17 (35%) of whom are surviving disease-free at a median of 494 days (range, 55-1263). No patient died as a direct consequence of low blood cell counts. These data demonstrate that PBSC products containing 1.17-2.48 x 10^6 CD34+ cells/kg resulted in relatively prompt neutrophil recovery in all patients but approximately 10% had delayed platelet recovery.

The results of infusing PBSC with a low CD34+ cell content are remarkably similar to results of autologous BM transplantation (45) and suggest that HDC supported by a relatively low CD34+ cell dose is a reasonable option for some patients if warranted by the clinical situation.

<table>
<thead>
<tr>
<th>Number</th>
<th>Regimen</th>
<th>Disease</th>
<th>Phase</th>
<th>TRM</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,000</td>
<td>Varied</td>
<td>Varied</td>
<td>Relapsed</td>
<td>3.4%</td>
<td>46</td>
</tr>
<tr>
<td>208</td>
<td>BEAC</td>
<td>Malignant Lymphoma</td>
<td>Relapsed</td>
<td>3.6-10%</td>
<td>49,50,19,51</td>
</tr>
<tr>
<td>55</td>
<td>Mel x 2</td>
<td>Multiple Myeloma</td>
<td>Newly diagnosed</td>
<td>5%</td>
<td>52</td>
</tr>
<tr>
<td>93</td>
<td>CTCb</td>
<td>Breast Cancer</td>
<td>Metastatic, Early</td>
<td>0%</td>
<td>47</td>
</tr>
<tr>
<td>95</td>
<td>CTCb</td>
<td>Breast Cancer</td>
<td>Stage II-III</td>
<td>0%</td>
<td>48</td>
</tr>
<tr>
<td>315</td>
<td>CTCb</td>
<td>Breast Cancer</td>
<td>Stage II-III</td>
<td>0.3%</td>
<td>26</td>
</tr>
<tr>
<td>29</td>
<td>MMC</td>
<td>Ovarian Cancer</td>
<td>Relapsed</td>
<td>6.9%</td>
<td>53</td>
</tr>
</tbody>
</table>

BEAC = carmustine, etoposide, cytarabine and cyclophosphamide; Mel = melphalan, BuMelTT = busulfan, melphalan and thiopeta, CTCb = cyclophosphamide, thiopeta and carboplatin, MMC = melphalan, mitoxantrone and carboplatin; TRM = treatment-related mortality

survival benefit of purging the most rational approach is to not purge the graft.

20. TREATMENT RELATED MORTALITY

Several published HDC regimens with hematopoietic stem cell support have become widely used. Treatment related mortality (TRM) following commonly used HDC regimens administered in community cancer centers was determined and the results are summarized in table 3 (46). This retrospective study evaluated 1,000 consecutive patients with AML, NHL, Hodgkin’s disease, multiple myeloma, sarcoma, ovarian cancer, or breast cancer who received 1 of 5 published HDC regimens followed by PBSC infusion over a 5 year period. Fifty-nine patients (5.9%) died within 100 days of PBSC infusion. Twenty-five patients (2.5%) died predominantly of causes related to disease progression. Thirty-four patients (3.4%) died of TRM, 15 (1.5%) from infection and 19 (1.9%) from regimen related toxicities. In a logistic model, increasing age (p=0.001) and lower numbers of CD34+ cells infused (p=0.003) were associated with an

...
Autologous peripheral blood stem cell transplantation

Table 4. Results of Clinical Trials of HDC and Autologous PBSC Infusion in Community Cancer Centers

<table>
<thead>
<tr>
<th>Number</th>
<th>Disease</th>
<th>Phase</th>
<th>OS %</th>
<th>EFS %</th>
<th>Time Months</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>83</td>
<td>NHL, high and inter.</td>
<td>Relapse</td>
<td>49</td>
<td>38</td>
<td>36</td>
<td>51</td>
</tr>
<tr>
<td>49</td>
<td>NHL, low grade</td>
<td>Relapse</td>
<td>58</td>
<td>36</td>
<td>43</td>
<td>50</td>
</tr>
<tr>
<td>28</td>
<td>Hodgkin’s Disease</td>
<td>Relapse</td>
<td>77</td>
<td>64</td>
<td>36</td>
<td>49</td>
</tr>
<tr>
<td>55</td>
<td>Multiple Myeloma</td>
<td>Early</td>
<td>84</td>
<td>76</td>
<td>18</td>
<td>52</td>
</tr>
<tr>
<td>93</td>
<td>Breast Cancer</td>
<td>Metastatic</td>
<td>42</td>
<td>19</td>
<td>42</td>
<td>47</td>
</tr>
<tr>
<td>96</td>
<td>Breast Cancer</td>
<td>II-III, ≥10+ Nodes</td>
<td>77</td>
<td>61</td>
<td>48</td>
<td>48</td>
</tr>
<tr>
<td>48</td>
<td>Breast Cancer</td>
<td>II-III, 5-9 + Nodes</td>
<td>77</td>
<td>67</td>
<td>48</td>
<td>55</td>
</tr>
<tr>
<td>31</td>
<td>Ovarian Cancer</td>
<td>Advanced Relapse</td>
<td>60</td>
<td>30</td>
<td>18</td>
<td>53</td>
</tr>
</tbody>
</table>

OS = overall survival, EFS = event-free survival, Time = Time of Estimate of Probability of OS or EFS, II-III = stage of disease; NHL = non-Hodgkin’s lymphoma

21. TREATMENT RELATED MORBIDITY

At the present time, approximately 90% of patients receiving HDC with PBSC support are admitted to the hospital with average stays of 9-12 days.(19,26,46-53) Hospitalization time will depend on the intensity of the HDC regimen, prior chemotherapy exposure and age of the patient. However, with further improvements in the availability of 24 hour outpatient care it should be possible to decrease the fraction of patients requiring admission and to decrease the number of days in the hospital for those that are admitted.

22. OUTCOMES OF CLINICAL TRIALS OF OUTPATIENT HDC WITH PBSC SUPPORT

The outpatient administration of HDC with PBSC support has focused on four diseases where this treatment modality is considered to be of proven effectiveness: breast cancer, malignant lymphoma, multiple myeloma and ovarian cancer. Results of clinical trials of HDC with autologous PBSC support in community cancer for these four diseases will be summarized below.

23. RESULTS OF HDC IN PATIENTS WITH BREAST CANCER

23.1. Patients with Metastatic Breast Cancer

One hundred fourteen patients with untreated stage IV breast cancer, with a median age of 46 years (range, 24-62), were entered on a Phase II trial consisting of: doxorubicin, 5-flurouracil and methotrexate (AFM) x 4 courses at 2 week intervals; (2) CEP, G-CSF (6 µg/kg/day) and PBSC collection; (3) Cy (6 g/m2), thiotepa (500 mg/m2), carboplatin (800 mg/m2)(CTCb) followed by PBSC infusion.(47) All patients agreed to this sequence of therapy at the time of initial treatment. Analyses were performed on an intent to treat basis. The outcome of this trial is summarized in table 4 (47).

All patients received AFM, 107 (94%) received CEP and 106 (99%) received CTCb and PBSC as per protocol and 99 (87%) ultimately received HDC and PBSC. Fourteen patients (13%) did not receive HDC predominantly because of progressive disease. There was 1 infectious death after AFM and all other deaths were associated with progressive disease. Fifty-two patients (46%) are alive, 21 (18%) without progression, at a median 31 months (range, 22-47). The probabilities of OS and EFS at 3.5 years were .40 and .17, respectively. All 62 patients with visceral disease and/or a prior history of doxorubicin adjuvant therapy have relapsed or progressed.

It was concluded that the sequential administration of AFM, CEP and CTDb followed by PBSC resulted in long-term EFS in patients who were NED, had bone-only disease or had lymph node or soft tissue disease with or without bone disease. This study also demonstrated that 13% of newly diagnosed patients did not receive HDC. Future studies of HDC should be performed on an intent to treat basis in order to obviate the bias of reporting those patients who actually receive HDC.

Current clinical trials in patients with metastatic breast cancer include evaluations of: a more intensive treatment regimen of busulfan, melphalan and thiotepa (BuMeITT),(54) the addition of paclitaxel to the induction regimen and an intensive induction regimen of docetaxel and doxorubicin. Future studies will include the evaluation of Her-2 Neu monoclonal antibody infusion after HDC and PBSC infusion and hopefully post-transplant vaccines.

24. PATIENTS WITH STAGE II-III BREAST CANCER WITH ≥10+ NODES

The outcomes for patients with localized high-risk breast cancer undergoing sequential outpatient treatment with conventional-dose adjuvant therapy, chemotherapy and growth factor mobilization of PBSC and HDC with PBSC support in community cancer centers were determined.(48) Patients were enrolled on this study at the time of diagnosis and all results were analyzed on an intent to treat basis. The outcome of this trial is summarized in table 4. Ninety-six patients with stage II-IIIb non-inflammatory breast cancer with ≥10 positive lymph nodes, and a median age of 46 years (range, 22-60), were treated with: (1) AFM x 4 courses at 2 week intervals; (2) CE and G-CSF (6 µg/kg/day) and PBSC harvest; (3) CTCb followed by PBSC infusion.

All 96 patients received AFM, 95 (99%) received CE and 95 (99%) received CTCb with a median hospital stay of 12 days (5-34) for all phases of treatment. Sixty-
autologous peripheral blood stem cell transplantation

nine patients (72%) are alive, 55 (57%) without relapse at a median followup of 53 months (range, 37-77). One patient (1%) died of AML and all other deaths were associated with recurrent breast cancer. The probabilities of EFS at 4 years for patients with or without locally advanced disease were .37 and .69, respectively (p=0.004) and .71 and .48, respectively, for patients who were ER(PR)+ or ER(PR)-, respectively (p=0.016). In multivariate analyses, locally advanced disease (RR=2.3, p=0.021) and ER(PR-) hormone receptor status (RR=2.2, p=0.014) were the only adverse risk factors for EFS identified. Patients with 0, 1 or 2 of these adverse risk factors had 4 year EFS of .80, .56 and .33, respectively.

25. PATIENTS WITH STAGE II-III BREAST CANCER WITH 5-9+ NODES

Forty-three patients with stage II-III disease with 5-9+ axillary lymph nodes, with a median age of 44 years (range, 27-60), were enrolled on a study which included (1) standard dose AFM adjuvant therapy (2) CE and G-CSF mobilization of PBSC; (3) high-dose CTCb followed by PBSC infusion.(55) The outcome of this trial is summarized in table 4. All 43 patients received AFM, 42 (98%) received CE and 41 (95%) received CTCb. Thirty-two patients (74%) are alive, 28 (65%) without relapse at a median of 55 months (range, 41-87). Two died (5%) of treatment-related causes, (subclavian catheter complication after CE and late radiation pneumonitis) with 9 other deaths (21%) being associated with recurrent breast cancer. The probabilities of OS and EFS at 4 years were .77 and .67, respectively, compared to .82 and .69, respectively, for 72 similar patients with ≥10+ axillary nodes receiving the same sequence of therapy. Thus, patients with 5-9+ axillary lymph nodes have a similar risk of failure following HDC and PBSC support as patients with ≥10+ axillary lymph nodes.

26. CONCLUSIONS CONCERNING ADJUVANT THERAPY FOR PATIENTS WITH BREAST CANCER

It was concluded that the sequential administration of AFM, CE or CEP and CTCb followed by PBSC in an outpatient community setting was well tolerated in patients with high-risk stage II-III breast cancer. More intensive and/or more novel treatment strategies will be required to decrease relapses in patients who have ER(PR-) tumors and/or have locally advanced disease.

Current studies are evaluating the effects of paclitaxel following AFM induction. A randomized trial comparing BuMeITT to CTCb is also being initiated in patients with locally advanced breast cancer. Patients with locally advanced and/or inflammatory breast cancer are also receiving intensive neoadjuvant chemotherapy prior to surgery followed by HDC. The post-transplant administration of a Her-2 Neu antibody will be performed in patients with Her-2 Neu positive tumors.

27. RESULTS OF HDC IN PATIENTS WITH MALIGNANT LYMPHOMA

27.1. Patients with Hodgkin’s Disease

Thirty-eight patients with relapsed or refractory Hodgkin’s disease (HD) received CE or CEP and G-CSF for mobilization of PBSC with the intent to treat with HDC with carmustine, etoposide, cytarabine and Cy (BEAC).(49) Analyses were performed on an intent-to-treat basis. A median of 6.4 x 106 CD34+ cells/kg (range, 0.66-2.3) was collected with a median of 3 (range, 2-9) aphereses. Twenty-eight of 38 (74%) patients harvested ≥2.5 x 106 CD34+ cells/kg. Analyses of variables potentially effecting mobilization revealed that the amount of prior chemotherapy statistically influenced the yield of CD34+ cells (p = 0.005). Twenty-eight patients (74%) received BEAC followed by PBSC infusion. The 3-year probabilities of OS and EFS for all 38 patients were 65% and 53%, respectively. The 3-year probabilities of OS and EFS for the 28 patients receiving BEAC were 77% and 64% respectively vs. 33% and 30% for the 10 patients not receiving BEAC. The strategy of administering CE or CEP followed by BEAC was well tolerated with a 100-day TRM of 3.6%. Although development of better strategies to mobilize PBSC may benefit additional patients, currently the best strategy is to collect PBSC early before patients have received extensive chemotherapy. Collection of PBSC immediately following initial relapse or induction failure using CE or CEP allows sufficient CD34+ cells to be collected in greater than 90% of patients.

28. PATIENTS WITH LOW GRADE NHL

Forty-nine patients with low-grade NHL received HDC with busulfan and Cy (BuCy) or BEAC followed by unpurged autologous PBSC infusion.(50) All patients had failed initial chemotherapy or progressed after an initial complete remission. Peripheral blood stem cells were mobilized with Cy alone (n=1), CE (n=19), or CEP (n=29) followed by G-CSF. Twenty-two patients received Bu, 16 mg/kg, and Cy, 120 mg/kg. Twenty-seven patients received BEAC. Four patients (8%) died of non-relapse causes, two (9%) in the BuCy group and two (7%) in the BEAC group. Twenty-seven patients (55%) relapsed or progressed at a median of 9.4 months (range, 2-38) from PBSC infusion. Ten patients who relapsed are alive a median of 31 months (range, 6-47) after relapse. The probabilities of relapse at 3.6 years for patients receiving BuCy or BEAC were .57 and .70, respectively (p=0.92). Twenty-seven patients (55%) are alive at a median of 3.6 years (range, 1-5). The probabilities of OS at 3.6 years for patients receiving BuCy or BEAC were .58 and .55, respectively (p=0.72). The probabilities of EFS at 3.6 years for patients receiving BuCy or BEAC were .36 and .28, respectively (p=0.82). It was concluded that BuCy is an active regimen for the treatment of patients with low-grade NHL.

29. PATIENTS WITH INTERMEDIATE AND HIGH-GRADE NHL
Autologous peripheral blood stem cell transplantation

Eighty-three patients with NHL, who had failed conventional chemotherapy, underwent mobilization of PBSC with chemotherapy and G-CSF in an outpatient facility. At a median of 40 days (range, 26-119) after mobilization chemotherapy all received BEAC followed by infusion of unmanipulated PBSC in an outpatient facility. The probabilities of TRM, relapse/progression, OS and EFS at 3 years for all 83 patients were .07, .57, .49 and .38, respectively. The probabilities of relapse/progression, OS and EFS at 3 years for 28 patients who had failed primary induction chemotherapy were .55, .42 and .38, respectively. The probabilities of OS and EFS for 27 patients in untreated first relapse were .52 and .44, respectively as compared to .56 and .32, respectively for 18 patients who had reinduction attempts prior to receiving mobilization chemotherapy (p=.81 for OS and 0.99 for EFS). No significant risk factors for the outcomes of TRM, relapse/progression, OS or EFS could be identified.

These data demonstrate that approximately 40% of patients with NHL who have failed conventional chemotherapy become long-term disease-free survivors after mobilization chemotherapy, high-dose BEAC and PBSC infusion administered in an outpatient setting in community cancer centers with the major cause of failure being relapse. Results obtained in this study are comparable to published data in similar patient populations receiving therapy as inpatients suggesting that clinical trials involving well tested HDC regimens can be carried out safely in this setting. These data also suggested that HDC should be performed promptly when patients fail initial induction and that reinduction attempts are probably of limited value. Reinduction attempts can also severely limit the quantity of CD34+ cells subsequently mobilized.

30. CURRENT ONGOING CLINICAL TRIAL IN PATIENTS WITH MALIGNANT LYMPHOMA

Current ongoing clinical trials include evaluations of: the more intensive HDC regimen of BuMelTT,(57) post-transplant interferon, post-transplant anti CD20 antibody,(58) HDC in first CR for patients with adverse risk factors for failure of conventional therapy and the role of re-induction chemotherapy in patients at first relapse.

31. RESULTS OF HDC IN PATIENTS WITH MULTIPLE MYELOMA

A study was designed to determine the maximum tolerated dose (MTD) of high-dose melphalan (HDM), with PBSC support, that could be given twice within 90 days to patients with newly diagnosed multiple myeloma.(52) Twenty patients received tandem HDM at 160, 180 or 200 mg/m² and a total of 55 were treated at the estimated MTD of 200 mg/m². Seventeen of 55 (31%) did not receive cycle 2; 6 because of low CD34+ cell yields, 3 because of severe (n=1) or fatal toxicities (n=2) and 8 for other reasons. The median interval between doses for 38 patients was 70 days (range, 41-225). Three of 55 patients (5%) died of treatment-related causes. In patients completing two cycles of HDM, at any dose level, the complete remission rate improved from 15% following cycle one to 55% following cycle two. The probabilities of OS, EFS and relapse or progression at 18 months for the 55 patients treated at the MTD were .84, .76 and .20, respectively, with a median followup of 19 months (range, 9-36) from mobilization chemotherapy. It was concluded that 2 cycles of HDM, 200 mg/m², could be administered to approximately 70% of patients under the age of 66 with multiple myeloma in a median interval of 70 days with improvement in CR rates.

Current studies in patients with multiple myeloma are designed to further evaluate two cycles of melphalan administered at the MTD followed by maintenance therapies. The current study evaluates long-term administration of GM-CSF for the prevention of relapses.(59)

32. RESULTS OF HDC IN PATIENTS WITH OVARIAN CANCER

The purpose of this study was to develop a HDC and PBSC regimen for treatment of patients with ovarian carcinoma that could be administered in an outpatient setting.(53) Fourteen patients with advanced ovarian (N=9) or breast (N=5) carcinoma, who had failed conventional chemotherapy, were entered into a dose-escalation trial to determine the MTD of carboplatin that could be administered with fixed doses of melphalan (160 mg/m²) and mitoxantrone (50 mg/m²). Twenty-five additional patients were included in a phase II trial at the MTD.

Two of 2 patients who had grade 4 severe RRT, 1 fatal, at a dose level of 1600 mg/m². Two of 29 patients (6.9%) treated at the MTD (carboplatin, 1400 mg/m²) died of RRT. All 3 patients who died of toxicity had a calculated AUC for carboplatin > 30 mg/ml/min. Thirty-one patients with ovarian cancer who had failed chemotherapy were treated, 24 at the MTD. Fourteen of 20 patients (70%) with ovarian carcinoma with evaluable disease achieved a CR and 7 (35%) are alive disease-free a median of 20 months (range, 7-26). Five of 7 patients with ovarian cancer who had failed chemotherapy but were rendered clinically disease-free following surgery survive without progression a median of 13 months (range, 9-19). Eight of 16 (50%) platinum-resistant and 4/12 (33%) platinum-sensitive patients with ovarian cancer survive disease-free. The current study utilizes an AUC of 20 µg/ml/min of carboplatin rather than a dose based on body surface. Current studies are focusing on earlier intervention with the MMC regimen in order to improve outcomes.

33. WHAT IS THE FUTURE OF HDC WITH PBSC SUPPORT

33.1. Use of PBSC will Expand for Indicated Therapy and in the Evaluation of New Therapies

The use of PBSC for supportive care of patients receiving high-doses of chemotherapy for patients with chemosensitive malignancies will undoubtedly continue to
expand. If PBSC are collected early in the malignant disease course there is no reason not to incorporate their use into the management strategies. High-dose chemotherapy with PBSC support is best suited for diseases where intensive consolidation is an integral component of disease management. In this setting it makes sense to assure hematopoietic and immunologic recovery by the infusion of PBSC that have not been extensively exposed to chemotherapy or radiotherapy. However, at the present time HDC with PBSC support should only be carried out in the context of clinical trials generating meaningful outcome data.

33.2. Immune Therapies will be Evaluated after HDC with PBSC Support

High-dose chemotherapy support can provide significant cytoreduction of patients already in remission but who still have a high probability of relapse. This creates an ideal setting of minimal residual disease for the evaluation of biological modifiers (IL-2, IL-12) monoclonal antibodies (Rituximab, HER2-Neu) and vaccines. In addition, the infusion of PBSC that have not been extensively exposed to chemotherapy and radiation may result in a more immunocompetent patient than one who has been extensively treated without cellular support.

Studies of immune therapies will require enrollment of large numbers of patients in clinical trials to document benefit. For example, one could envision evaluating an immune therapy where the cure rate is 50% with HDC and PBSC support. In order to detect a 20% decrease in relapses one would have to enroll over 200 patients in each arm and even more if one wanted to detect a 10% difference. These kinds of studies will require access to large numbers of patients which can best be achieved by including patients being treated in community cancer centers.

Neutrophil and platelet recovery following infusion of ≥5.0 x 106 CD34+ cells/kg in patients with breast cancer receiving high-dose cyclophosphamide, thiotepa and carboplatin. ROI Treatment Sites

34. REFERENCES

14. High-dose cancer therapy (pharmacology, hematopoietins, stem cells), (Ed, Armitage, J. O. and
Autologous peripheral blood stem cell transplantation


33. Tricot, G., Jagannath, S., Vesole, D., Nelson, J., Tindle, S., Miller, L., Cheson, B., Crowley, J. & Barlogie, B.:
46. Weaver, C.H., Schwartzberg, L.S., Hainsworth, J., Greco, F.A., Li, W., Buckner, C.D. & West, W.: Treatment related mortality in 1,000 consecutive patients receiving high-dose chemotherapy and peripheral blood progenitor cell transplantation in community cancer centers Bone Marrow Transplant, 19, 671-8 (1997)
47. Weaver, C.H., West, W., Schwartzberg, L.S., Birch, R., McAneny, B., Alberico, T., Hainsworth, J., Greco, F.A., Leff, R. & Buckner, C.D.: Induction, mobilization of peripheral blood stem cells (PBSC), high-dose chemotherapy and PBSC infusion in patients with untreated stage IV breast cancer: outcomes by intent to treat analyses Bone Marrow Transplant, 19, 661-70 (1997)
Autologous peripheral blood stem cell transplantation


Key Words: AU: Please provide key words

Send correspondence to: C. Dean Buckner, M.D., Response Oncology, Inc., 600 Broadway, Suite 112, Seattle, Washington 98122, Tel: 206-726-8921, Fax:206-726-9068, E-mail: dbuckner@responseoncology.com

Received 5/4/98 Accepted 7/21/98

AU:

1. The manuscript has been reformatted. Please check the table of contents and make changes to the numbers that are used in the table of contents and in the text. Change if necessary.

2. Due to formatting, some special characters may be lost. Please read the galley carefully and substitute such characters preferably with their English correlates.

2. Please format the references as follows:

Journal citation:

Book citation:

Please note that the name of the journals is italicized.