Impact of Autologous Bone Marrow Infusion on Hematopoietic Recovery After High-Dose Cyclophosphamide, Etoposide, and Cisplatin

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Because of potential tumor contamination and inadequacy of current purging technique of bone marrow in patients with solid tumors, we investigated an alternative approach to high-dose therapy without autologous bone marrow (ABM) infusion. Three levels of nonmyeloablative doses of cyclophosphamide 4.5 to 5.25 g/m², etoposide 750 to 1,200 mg/m², and cisplatin 120 to 165 mg/m² (CVP) were administered to patients with metastatic solid tumors. Patients were randomized to ABM (n = 46) or no-ABM (NABM) (n = 46) infusion after CVP to study the impact of ABM on hematopoietic recovery, morbidity, and mortality. All patients had ABM harvested, underwent conventional chemotherapy, and then received CVP. Seventy-three patients received two courses of similar doses. The following were the median days to absolute neutrophil count (ANC) of 0.1 × 10^9/L: for the ABM arm, 19, 21, and 19 and for the NABM arm, 23, 20, and 21 at levels 1, 2, and 3, respectively, during course 1 (*P* = .01, .80, and .01, respectively). During course 2, ANCs to 0.1 × 10^9/L and 0.5 × 10^9/L were attained significantly faster at levels 1 and 3 in the ABM arm. ANC to 1.0 × 10^9/L was comparable in both arms. Incidence of infection and duration of fever were similar in both arms. Although mortality and the incidence of delayed hematopoietic recovery were more frequent in the NABM arm, this was not statistically significant. Platelet recovery was consistently prolonged in course 2 in both arms, with demonstrable benefit of ABM in course 2 when dose levels were collectively considered. We conclude that (1) ABM enhanced recovery of ANC to 0.1 × 10^9/L; (2) ABM did not decrease the incidence of infections and the duration of fever; and (3) CVP can be safely given without ABM to carefully selected patients.

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THE DOSE-RESPONSE relationship first demonstrated by Skipper[1,2] and Schabel et al[3] in preclinical models now forms an integral part of the principle of treatment for hematologic malignancies. High-dose chemotherapy supported by autologous bone marrow (ABM) infusion for refractory solid tumors has improved response rates; however, the duration of remission is only marginally prolonged.[4-9] Most patients entered into past studies have had advanced diseases, and the dose-response for solid tumors may be shallow in contrast to that of hematologic malignancies. The more recent generation of clinical studies with high-dose chemotherapy has included standard-dose combination chemotherapy as induction regimen to the point of maximal response, followed by the administration of high-dose chemotherapy for consolidation treatment. With this approach, there appears to be a consistent proportion of patients (10% to 30%) with metastatic estrogen receptor (ER)-negative breast cancer, neuroblastoma, lung cancer, or germ cell tumor who are long-term disease-free survivors.[10-14]

ABM infusion provides a potential means for supporting escalating doses of cytotoxic agents by both modifying the period of pancytopenia and preventing permanent marrow aplasia, which threaten the safety of such intensive approach. The availability of better supportive care and the development of more effective antimicrobial and antifungal agents have decreased the mortality from the early complications of high-dose chemotherapy.

Studies using immunocytochemical stains and in vitro culture have shown that 10% to 28% of histologically normal bone marrows from patients with breast cancer have involvement by tumor.[15-18] No in vitro clonogenic assays of adequate cloning

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efficiency for epithelial tumors exist to evaluate the efficacy of ex vivo elimination of tumor cells from bone marrows. Furthermore, no formal clinical studies have shown any impact of ex vivo attempts at tumor-cell purging on disease-free survival in solid tumors. Therefore, any advantages of ABM infusion if bone marrow is not absolutely necessary might be offset by the reinfusion of occult tumor cells in the marrow.

Therefore, we investigated a different strategy to dose intensification by developing a combination of drugs consisting of cyclophosphamide, etoposide, and cisplatin (CVP). These agents were used because sufficient in vitro experimental data and in vivo studies support the synergism of this combination.[19-26] Doses of these drugs were escalated to levels approaching the intensity of other cytoreductive regimens so that, when given for two courses over a short period of time, they would be at least equivalent. We anticipated that this combination would be associated with reversible neutropenia and may not require ABM infusion for hematopoietic recovery.

We designed a randomized trial of ABM versus no-ABM (NABM) infusion after CVP in an attempt to determine whether the use of ABM infusion significantly alters the rate of hematopoietic recovery and whether an accelerated hematopoietic recovery results in significant reduction in mortality and morbidity measurable as the number of febrile days, the episodes of bacteremia, and the incidence and severity of other toxicities after nonmyeloablative regimens. Each patient was to receive two courses of similar doses of CVP, allowing us to evaluate the effect of ABM infusion in each course. Additionally, this study allowed us to examine for any predictive parameters that might identify the necessity of early ABM infusion in patients who did not receive ABM infusion.

PATIENTS AND METHODS

Patients with histologically confirmed metastatic solid tumors were entered onto the study from April 1986 to March 1989. Patients with ER-negative breast cancer or ER-positive breast cancer with primary refractoriness to hormonal maneuvers were eligible. All patients had a performance status ≤ 2 (Zubrod scale). All patients had an ejection fraction of ≥ 50% by cardiac scan; forced expiratory volume in 1 second, and a diffusion capacity ≥ 50% of predicted; and a serum creatinine level ≤ 133 μmol/L (1.5 mg%), a creatinine clearance of at least 1.00 mL/s (60 cc/min), and total bilirubin level of less than 35 μmol/L (2 mg%). All patients were negative for hepatitis B surface antigen and human immunodeficiency virus antibody. Patients with histologic evidence of tumor cells in the bone marrow were excluded.

Patients were restricted to no more than 12 prior courses of chemotherapy within the last 2 years. Patients who had received prior nitrosourea or mitomycin were excluded. The last chemotherapy or radiotherapy must have been completed at least 3 weeks before entry onto this study. Most patients underwent initial therapy with conventional combinations, the majority of which were doxorubicin-containing regimens; other patients received cisplatin-based or etoposide-based combinations, or both. Patients with stable or responding disease were then eligible to receive intensification with high-dose chemotherapy.

Pretreatment Evaluation

All patients had history and physical examination, complete blood cell counts, differential count, chemical survey, chest radiograph, pulmonary function tests including diffusion capacity, multigated cardiac scan, ECG, bilateral bone marrow aspirates and biopsies, 24-hour creatinine clearance, and appropriate tumor markers. All patients were restaged before entry into the study. Computed tomographic scan of the thorax and/or abdomen when deemed necessary were obtained to measure sites of the disease.

Bone Marrow Harvest and Storage

Technique was as previously described.[10] Patients on both the ABM and NABM infusion arms had 800 to 1,000 mL of bone marrow harvested from bilateral posterior iliac crests under general anesthesia. This was adequate for two courses of high-dose chemotherapy. At least 2×10^8 nucleated cells per kilogram body weight and a minimum postthaw in vitro colony growth of 2×10^4 colony-forming units–granulocyte-macrophage (CFU-GM) per kilogram were required for entry into the study.

Treatment Plan

As approved by the institutional review board, written informed consent acknowledging the investigational nature of the study was obtained from all patients. On admission for high-dose CVP, patients were randomized to ABM or NABM infusion. All patients had a double-lumen central venous catheter inserted before the initiation of CVP infusion. The three dose levels of CVP and the number of patients receiving each are shown in Table 1. Patients were nursed in private rooms. Vigorous hydration to maintain a high urine output was started 24 hours before chemotherapy and continued for 3 days after chemotherapy. Cyclophosphamide in 250 mL 5% dextrose in water was given

Table 1. Patient Distribution and Dose Levels

	No. of Patients		Dosages (mg/m²)		
Dose Level	NABM	ABM	Cyclophosphamide	Etoposide	Cisplatin
1	11	11	4,500	750	120
2	14	12	4,500	900	150
3	21	23	5,250	1,200	165

intravenously over 1 hour on days 1, 2, and 3; etoposide in 0.9% normal saline was infused over 4 hours every 12 hours on days 1, 2, and 3; and cisplatin in 500 mL of normal saline with 40 g mannitol, 30 mEq potassium chloride, and 8 mEq magnesium sulfate was infused over 2 hours on days 1, 2, and 3. Antiemetic consisted of any combinations of metoclopramide, perchlorphenazine, diphenhydramine, and lorazepam.

The second course was given as soon as the patient's absolute neutrophil count (ANC) was greater than 1.5×10^9/L and the platelet count was greater than 0.1×10^{12}/L, and after all the extramedullary toxicities from course 1 had resolved. Toxicities were graded according to the Eastern Cooperative Oncology Group criteria.[27] Standard criteria for response determination were used.[28]

Bone Marrow Infusion and Supportive Care

Patients randomized to receive ABM were premedicated with 50 mg hydrocortisone and 25 mg diphenhydramine intravenously 30 minutes before ABM infusion. Half of the cryopreserved bone marrow was rapidly thawed to 37°C at the patient's bedside and infused on day 7 from the start of chemotherapy. For patients who were randomized to the NABM infusion arm, half of their ABM was infused on day 28 if their ANC was less than 0.5×10^9/L or on day 35 if their platelet count was less than 0.02×10^{12}/L.

All blood products were irradiated with 25 cGy. Patients' hemoglobin were maintained above 1.24 mmol/L (8 g/dL) with packed RBC transfusion, and platelets were maintained above 0.02×10^{12}/L with single-donor or random-donor platelet transfusions. At the initiation of chemotherapy, all patients were placed on prophylactic trimethoprim-sulfamethoxazole and ketoconazole. During the period of neutropenia, patients were started immediately on vancomycin and a third-generation cephalosporin when their temperature was 38.5°C or higher after cultures.

Statistical Methods

Median days to recovery of a given ANC and platelet count for patients in the two arms of the study were compared using the Wilcoxon rank analysis. Differences in the characteristics of patients between the two arms and difference in the number of febrile days and episodes of bacteremia were analyzed by χ^2 analysis. A P value less than .05 was considered significant.

RESULTS

Ninety-two patients were registered in the study, 46 in each arm: 11, 14, and 21 patients at dose levels 1, 2, and 3, respectively, on the NABM arm, and 11, 12, and 23 patients at dose levels 1, 2, and 3, respectively, on the ABM arm (Table 1). Patient characteristics such as age, tumor type, number of prior chemotherapy cycles, prior radiation therapy, and number of sites of metastases were well matched, as shown in Table 2. Performance status (Zubrod scale) was 0 in 42 patients, 1 in three patients, and 2 in one patient on the NABM infusion arm; 0 in 42 patients and 1 in four patients on the ABM arm. There was no significant difference in the characteristics of the patients in the two arms. Sixty-three percent of the patients had breast cancer. One patient who had had 16 cycles of prior chemotherapy completed her last chemotherapy 9 years before entering this study. Eight patients on the NABM arm had also received adjuvant chemotherapy: five with doxorubicin-based regimens and three with nondoxorubicin-containing regimens. Fifteen patients on the ABM arm had received adjuvant chemotherapy: eight with doxorubicin-based regimens and seven with nondoxorubicin-based regimens.

Table 2. Patient Characteristics

Characteristic	NABM	ABM
No. of patients		
Course 1	46	46
Course 2	35	38
Median age, years (range)	42 (28-66)	45 (27-62)
Tumor types		
Breast cancer	34	34
Lung cancer	7	7
Miscellaneous	5	5
Median no. of prior chemotherapy cycles (range)	4 (2-13)	5 (0-16)
Patient with prior radiation	17	16
No. of sites of metastases		
>2	13	12
2	15	13
1	18	19
0	0	2
Sites of metastases		
Skin and subcutaneous tissues	13	13
Lymph nodes	18	20
Mediastinum	8	9
Bone	14	15
Lung	17	13
Liver	6	8
Other	9	3

Seventy-nine percent of patients received a second course of CVP (35 of 46 patients on the NABM arm and 38 of 46 patients on the ABM arm). The median number of weeks between the two courses for both arms was 5 (range, 3 to 10). Eleven patients on the NABM arm did not receive the second course of high-dose chemotherapy: four died during course 1 (one at dose level 1 and three at level 3), three had progressive disease during or shortly after receiving course 1, two had life-threatening toxicity during course 1, and two refused to proceed to course 2. Eight patients in the ABM arm did not receive the second course:

one died during course 1 (at dose level 1), one had progressive disease, two had severe toxicity, and four refused further CVP.

Differences between the ABM and NABM arms in the median number of days to ANC of $\geq$ 0.1 $\times$ 10^9/L from day 1 of chemotherapy were statistically significant at dose levels 1 and 3, during courses 1 and 2 (Table 1 and Fig 1). The median number of days to ANC $\geq$ 0.5 $\times$ 10^9/L at each level of each course is shown in Table 3. During course 1, the median numbers of days to ANC of $\geq$ 0.5 $\times$ 10^9/L at levels 1, 2, and 3 were 25, 21, and 23 in the NABM arm, respectively, compared with 21, 24, and 22 in the ABM arm (P = .08, .43, and .50, respectively). A different pattern exists when repeated cycles of CVP were used. There was a trend toward delayed recovery in the NABM arm during course 2, reaching statistical significance at dose levels 1 and 3 (P = .02 and .03, respectively). ABM had no effect on the recovery of ANC to 1.0 $\times$ 10^9/L at the different dose levels or on repeat course (Table 3).

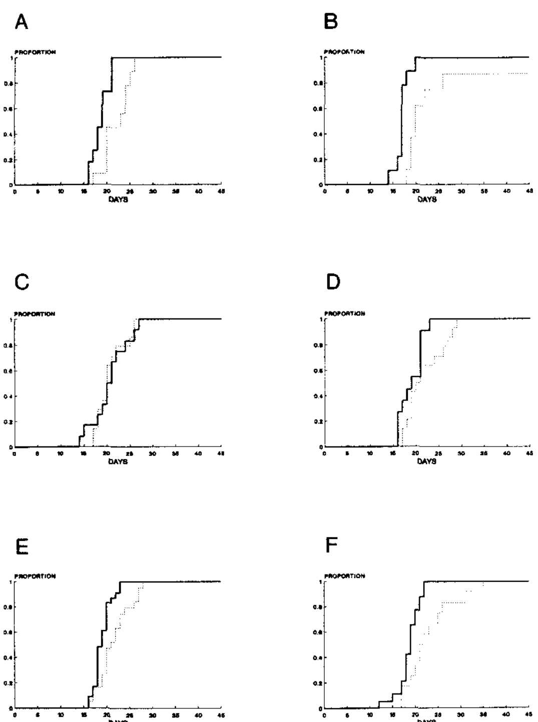

Fig 1. Cumulative distribution of days to ANC $\geq$ 0.1 $\times$ 10^9/L for the ABM infusion arm (—) and for the NABM infusion arm (····). (A) Level 1, course 1, P = .006; (B) level 1, course 2, P = .001; (C) level 2, course 1, P = .796; (D) level 2, course 2, P = .091; (E) level 3, course 1, P = .011; (F) level 3, course 2, P = .011.

We are aware that, because of the small number of patients in each level of each arm, any true difference in the neutrophil recovery may escape detection. When comparing ABM and NABM arms without dose level stratification, ANC recovery to 0.1 $\times$ 10^9/L was similarly hastened on both courses on the ABM arm. ANC recovery to 0.5 $\times$ 10^9/L was significantly faster on the ABM arm only on course 2 (P = .01).

The median number of days to a given platelet count did not differ significantly between the two treatment arms at each dose level except for recovery to a count of 0.10 $\times$ 10^{12}/L at level 1, course 2 (Table 4). When all the dose levels were combined, platelet recovery to 0.05 $\times$ 10^{12}/L and 0.10 $\times$ 10^{12}/L were significantly accelerated during course 2 on the ABM arm compared with the NABM arm (P = .03 and .01, respectively). When comparing courses 1 and 2 within each arm, particularly at dose level 3, course 2 was associated with a significantly prolonged platelet recovery than course 1 in both the ABM and the NABM groups (P < .01 for platelet recovery to 0.02 $\times$ 10^{12}/L, 0.05 $\times$ 10^{12}/L, and 0.10 $\times$ 10^{12}/L).

Eight patients on the NABM arm received ABM infusion: three at level 1, three at level 2, and two at level 3. One patient at level 1, course 2 had an ANC of 0.5 $\times$ 10^9/L at day 28 from the start of chemotherapy and received ABM salvage because of persistent fever despite appropriate intravenous antibiotics. One patient had achieved full hematopoietic reconstitution (ANC 1.7 $\times$ 10^9/L at day 24) but was infused with ABM for secondary loss of engraftment on day 41. Therefore, only six patients were assessable for the effect of ABM salvage. Two patients attained an ANC of 0.5 $\times$ 10^9/L 3 days immediately after infusion of ABM. Three patients recovered their ANCs to 0.5 $\times$ 10^9/L 7, 12, and 21 days after ABM infusion. The remaining one patient who received ABM salvage for delayed platelet recovery never became platelet transfusion-independent and finally succumbed to disseminated aspergillosis. When the ABM arm was examined retrospectively, seven patients with ANCs less than 0.5 $\times$ 10^9/L by day 28 (four during course 1 and three during course 2) and one patient with platelet count less than 0.02 $\times$ 10^{12}/L at day 35 would also fulfill the criteria for ABM salvage. All of these patients eventually engrafted without additional ABM infusion. No identifiable factor predicted for the necessity of ABM salvage

Table 3. Median Days (Range) to Neutrophil Recovery From First Day of CVP

ANC Count at Dose Level	Course 1 NABM	Course 1 ABM	Course 2 NABM	Course 2 ABM
≥ 0.1×10^9/L				
1	23 (17-26)	19 (16-21)*	20 (18-56)	17 (14-20)†
2	20 (17-26)	21 (14-27)	20 (17-28)	19 (16-23)
3	21 (15-28)	19 (16-23)‡	22 (17-35)	17 (15-22)‡
≥ 0.5×10^9/L				
1	25 (18-28)	21 (17-26)	21 (20-56)	20 (18-23)§
2	21 (18-28)	24 (16-32)	23 (17-35)	22 (18-30)
3	23 (15-35)	22 (17-30)	28 (18-45)	22 (14-35)‖
≥ 1.0×10^9/L				
1	28 (19-30)	24 (17-43)	24 (21-64)	22 (19-30)
2	22 (18-40)	26 (17-42)	29 (18-44)	25 (18-40)
3	25 (15-40)	24 (17-36)	29 (19-55)	26 (18-42)

*P = .006.
†P = .001.
‡P = .011.
§P = .017.
‖P = .03.

in these patients. Their median number of previous chemotherapy cycles was five, which was not different from that of the whole group. However, one patient had nine prior cycles of chemotherapy. Three patients had had prior combined radiation therapy and chemotherapy.

The difference in the incidence of febrile episodes or infections between patients in the ABM and NABM arms was not significant. The median numbers of febrile days were 7.0 (range, 0 to 42) and 7.5 (range, 0 to 36) in the NABM and the ABM arms, respectively. The incidence of documented infections (those for which blood cultures were positive) were 51% and 46% in the ABM and NABM arms, respectively. The distribution of infections among dose levels was not different in the two arms. Gram-positive bacteremia was the most common infection, followed by alpha-hemolytic streptococcus, which in two patients resulted in septic shock syndrome.

The overall mortality rate was 9%. Although there were more deaths in the NABM arm (six *v* two), the difference was not statistically significant (P = .27). Furthermore, four of the six deaths in the NABM arm occurred very early (day 13 to day 16 from first day of chemotherapy, or day 5 to day 9 from the supposed day of ABM infusion if they had been randomized to ABM arm) when ABM effect would not yet have been seen, since the median days to an ANC of 0.1×10^9/L was 19, or day 12 from ABM infusion. One other death in the NABM arm was on day 65 from a fungal infection in a patient who had already achieved an ANC of 1.0×10^9/L by day 24. Causes of early death were

Table 4. Median Days (Range) to Platelet Recovery From First Day of CVP

Platelet Count at Dose Level	Course 1 NABM	Course 1 ABM	Course 2 NABM	Course 2 ABM
≥ 0.02×10^{12}/L				
1	20 ((17-30)	18 (16-24)	23 (16-56)	19 (14-25)
2	17 (14-26)	19 (13-27)	23 (15-38)	19 (16-43)
3	21 (15-28)	19 (15-30)	23 (18-65)	22 (15-36)
≥ 0.05×10^{12}/L				
1	22 (17-32)	20 (16-26)	30 (17-56)	23 (19-35)
2	21 (16-30)	20 (16-28)	35 (19-59)	33 (19-69)
3	22 (15-31)	21 (17-35)	28 (19-65)	26 (17-67)
≥ 0.10×10^{12}/L				
1	25 (19-36)	23 (19-29)	45 (36-90)	28 (21-37)*
2	24 (19-39)	23 (12-30)	37 (23-70)	34 (22-46)
3	24 (15-34)	24 (18-41)	38 (24-98)	35 (19-110)

*P = .02 when compared with NABM arm.

two gram-positive sepses, one gram-negative sepsis, two invasive fungal infections, one case of adult respiratory distress syndrome, and one cerebral hemorrhage. Tumor responses to high-dose CVP and nonhematopoietic toxicities were previously reported.[10] The most common toxicity was nausea and vomiting followed by diarrhea and mucositis. Bleeding and renal toxicities were less frequent. Neurotoxicity in the form of high frequency hearing loss, peripheral neuropathy, or both developed in 23% of patients.

DISCUSSION

Most studies on dose intensification using severely myelotoxic regimens have used ABM infusion because of dose-limiting myelosuppression. However, whether ABM infusion is absolutely necessary in regimens with inevitable but reversible pancytopenia is not clear. This trial allowed us to study the degree of myelotoxicity of the CVP combination. Each component of CVP has modest myelotoxicity when used alone. Using cyclophosphamide at 7 g/m^2, Smith et al[29] found that spontaneous hematopoietic recovery occurred in those patients who did not receive ABM; furthermore, the recovery was similar to that of patients who did receive ABM. In a dose-escalation study of etoposide, Postmus et al[30] noted that hematologic toxic effects were completely reversible without the use of ABM even at the highest dose; at 3.5 g/m^2 of etoposide, the mean numbers of days with leukocyte count under 0.1×10^9/L and 0.5×10^9/L were 2 and 6.5 days, respectively. Cisplatin in standard doses results in mild myelosuppression; however, high doses reportedly cause severe but reversible leukopenia and thrombocytopenia.[31]

The probability of infusing potentially tumor-contaminated bone marrow and the impact of ABM infusion on the course of the disease are still unresolved, especially in tumors with a predilection for bone marrow involvement. Current methods of purging bone marrow of tumor cells are still nonspecific and unproven. In vitro purging by chemotherapy may result in a loss of hematopoietic stem cells. Conversely, the use of monoclonal antibodies may allow some tumor cells to escape eradication because of the lack of expression of the tumor antigen on their surfaces. Until effective means of purging tumor cells from the bone marrow emerge and until the biology of marrow contamination can be elucidated, infusion of occult tumor-contaminated marrow will continue to be a concern. We conducted a prospective randomized trial of ABM versus NABM in 92 patients with metastatic solid tumors after escalating doses of CVP in an attempt to determine whether the use of ABM infusion significantly alters the rate of hematopoietic recovery and whether an accelerated hematopoietic recovery results in significant reduction in mortality and morbidity.

ABM hastened early neutrophil recovery (ANC to 0.1×10^9/L), possibly by contributing additional myeloid progenitors to the endogenous pool remaining after high-dose chemotherapy, resulting in a distinct early rise in neutrophils. In contrast, endogenous hematopoietic reconstitution played a major role in the latter part of neutrophil recovery (ANC to 0.5×10^9/L and 1.0×10^9/L), consequently diminishing the effect of ABM. Endogenous myeloid recovery occurred in the NABM arm, and hematopoietic recovery was virtually complete within 5 weeks in almost all patients in this arm, suggesting that the true stem-cell compartment is not markedly depleted with this regimen.

In the present study, ABM demonstrated no benefit over NABM in enhancing platelet recovery during course 1. ABM may provide platelet progenitors, but unlike myeloid progenitors, the number of platelet progenitors in the inoculum may be less than the remaining endogenous pool in the host and, therefore, insufficient to affect recovery. Furthermore, the effect of cryopreservation on platelet progenitors may play a role. The fact that spontaneous, albeit slightly delayed, platelet recovery (shown in patients in the NABM arm) occurred before day 35 suggests that residual platelet precursors remain in the patient.

Platelet recovery during course 2 was more protracted than that in course 1 within each arm and also was more protracted in the NABM arm than in the ABM arm when the dose levels were not stratified. Interestingly, this pattern of delayed recovery of the platelets with course 2 within each arm was not observed with the myeloid component. Thrombopoietin, a major regulator in thrombocytopoiesis, has been isolated from the media of human embryonic kidney cell cultures and kidney cell cultures from adult animals, suggesting that the kidney is a major source of thrombopoietin.[32-34] It is possible that subclinical renal changes induced by high-dose cisplatin used in this study may result in decreased production of thrombopoietin after the first course of CVP leading to a selective delay in platelet recovery during the second course. Additionally, CVP could have depleted the endogenous platelet progenitors, which have limited self-renewing capacity, thereby creating a greater void in the megakaryocytic compartment and allowing a distinct advantage of ABM over NABM arm in course 2. The mechanisms of thrombocytopoiesis are not fully understood. Whereas CFU-GM has been shown in some studies to predict myeloid recovery,[35,36] colony-forming unit–megakaryocyte (CFU-MK) has not been clearly associated with platelet recovery and present methods of quantitating platelet progenitors proximal to the megakaryocytes in the bone marrow need refinement. In long-term cultures, the number of CFU-MK dropped over time, suggesting that CFU-MK may have limited self-renewal capacity.[37] The small mononuclear cells believed to be the transitional cells between megakaryocyte progenitor cells and megakaryocytes do not divide but undergo endomitosis.[37,38] Megakaryocyte–colony-stimulating factor, thrombopoietin, interleukin-3, interleukin-6, erythropoietin, and granulocyte-macrophage–colony-stimulating factor are awaiting further characterization in the regulatory mechanisms in the differentiation and maturation of platelets. The integration of in vitro studies of cytokines into the clinical studies may further define thrombocytopoiesis.

An alternative approach to the modification of CVP is the administration of recombinant growth factors. Studies using recombinant human granulocyte-macrophage–colony-stimulating factor (rhGM-CSF)[39-42] and granulocyte colony-stimulating factor (rhG-CSF)[43-47] showed consistent results in hastening leukocyte and neutrophil recovery; however, absolute neutropenia is not totally abolished. Published data[46] using doses equivalent to level 3 CVP demonstrate that the absolute neutropenia is shortened by 1 day as compared with a course of CVP of comparable intensity without growth factors. The terminal component of neutrophil recovery that is less important in febrile neutropenia is more impressively hastened. Our own study with rhGM-CSF also showed a persistent absolute neutropenia of 7 to 8 days' duration.[48] We are presently investigating if the addition of mobilized peripheral blood to bone marrow and rhGM-CSF will ameliorate the persistent absolute neutropenia of this therapy. The elimination of the major morbidity of CVP will require carefully designed studies incorporating different growth factors with stem-cell support.

Neidhart et al[49] reported on the toxicities of a similar combination. The hematopoietic recovery of their study is not comparable with this study because of different study design, patient population, and supportive measures. Nevertheless, both studies showed that CVP combination is myelotoxic but not myeloablative; furthermore, both observed delayed neutrophil and platelet recoveries with subsequent cycles of high-dose chemotherapy. Their high mortality of 35% (15 of 42 patients) was in marked contrast with the 9% we obtained with a similar regimen without the use of any growth factors. The inclusion of patients with poor performance status in their study could have contributed to the high mortality.

A majority of our patients (79%) received two courses of the same CVP dose. Extramedullary toxicities are acceptable. The small increment in mortality in the NABM arm could be attributed to poor performance status in one patient, very early death in four patients which was unlikely to be impacted on by ABM infusion, and one late death occurring after endogenous marrow recovery took place. We could not identify any factors that were predictive of delayed hematopoietic recovery and, therefore, the need for ABM rescue. We conclude that programs of high-dose chemotherapy can be designed to use selectively highly active drugs with reversible myelotoxicity without compromising intensity or efficacy.

We have shown that despite its effecting a significantly faster recovery of early myeloid progenitors, ABM infusion had no discernible clinical impact on the incidence and duration of febrile episodes or the rate of infection. High-dose CVP can be safely given without ABM infusion and in repeated cycles in carefully selected patients. Caution should be exercised in applying these data to patients who have had previous exposure to stem-cell–toxic agents, ie, mitomycin, nitrosoureas, or busulfan, or to high-dose cytoreductive therapy incorporating such agents.

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