High-Dose Etoposide and Cyclophosphamide Without Bone Marrow Transplantation for Resistant Hematologic Malignancy


Seventy-five patients with resistant acute leukemia or lymphoma received high-dose cyclophosphamide and etoposide to explore the activity of this combination in resistant hematologic malignancies, and to determine the maximum doses of these drugs that can be combined without bone marrow transplantation. Etoposide was administered over 29 to 69 hours by continuous infusion corresponding to total doses of 1.8 g/m² to 4.8 g/m². Cyclophosphamide, 50 mg/kg/d, was administered on 3 or 4 consecutive days (total 150 to 200 mg/kg ideal body weight). At all dose levels myelosuppression was severe but reversible. Mucosal toxicity was dose-limiting with the maximum tolerated dose level combining etoposide 4.2 g/m² with cyclophosphamide 200 mg/kg. Continuous etoposide infusion produced stable plasma levels that were lower than would be achieved after administration by short intravenous infusion, and this could explain our ability to escalate etoposide above the previously reported maximum tolerated dose. There were 26 complete (35%) and 12 partial (16%) responses. Median duration of complete response (CR) was 3.5 months (range 1.1 to 20+). Seventeen of 40 patients (42%) with acute myelogenous leukemia (AML) achieved CR, including 6 of 20 (30%) with high-dose cytosine arabinoside resistance. We conclude that bone marrow transplantation is not required after maximum tolerated doses of etoposide and cyclophosphamide. This regimen is active in resistant hematologic neoplasms, and the occurrence of CR in patients with high-dose cytosine arabinoside-resistant AML indicates a lack of complete cross-resistance between these regimens.

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High-dose therapy with bone marrow transplantation (BMT) is effective treatment for acute leukemia or lymphoma that is resistant to conventional chemotherapy. However, many patients who might benefit are excluded because allogeneic BMT is limited to younger patients with histocompatible donors, while autologous BMT requires histologically normal bone marrow that is free of tumor. Recent clinical trials have shown that several drugs formerly thought to be limited by myelosuppression can be administered as single agents at maximum tolerated dose without BMT. Two of these, etoposide and cyclophosphamide, are active in hematologic malignancies and have different dose-limiting toxicities, suggesting that these drugs might be combined at their full single-agent doses if permitted by myelosuppression. We set out to determine the maximum doses of etoposide and cyclophosphamide that can be used in combination without BMT to treat patients with resistant acute leukemia and lymphoma.

**Materials and Methods**

*Eligibility criteria.* Eligibility criteria included: diagnosis of myelodysplasia, acute leukemia, chronic myelogenous leukemia in blast phase or lymphoma; resistance to conventional therapy or no effective therapy available; no prior high-dose cyclophosphamide (single dose ≥ 50 mg/kg) or etoposide (single dose ≥ 1 g/m²); no severe organ dysfunction unless related to malignancy; Eastern Cooperative Oncology Group performance status 0, 1, 2; and age less than 70 years. Informed consent was obtained from all patients.

*Toxicity.* Because we expected toxicity similar to that produced by BMT regimens, toxicity was graded according to cooperative group guidelines for reporting adverse drug reactions after autologous BMT. In this system, grade 4 indicates fatal toxicity except for hematologic toxicity, which is grade 4 only when death from infection or hemorrhage occurs in pancytopenic patients more than 8 weeks after treatment.

Neutrophil recovery was defined as a blood neutrophil count above 500/µL. Platelet recovery was defined as a blood platelet count above 20,000/µL, independent of platelet transfusion. The day of neutrophil or platelet recovery was the first day these criteria were met (day 1 defined as the first day of chemotherapy). Patients were considered to have achieved hematologic recovery after recovery of both neutrophils and platelets.

**Treatment regimen.** The starting dose level combined etoposide 1.8 g/m² with cyclophosphamide 150 mg/kg (VP1.8/CY150), approximately 75% of the single agent maximum tolerated doses (Table 1). At least five patients were treated at each dose level and observed for a minimum of 6 weeks before dose escalation. Dose escalation proceeded until the combined incidence of grade 3 (life-threatening) and grade 4 toxicity exceeded 20% with P > 0.16. The dose level below that producing dose-limiting toxicity was the maximum tolerated dose. All patients received one course of therapy.

Etoposide was dissolved in normal saline at 0.4 mg/mL and administered by continuous intravenous (IV) infusion at 175 mL/m²/h (70 mg/m²/h) over 26 to 69 hours. At this concentration etoposide solutions are stable for 48 hours. When etoposide infusion was complete, IV fluids were begun at 150 mL/m²/h and continued until 24 hours after completing chemotherapy. Cyclophosphamide, 50 mg/kg, was dissolved in 500 mL D5W and administered over 2 hours on 3 or 4 consecutive days (total dose 150 to 200 mg/kg). Cyclophosphamide dose was based on ideal or true body weight, whichever was less. The first cyclophosphamide dose was administered 6 to 12 hours after completion of etoposide infusion, with subsequent doses at 24-hour intervals. Furosemide, 10 to 20 mg, was administered IV 2 hours after each cyclophosphamide dose, and as...
needed to maintain urine flow above 100 mL/h for 24 hours after completing chemotherapy. Prophylactic continuous bladder irrigation was not used.

Standard supportive care was provided as previously described.\textsuperscript{18}

\textit{Definition of response and statistical analysis.} Patients with acute leukemia, myelodysplasia, or chronic myelogenous leukemia in blast phase underwent bone marrow examination at the time of hematologic recovery. Within 1 month of hematologic recovery all patients with lymphoma underwent restaging, which consisted of repeating all studies that demonstrated disease before treatment.

For patients with acute leukemia, myelodysplastic syndrome, or chronic myelogenous leukemia in blast phase, complete response (CR) required a normocellular bone marrow with less than 5% blasts and normal peripheral blood counts. Partial response (PR) was defined as 5% to 15% blasts in the bone marrow with normal peripheral blood counts. For patients with lymphoma, CR was defined as no evidence of tumor by all previous clinical and roentgenographic methods used to demonstrate tumor. Partial response was defined as a greater than 50% reduction in the sum of the products of the perpendicular measurements of all tumors without progression at any site with stable or improving performance status.

Response and survival duration were calculated from the first day of chemotherapy (day 1) with follow-up through October 1, 1989. Minimum response duration was 1 month. Patients who received additional treatment after high-dose etoposide and cyclophosphamide were censored from analysis of response duration on the first day of subsequent treatment.

Median day of neutrophil and platelet recovery was calculated using a life-table technique in which patients dying of toxicity were censored from analysis on the day of death.\textsuperscript{19} Proportions were compared by chi-squared analysis or Fisher's exact test, and confidence intervals were calculated using standard formulas.\textsuperscript{15,16}

\textit{Determination of etoposide concentration.} Serial plasma etoposide levels were determined in eight patients (four receiving VP3.6/CY200 and four receiving VP4.2/CY200). For this purpose, 10 mL of plasma was collected immediately before beginning etoposide infusion, and then every 12 to 24 hours for 72 to 96 hours. Etoposide levels were analyzed by high-pressure liquid chromatography and kinetic parameters were calculated as previously described.\textsuperscript{21}

\textbf{RESULTS}

Between August 1, 1986 and January 15, 1989, seventy-five patients with resistant hematologic malignancies received high-dose etoposide and cyclophosphamide (high-dose VP/CY) (Table 2). One patient with secondary acute myelogenous leukemia (AML) and two with chronic myelogenous leukemia in blast phase were previously untreated. The other 72 patients (96%) had progressive disease after conventional chemotherapy. Thirty-nine of 40 patients with AML had previously received high-dose cytosine arabinoside (cytosine arabinoside 1.5 to 3.0 g/m\textsuperscript{2} every 12 hours for 8 to 12 doses). Twenty patients with AML (50%) were considered high-dose cytosine arabinoside-resistant because of failure to achieve CR with high-dose cytosine arabinoside immediately before high-dose VP/CY. Of these patients, 18 failed induction with high-dose cytosine arabinoside and two failed treatment in first relapse. Patients who failed induction with high-dose cytosine arabinoside had received no prior therapy for acute leukemia, and were considered to have failed

\begin{table}[h]
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\caption{Dose Levels and Toxicity}
\begin{tabular}{|c|c|c|c|c|}
\hline
Dose Level & No. of Patients & Grade 2 Mucositis\textsuperscript{*} & Grade 3 Mucositis\textsuperscript{†} & Delayed Neutrophil Recovery\textsuperscript{‡} & Toxic Death\textsuperscript{§} \\
\hline
VP1.8/CY150 & 11 & 4/11 (36) & 0/11 (0) & 3/7 (43) & 3/11 (27) \\
VP2.4/CY150 & 8 & 2/8 (25) & 0/8 (0) & 2/6 (40) & 1/8 (13) \\
VP2.4/CY200 & 19 & 1/19 (5) & 0/19 (0) & 5/13 (38) & 3/19 (16) \\
VP3.0/CY200 & 8 & 3/8 (37) & 0/8 (0) & 5/6 (83) & 0/8 (0) \\
VP3.6/CY200 & 9 & 3/9 (33) & 0/9 (0) & 4/7 (57) & 0/9 (0) \\
VP4.2/CY200 & 9 & 4/8 (50) & 1/9 (11) & 2/7 (29) & 0/9 (0) \\
VP4.8/CY200 & 11 & 3/3 (100) & 5/8 (62) & 5/11 (45) & 6/11 (54) \\
All & 75 & 20/66 (30) & 6/72 (8) & 26/56 (46) & 13/75 (17) \\
\hline
\end{tabular}
\textsuperscript{*}Toxicity grades defined in Materials and Methods. Excludes three patients not evaluable for mucosal toxicity and six patients with grade 3 mucosal toxicity. \(P < .05\) comparing two highest doses to all lower doses combined.

\textsuperscript{†}Recovery of neutrophils (>500/\mu L) or death from infection without neutrophil recovery more than 27 days after initiating treatment. Pancytopenic patients with persistent leukemia or myelodysplasia (\(n = 19\)) were excluded.

\textsuperscript{‡}Deaths all resulted from infection. Frequency of toxic death at VP4.8/CY200 significantly higher than for all lower doses combined (\(P = .002\)).

\textsuperscript{§}Recovery of neutrophils (>500/\mu L) or death from infection without neutrophil recovery more than 27 days after initiating treatment. Pancytopenic patients with persistent leukemia or myelodysplasia (\(n = 19\)) were excluded.

\end{table}

\begin{table}[h]
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\caption{Patient Characteristics and Response}
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\hline
Diagnosis & No. & CR(\%) & PR(\%) \\
\hline
AML & 40 & 17 (42) & 5 (12) \\
Myelodysplasia & 3 & 1 & 1 \\
CML-BP\textsuperscript{*} & 6 & 2 (33) & 0 \\
ALL/LL\textsuperscript{†} & 14 & 4 (28) & 2 (14) \\
Non-Hodgkin's\textsuperscript{‡} & 8 & 2 (25) & 6 (75) \\
Hodgkin's & 4 & 1 & 2 \\
All & 75 & 27 (36) & 12 (16) \\
\hline
\end{tabular}
\textsuperscript{*}CML-BP, chronic myelogenous leukemia in blast phase.

\textsuperscript{†}ALL/LL: nine patients with TdT (+), CALLA (+) acute lymphoblastic leukemia and five with T-cell acute lymphoblastic leukemia or T-cell lymphoblastic lymphoma.

\textsuperscript{‡}Non-Hodgkins: 4 patients with small cleaved cell lymphoma, 2 with diffuse large cell lymphoma, 1 with Burkitt's lymphoma, 1 with HTLV I (+) T-cell lymphoma.

One patient with Hodgkin's not evaluable for response.
induction when persistent disease was documented after a single course of high-dose cytosine arabinoside.

**Mucosal toxicity.** Three patients were not evaluable for mucosal toxicity because of death or intubation before day 14. High-dose VP/CY produced dose-related and dose-limiting stomatitis and esophagitis (Table 1). Grade 3 mucosal toxicity (ulceration requiring parenteral narcotics for over 2 weeks) occurred in six patients (8%, 95% confidence interval [95% CI], 2% to 14%) and was significantly more common among patients receiving VP4.8/CY200 (62%, 95% CI, 28% to 96%) than among patients receiving lower doses (1.6%, 95% CI, 0% to 4.6%) (P < .001). Because of the prohibitive incidence of grade 3 mucositis among patients receiving VP4.8/CY200, the maximum tolerated dose level of high-dose VP/CY is VP4.2/CY200. As shown in Table 1, grade 2 mucosal toxicity (ulceration requiring parenteral narcotics for 2 weeks or less) was significantly more common among patients treated at the two highest dose levels (P < .05).

**Hematologic toxicity.** Severe pancytopenia (neutrophils less than 500/μL and platelets less than 20,000/μL) occurred in all patients. Nineteen patients with leukemia or myelodysplasia were not evaluable for hematologic toxicity due to persistent disease. This included three patients who died of toxicity with persistent disease. Ten patients died of toxicity without hematologic recovery and without evidence of persistent disease. These patients were censored from analysis of hematologic recovery on the day of death. Forty-six patients achieved hematologic recovery. Neutrophil recovery occurred on median day 27 (range 19 to 58), with platelet recovery on median day 30 (range 17 to 62) (Fig 1). Median times to neutrophil and platelet recovery were not affected by age or diagnosis. There were no hemorrhagic deaths and no grade 4 hematologic toxicity (death from complications of pancytopenia over 8 weeks after treatment).

To evaluate the effects of dose on hematologic recovery the proportion of patients with count recovery or toxic death occurring later than the median day of neutrophil or platelet recovery for the entire group was calculated for each dose level. Patients dying of toxicity with persistent leukemia or myelodysplasia were excluded. As shown in Table 1, dose escalation did not affect the proportion of patients with neutrophil recovery or toxic death over 27 days after treatment (P = .79 comparing VP4.8/CY200 with lower dose levels). Similarly, dose escalation did not increase the proportion of patients experiencing late platelet recovery (data not shown).

Thirteen patients (17%, 95% CI, 8% to 26%) died from toxicity 8 to 45 days after treatment. All toxic deaths were the result of infection. Although the risk of toxic death did not increase with dose escalation from VP1.8/CY150 to VP4.2/CY200, there was a significant increase in the risk of toxic death among patients treated at the highest dose level (P = .002 comparing VP4.8/CY200 with lower doses). The risk of death from infection over 27 days after treatment was also increased at the highest dose level (3 of 11 patients at VP4.8/CY200 v 1 of 64 patients at lower doses, P = .005).

**Hepatic toxicity.** Six patients were not evaluable (1 with choledocholithiasis, 1 with hepatic candidiasis, and 4 dying before day 21 without hepatic toxicity). Asymptomatic elevation of bilirubin, alkaline phosphatase, or serum glutamic oxaloacetic transaminase (SGOT) occurred in most patients. Significant elevation of bilirubin (≥1.5 times normal) occurred in 26 of 69 patients (38%). Moderate to marked elevation of alkaline phosphatase or SGOT (greater than 5 times normal) occurred in 4% and 6% of patients, respectively. There was no relation between dose level and degree of hepatic enzyme elevation. Enzyme abnormalities peaked 15 to 30 days after treatment, and in all surviving patients returned to baseline within 3 months. No patient developed clinical evidence of liver failure.

**Additional toxicities.** Emesis was controlled with high-dose metoclopramide and inaprisine. A transient, hyperchloremic metabolic acidosis was common during etoposide infusion. Nadir bicarbonate ranged from 9 to 21 mmol/L.
(median 17 mmol/L) with blood pH 7.29 to 7.35. Hyperventilation was the only clinical manifestation. As postulated by Wolff et al,11 acidosis probably results from the solvent system provided for reconstitution of etoposide.

Four patients developed symptomatic hemorrhagic cystitis, including one patient who required surgery for bladder perforation. One patient developed dyspnea requiring supplemental oxygen 1.5 months after VP2.4/CY200. Lung biopsy showed interstitial pneumonitis that improved with corticosteroids.

There was no other grade 3 or 4 toxicity.

**Etoposide pharmacokinetics.** Mean plasma etoposide concentrations are shown in Fig 2. In each patient stable plasma etoposide levels were achieved within 24 hours of beginning etoposide and were maintained until completion of the infusion. Etoposide concentration during the plateau phase demonstrated significant inter-patient variation (range 37 to 111 µg/mL). The terminal etoposide half-life was 8.2 ± 2.0 hours. Volume of distribution was 15.0 ± 5.3 L/m². Etoposide clearance was 18.9 ± 4.4 mL/min/m². Area under the concentration-time curve, corrected for dose (AUC/dose), was 55.9 ± 13.6 (µg/mL x min)/mg/m².

**Response.** One patient with Hodgkin’s disease was not evaluable for response because of radiotherapy to all measurable disease immediately before high-dose VP/CY. For the remaining 74 evaluable patients there were 27 CR (36%, 95% CI, 25% to 47%) and 12 PR (16%, 95% CI, 8% to 24%) (Table 2). Median CR duration was 3.5 months (range 1.2 to 20+). Six of 22 patients (27%, 95% CI, 8% to 46%) with resistant lymphoid neoplasms (non-Hodgkin’s lymphoma, acute lymphoblastic leukemia) achieved CR. All evaluable patients with Hodgkin’s disease responded (1 CR, 2 PR). Two patients with Hodgkin’s disease continue in unmaintained CR 16.5+ and 20+ months after high-dose VP/CY, including the patient who received radiation therapy immediately before treatment. Both received high-dose VP/CY in relapse after treatment with MOPP (nitrogen mustard, vincristine, procarbazine, and prednisone) and an anthracycline-based regimen.

Seventeen of 40 patients (42%, 95% CI, 27% to 57%) with relapsed or refractory AML achieved CR (median duration 4.0 months, range 1.2 to 12), including 6 of 20 patients (30%, 95% CI, 10% to 50%) with high-dose cytosine arabinoside resistance. The longest unmaintained response was 12 months. One additional patient remains in unmaintained CR more than 9 months after treatment. All other patients with AML have relapsed.

**DISCUSSION**

Cyclophosphamide and etoposide are synergistic in selected tumor models,22,23 and BMT regimens that combine these drugs with total body irradiation or other alkylating agents can produce durable remissions in resistant hematologic malignancies.14-24 Administered as a single agent, stomatitis is dose-limiting for etoposide, with the maximum tolerated dose being 2.4 to 3.0 g/m².8,11 Cardiac toxicity limits the maximum cyclophosphamide dose to 200 mg/kg or 7.2 g/m².12-14 Administration of either drug at maximum tolerated dose does not require BMT. In the only previous trial of combined high-dose therapy with these drugs, 13 patients with resistant solid tumors received escalating doses of etoposide with high-dose cyclophosphamide (7.0 g/m²) and autologous BMT.7,3. Mucositis prevented escalation of etoposide above 2.0 g/m². Neutrophil recovery occurred a median of 22 days after beginning treatment with two toxic deaths (15%).

The maximum doses of etoposide and cyclophosphamide that can be combined without BMT have not been previously determined. We have shown that high-dose cyclophosphamide (200 mg/kg ideal body weight or approximately 7.2 g/m²) can be administered with etoposide 4.2 g/m² without BMT. As in previous trials of high-dose etoposide, mucosal toxicity was dose-limiting. Dose escalation did not affect the median day of neutrophil or platelet recovery. However, the risk of death from infection was significantly increased at the highest dose level, possibly as a result of severe mucositis with compromised mucosal barriers.

The median times to hematologic recovery and the incidence of death from infection are similar to figures reported by other investigators after dose-intensive therapy with autologous BMT.25-27 Therefore, it seems unlikely that autologous BMT would reduce the toxicity of high-dose VP/CY.

Transient elevation of hepatic enzymes was common, although clinically significant hepatic dysfunction did not occur. Reversible elevation of hepatic enzymes has been described after cumulative etoposide doses exceeding 6 g/m².28 We have not retreated patients with high-dose VP/CY because of concern that cumulative hepatic toxicity could occur.

The pharmacokinetics of high-dose continuous infusion etoposide has not been previously characterized. Pharmacokinetic parameters obtained in this study are similar to those described after administration of etoposide by intermittent, short (2- to 3-hour), IV infusions.21,28 Total drug exposure, as measured by AUC/dose, is comparable with the value reported by Hande et al.21 Despite achieving equivalent or
slightly higher AUC/dose values and using similar toxicity criteria, the maximum tolerated etoposide dose reported here is 75% higher than reported by Wolff et al.1 Wolff administered etoposide by 2- to 3-hour infusion on 3 consecutive days (maximum tolerated dose 2,400 mg/m² or 800 mg/m²/d for 3 days) and obtained peak plasma etoposide levels comparable with the plateau values reported here after administration of larger doses by continuous IV infusion. If mucosal toxicity is related to peak etoposide level, the difference in maximum tolerated dose could result from a reduction in peak levels associated with continuous infusion. Therefore, continuous infusion may reduce etoposide toxicity without compromising drug exposure (as quantitated by AUC/dose). Because none of the eight patients from whom drug levels were obtained developed moderate or severe mucosal toxicity, a relationship between drug levels and mucosal toxicity cannot be confirmed. We plan to obtain serial etoposide levels in additional patients to further investigate the relationship between drug levels and toxicity.

Despite the effectiveness of BMT regimens that include high-dose etoposide or high-dose cyclophosphamide, little is known about the activity of these drugs as single agents at high dose in resistant hematologic neoplasms. Santos et al.20 showed that high-dose cyclophosphamide with allogeneic BMT could produce CR in patients with resistant leukemia, but graft-versus-host disease and treatment-related mortality prevented assessment of remission duration. In a more recent trial, cyclophosphamide administered at 50% to 60% of the maximum tolerated dose (100 to 120 mg/kg) without BMT produced objective tumor regression (CR or PR) in 9 of 13 (69%) patients with resistant lymphoma.31 However, all but two responses were of less than 6 months duration. Conventional doses of etoposide (100 to 500 mg/m² every 14 to 28 days) produce CR of short duration in 5% to 20% of patients with relapsed AML or lymphoma.23,33 However, Van Echo et al.30 obtained no CRs after treatment of 12 patients with resistant AML using etoposide doses of 1.0 to 1.5 g/m². We were unable to find any report describing treatment of patients having resistant acute leukemia or lymphoma with single-agent etoposide at doses approximating the maximum tolerated dose.

High-dose cytosine arabinoside is one of the most active regimens available for resistant AML, with CR occurring in 41% to 71% of those treated, including a 20% CR rate among patients with resistance to conventional cytosine arabinoside and daunorubicin.10,35,36 In the present study all responding AML patients had previously received high-dose cytosine arabinoside, and 50% were resistant to such treatment, having failed to achieve CR with high-dose cytosine arabinoside immediately before treatment with high-dose VP/CY. Despite such intensive prior therapy, high-dose VP/CY produced CR in 42% of all patients with AML. The attainment of CR in 30% of patients with high-dose cytosine arabinoside-resistant AML distinguishes high-dose VP/CY as one of few regimens capable of producing CR in such patients, and indicates a possible lack of complete cross-resistance between these regimens.37 To further evaluate the activity of high-dose VP/CY in resistant AML we plan to treat additional patients at the maximum tolerated dose level.

The objective response rate of 64%, including 27% CR among patients with resistant lymphoid neoplasms, indicates that high-dose VP/CY merits further evaluation in these malignancies as well. Two of four patients with resistant Hodgkin's disease achieved durable CR. The activity of high-dose VP/CY in resistant Hodgkin's disease is not surprising since high-dose cyclophosphamide, etoposide, and carmustine (CBV) followed by autologous BMT produces CR in approximately 40% of such patients.3 Treatment of additional patients with resistant Hodgkin's disease is needed, but if the activity of high-dose VP/CY is confirmed this regimen would have the advantage of not requiring BMT.

A significant number of patients who could potentially benefit from dose-intensive therapy are excluded because they are not candidates for BMT. Allogeneic BMT is generally limited to patients under the age of 55 with histocompatible siblings. However, human leukocyte antigen identical sibling donors are available for only 35% to 40% of patients.48 Adding to this the restriction imposed by age, less than 25% of patients with resistant acute leukemia or lymphoma will be candidates for allogeneic BMT.39 Donor registries are an incomplete solution to this problem because the likelihood of identifying an HLA identical donor is less than 50%, even with registries exceeding 1 x 10⁶ potential donors.40 Autologous BMT can produce durable remissions in resistant lymphoma, but the effectiveness of in vitro purging of tumor cells is unknown, so that the curative potential of autologous transplantation in the setting of bone marrow involvement by tumor is unproven. Collection of hematopoietic progenitors from the peripheral blood by apheresis can provide an alternative source of stem cells for patients with lymphomatous involvement of the bone marrow.41 However, concern remains that these collections are contaminated by circulating tumor cells.

A requirement for hematopoietic stem cell support has not been documented for most high-dose regimens that are currently administered with BMT. On the contrary, the occurrence of incomplete chimerism after 1,000 to 1,320 cGy total body irradiation indicates that hematopoietic stem cells can survive therapy that is commonly considered to be myeloablative.42 Given the risks and restrictions imposed by BMT, it is important to determine if dose-intensive therapy requires stem cell support to be effective. Clinical trials of this sort also provide an excellent opportunity to determine the effects of cytokines on hematopoietic recovery after dose-intensive therapy.

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REFERENCES


