Transplantation Potential of Hematopoietic Cells Released Into the Circulation During Routine Chemotherapy for Non-Hodgkin’s Lymphoma

By Ruth Pettengell, Nydia G. Testa, Richard Swindell, Derek Crowther, and T. Michael Dexter

Primitive hematopoietic cells released into the peripheral blood (PB) were studied in 50 patients with high-grade non-Hodgkin’s lymphoma enrolled in a phase III trial of intensive weekly chemotherapy (VAPEC-B) alone or with granulocyte colony-stimulating factor (G-CSF). Mononuclear cell numbers were monitored and their in vitro growth potential assessed in clonogenic progenitor cell assays and in long-term culture. Total colony-forming cells (granulocyte-macrophage [GM], burst-forming unit, erythroid [BFU-E], Mix-CFC) were increased 40-fold (median) over baseline with chemotherapy alone and 106-fold with chemotherapy and G-CSF at the final dose. CD34⁺ cells were increased to a median of 4%, equivalent to that in normal bone marrow (BM) controls. Circulating colony-forming cell levels were maximal when the recovering total white blood cell (WBC) count reached 5 to 10 X 10⁹/L. The timing of the maximum was reproducible in individual patients. Therefore the WBC count can be used as a guide to the timing of leukapheresis. PB cells from normal controls and patients’ prechemotherapy were unable to sustain hematopoiesis in two-stage long-term cultures. In contrast, PB cells collected from patients primed with chemotherapy alone or chemotherapy with G-CSF at the time of predicted maximal colony-forming cell release were able to generate and sustain hematopoiesis in long-term cultures at a level comparable or superior to normal BM. These findings indicate that the use of G-CSF after routine outpatient chemotherapy stimulates maximal release of primitive hematopoietic cells into the circulation, including colony-forming cells and long-term culture–initiating cells. Their numbers are comparable with those in normal BM and are such that a single leukapheresis will usually yield enough cells for hematopoietic reconstitution after myeloablative chemotherapy.

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2239
weekly chemotherapy alone or with G-CSF. Eighty previously untreated patients aged 16 to 71 years with histologically documented high-grade NHL (Kiel classification) of any stage and performance status were randomized to receive chemotherapy alone or chemotherapy with G-CSF. Fifty patients able and willing to attend for additional sampling underwent detailed blood studies. The study was approved by the District Ethics Committee, and all patients gave informed consent before entry into the trial.

Thirteen patients were studied in the group treated with chemotherapy alone. Their median age was 56 years (range 23 to 67 years). There were 10 men and 3 women. BM infiltration was present in two patients at the start of chemotherapy.

Thirty-seven patients were studied in the group treated with chemotherapy plus G-CSF. Their median age was 47 years (range 16 to 67). There were 21 men and 16 women. BM involvement was present at the start of chemotherapy in six patients.

**Chemotherapy**

Patients received treatment with either 11 weeks of VAPEC-B chemotherapy alone or VAPEC-B with G-CSF (Fig 1). For all patients, chemotherapy comprised alternating myelosuppressive (doxorubicin, 35 mg/m², intravenously [IV], at weeks 1, 3, 5, 7, 9, and 11; cyclophosphamide, 350 mg/m², IV at weeks 1, 5, and 9; etoposide 100 mg/m², orally [po] daily for 5 days at weeks 3, 7, and 11), and nonmyelosuppressive chemotherapy (vincristine, 1.4 mg/

![Fig 1. The VAPEC-B treatment schedule (above) and absolute neutrophil counts (below) on the planned day of treatment for patients receiving chemotherapy alone or chemotherapy and G-CSF. Weekly cycles of treatment are given. A, Adriamycin, 35 mg/m², IV; C, cyclophosphamide, 350 mg/m², IV; V, vincristine, 1.4 mg/m², IV (maximum 2.8 mg); B, bleomycin, 10 mg/m², IV; E, etoposide, 100 mg/m², po daily for 5 days. Enteric-coated prednisolone, 50 mg/d, is administered for 5 weeks, then 25 mg/day for 5 weeks, and then reduced to zero over 2 weeks. Cotrimoxazole, 960 mg, twice a day po, and ketoconazole, 200 mg, twice a day are orally administered for 12 weeks. The shaded areas represent the days of administration of G-CSF, 230 μg/m²/d sc. G-CSF was discontinued at week 13 or when the absolute neutrophil count (ANC) reached 20 × 10⁹/L, whichever was the sooner. Data points represent median ± interquartile range.](#)
CD34+ Cell Population Analysis

An indirect immunofluorescent technique was used to label cells with a CD34+ monoclonal antibody (MoAb) (HPCA-1, Becton-Dickinson, Mountain View, CA). The percentage of CD34+ cells was estimated on a fluorescent-activated cell sorter (FACS).

Colony-Forming Cell (CFC) Assays

For clonogenic progenitor cell assays, Ficoll-separated PB mononuclear cells were plated in IMDM supplemented with 4 × 10^{-5} mol/L glutamine, 2.5 × 10^{-4} mol/L sodium selenite, 0.25% trypsin at 37°C. After 10 minutes, adherent cells were depleted by incubation at 2°C for 5 minutes. The resulting single-cell suspensions were depleted of red blood cells (RBC) by gravity sedimentation with 1% sodium bicarbonate. The percentage of CD34+ cells was determined by flow cytometry using a CD34+ MoAb (HPCA-1, Becton-Dickinson, Mountain View, CA).

Long-Term Cultures

Two-stage long-term cultures were used. To prepare the adherent stromal cell layers, BM cell suspensions from normal donors were depleted of red blood cells (RBC) by gravity sedimentation with 1% sodium bicarbonate. The percentage of CD34+ cells was determined by flow cytometry using a CD34+ MoAb (HPCA-1, Becton-Dickinson, Mountain View, CA).

Cell Release Into PB

Mononuclear Cells

Before chemotherapy, the numbers of mononuclear cells and CFC per milliliter of blood were comparable with those of a control group of normal individuals. The mononuclear cell fraction at cycles 7 and 11 before commencing AE were not significantly different from baseline pretreatment levels. The peak number of mononuclear cells recovered after Ficoll separation in the G-CSF–treated group doubled after cycle 1 and trebled after cycles 7 and 11 of chemotherapy compared with the pretreatment baseline levels (Table 1). No significant increase was seen in the control group.

Primitive Hematopoietic Cells

Numbers of CFC. An increase in circulating CFC over baseline levels was observed after chemotherapy alone (Table 1). After AC at cycle 1, a seven-fold increase in peak colony numbers over pretreatment levels was observed.
Total colonies shown.

GM-CFC Data are shown as median (range) with the fold increase over pretreatment levels. The contribution Mix CFC Fold increase Fold increase Fold increase Fold increase Fold increase Fold increase

MNC 965 (288-1967) 392 (137-1085) 949 (282-5277) 2218 (584-7252) 3074 (376-8389) 2755 (801-18128)

GM-CFC 16 (1-129) 142 (64-1902) 734 (67-2593) 1927 (334-7185) 5018 (1070-12343) 6796 (135-14723)

GM-CFC 9 46 120 314 425

BFU-E 107 (0-571) 783 (17-8413) 4005 (542-10526) 5259 (286-18293) 9839 (1468-16023) 8186 (171-21211)

BFU-E 1 29 80 184 95

BFU-E 0 (0-5) 1 (0-29) 29 (0-165) 80 (0-212) 184 (0-943) 95 (0-547)

BFU-E 1 29 80 184 95

Hematopoietic progenitor release during VAPEC-B chemotherapy. A, Adriamycin (day 0), E, etoposide (days 0-4), C, cyclophosphamide (day 0). Data are shown as median (range) with the fold increase over pretreatment levels. The contribution of each colony type to total colony number is shown.

This contrasts with a 40-fold increase in colony numbers after AE at cycle 11 (Table 1).

CFC release after chemotherapy was markedly enhanced by G-CSF administration (Table 1). At cycle 1, total colony numbers per milliliter of blood increased 56-fold and at cycles 7 and 11, 124-fold and 106-fold, respectively (P < .0005, Kruskal-Wallis test). Colony numbers per milliliter of blood before myelosuppressive chemotherapy at cycles 1, 7, and 11 were not significantly different, so there was not an additive effect from 11 cycles of chemotherapy.

The chemotherapy-alone patients showed little increase in colony number after cycle 1, whereas the chemotherapy plus G-CSF patients showed increase in colony numbers. After cycle 11, an initial decrease in colony numbers was followed by an exponential increase. The G-CSF patients showed a more rapid recovery and increased to a 10-fold higher peak colony number than the chemotherapy-alone group. Colony numbers remained high for 2 to 3 days before returning toward baseline. Megakaryocyte colony numbers paralleled this release pattern with a median eight-fold (range 1.5 to 73) increase over the baseline at day 0 of cycle 7.

Kinetics of CFC release. Table 2 shows the day of maximal CFC release from day 0 of chemotherapy in each cycle. Although the day of maximum CFC release appears similar after AC and AE, the prolonged administration of AE (5 days v 1 day for AC) conceals the finding that CFC release occurs relatively earlier after the more myelosuppressive AE treatment. This applied to both groups of patients. Those receiving chemotherapy plus G-CSF achieved maximal CFC release earlier than those receiving chemotherapy alone. In individual patients, the day of maximal progenitor release was reproducible after the same myelosuppressive stimulus unless the patient became septic.

In individuals who developed sepsis during treatment, progenitor release was delayed until resolution of the infection and the numbers of colonies remained at levels seen in patients receiving chemotherapy alone. In these patients, release was normal in subsequent cycles. Progenitor release was also lower in patients with poor performance status at presentation (data not shown).

Prediction of maximal CFC release. The release of primitive hematopoietic cells parallels the WBC counts and mononuclear cell counts but precedes them (Fig 2). In patients receiving VAPEC-B and G-CSF, the nadir of CFC after cycle 11 (AE) falls on median day 7 (range: 6 to 9) and the WBC count nadir on median day 9 (range: 4 to 11). The peak release of CFC occurs on median day 11 (range: 9 to 15) and the WBC peak on median day 15 (range: 7 to 18). The WBC decreased rapidly after stopping G-CSF, so that the last day of G-CSF administration was always the day of peak WBC. G-CSF treatment was continued beyond the CFC peak in 19 of the 30 G-CSF-treated patients. Progenitor cells peaked and fell despite a continuing increase in

| Table 1. Maximum Number of Mononuclear Cells (MNC) and CFC per Milliliter of Blood |
|-------------------------------|-------------------|-------------------|-------------------|-------------------|
| Pretreatment | Chemotherapy Alone | Chemotherapy and G-CSF |
| (N = 16) | (N = 6) | (N = 11) | (N = 18) | (N = 8) | (N = 22) |
| MNC | 965 (288-1967) | 392 (137-1085) | 949 (282-5277) | 2218 (584-7252) | 3074 (376-8389) | 2755 (801-18128) |
| Fold increase | - | 0.5 | 1 | 2 | 3 | 3 |
| Total colonies | 133 (3-661) | 918 (66-10344) | 5339 (593-13284) | 7383 (836-23407) | 15463 (2274-23564) | 14080 (226-36110) |
| Fold increase | - | 7 | 40 | 56 | 124 | 106 |
| GM-CFC | 16 (1-129) | 142 (64-1902) | 734 (67-2593) | 1927 (334-7185) | 5018 (1070-12343) | 6796 (135-14723) |
| Fold increase | - | 9 | 46 | 120 | 314 | 425 |
| BFU-E | 107 (0-571) | 783 (17-8413) | 4005 (542-10526) | 5259 (286-18293) | 9839 (1468-16023) | 8186 (171-21211) |
| Fold increase | - | 7 | 37 | 49 | 92 | 58 |
| MNC | 0 (0-5) | 1 (0-29) | 29 (0-165) | 80 (0-212) | 184 (0-943) | 95 (0-547) |
| Fold increase | - | 1 | 29 | 80 | 184 | 95 |

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<th>Table 2. Day of Maximal Progenitor Cell Release During VAPEC-B Chemotherapy From the First Day (Day 0) of Each Cycle</th>
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Timing of progenitor release during VAPEC-B chemotherapy from the first day of each cycle. Data are shown as median day of maximum release (range) after cycle 1 (AC) and cycles 7 and 11 (AE) for patients receiving chemotherapy alone or chemotherapy with G-CSF.
Fig 2. Temporal relation between total WBC count and PB progenitor release after myelosuppressive chemotherapy (AE) in eight patients in whom G-CSF was continued past the colony peak in cycle 11. In all patients, the G-CSF was started 24 hours after the last chemotherapy (day 6) and was discontinued at the WBC count peak. Peak progenitor release coincides with the early phase of the exponential increase in WBC count.
WBC counts (Fig 2). No patient achieved a WBC peak before the peak in CFC. In all patients, peak progenitor release coincided with the exponential increase in the WBC. Therefore, maximal hematopoietic progenitor release was predicted by the early exponential phase of increasing WBC. Progenitor numbers remained high for several days in some patients but fell rapidly in others.

**CD34+ cell analysis** At the time of peak progenitor release after cycle 1 chemotherapy and G-CSF, a median of 4.0% (range: 0.5 to 6.0, N = 24) CD34+ cells were observed in the mononuclear cell population. This compares with 0.18% (range: 0.11 to 1.54, N = 8) of CD34+ cells present in the mononuclear cell population of normal individuals and 1.79% (range: 0.75 to 8.3, N = 7) of CD34+ cells present in the mononuclear cells of normal BM.

**Generation of Hematopoiesis in Long-term Culture**

**Normal Controls**

PB mononuclear cells from normal individuals, seeded on irradiated BM stroma were unable to generate long-term hematopoiesis in two-stage long-term cultures. Numbers of nonadherent cells per culture fell rapidly to 10^5 or less for the duration of the culture. Very few CFC were detected throughout the culture period, and in all cases their number steadily declined to 10 or less after only 1 week of culture (Fig 3). No CFC were detected in the adherent cell layers harvested at weeks 3 to 6 of culture (Fig 4).

**Preceding Chemotherapy**

PB mononuclear cells collected both pretherapy and before the administration of AE at cycles 7 and 11 from patients receiving chemotherapy alone and chemotherapy with G-CSF were unable to sustain hematopoiesis, giving similar values to normal controls (Figs 3 and 6).

**Postchemotherapy Alone**

Cultures were initiated from cells obtained at the time of peak progenitor release after cycles 1 and 11 of the VAPEC-B chemotherapy regimen. The numbers of CFC measured in the supernatant or in the adherent layer (Fig 4) were comparable with those obtained when BM cells were seeded.

**Postchemotherapy and G-CSF**

Mononuclear cells collected at the time of peak progenitor release after chemotherapy cycles 1, 7, and 11 from patients treated with VAPEC-B and G-CSF were found to have an in vitro repopulating capacity similar to control cultures of adherent cell-depleted BM from normal individuals when cultured on irradiated stroma. These cultures plateau above the initial inoculum density from weeks 3-6 to the termination of the cultures (Fig 3).

The pattern is similar in colony numbers in the adherent layer measured at weeks 3 and 6 with a significant increase in all groups including cycle 1 over baseline values (P < .0005, Mann-Whitney U-test, unpaired; Fig 4). The numbers of CFC in the adherent layer are 300-500-fold increased over those observed in cultures of normal peripheral blood and up to a threefold increase relative to normal BM. This represents a 50- to 100-fold enrichment of primitive hematopoietic cells over those primed by chemotherapy alone.

A comparison of the capacity to generate hematopoiesis between normal BM mononuclear cells and PB mononuclear cells primed by chemotherapy plus G-CSF is shown in...
Fig 4. GM-CFC in the adherent layer of two-stage long-term culture 3 weeks (H) and 6 weeks ( ) after seeding 10⁶ mononuclear cell from PB (5 normal individuals), BM (5 normal BMs), cycle 11 chemotherapy (C) (11 patients receiving AE alone at cycle 11), cycle 7 C + G-CSF (8 patients receiving AE and G-CSF at cycle 7), cycle 11 C + G-CSF (19 patients receiving AE and G-CSF at cycle 11). Data are shown as median colony number per flask ± range.

Fig 5. In vitro hematopoiesis is not only enriched 10-fold in the primed PB mononuclear cells but is also sustained for longer.

Sustained Hematopoiesis

A comparison of the area under the curve (AUC) for the 6 weeks from the initiation of the long-term culture for cell numbers per culture showed no statistical difference between PB from normal individuals, pretreatment PB, and PB mononuclear cells collected before treatment with AE in patients receiving chemotherapy alone or chemotherapy with G-CSF. Neither was there a significant difference when the AUC for total colony numbers in these cultures were compared. However, there was a trend to higher colony numbers at day 0 of cycles 7 and 11 in the group receiving both chemotherapy and G-CSF (Fig 6).

The AUC for nonadherent cell numbers per flask in cultures seeded after cycle 11 in patients receiving chemotherapy alone were significantly increased over control PB (P = .001, Kruskal-Wallis test) and were not significantly different from BM (Fig 6).

The AUC for mononuclear cells and colonies per flask in the nonadherent layer in long-term cultures from normal BM and PB of patients receiving chemotherapy with G-CSF at cycle 7, and cycle 11 cultures were significantly increased over control PB (P < .0005, Mann-Whitney U-test, unpaired) but were not significantly different from each other (Fig 6).

DISCUSSION

PB offers a source of hematopoietic stem cells for transplantation in patients without an allogeneic BM donor. In humans, more GM-CFC/kg body weight are considered necessary for successful engraftment with PB cells than with BM.²⁶,²⁷ Consistent with this, we have shown that PB mononuclear cells from normal controls and patients with NHL before chemotherapy contain few CD34⁺ cells (0.18%) and are unable to initiate hematopoiesis in an in vitro model of transplantation—the two-stage long-term culture assay.

In contrast, after chemotherapy and G-CSF, CD34⁺ cells increased to a median of 4% and PB mononuclear cells had a repopulating capacity at least equal to BM. Indeed, the delayed onset of GM-CFC production and mature cell out-
put in the two-stage long-term cultures initiated with mobilized PB mononuclear cells (Fig 3) and the magnitude and duration of generated progenitor cells (Fig 5) suggest that the inoculum contains relatively more primitive cells than normal blood or BM. This is supported by finding that more clonogenic cells are present in the adherent cell layer from cultures initiated with PB mononuclear cells obtained after treatment with chemotherapy and G-CSF than BM or those primed with chemotherapy alone (Fig 4).

Previous studies have used seriously high doses of myelosuppressive agents to mobilize progenitors into the PB with or without hematopoietic growth factors.\textsuperscript{15,21,28} We have shown that patients with high-grade NHL receiving routine outpatient induction chemotherapy with VAPEC-B achieved a modest increase in PB progenitor cells after chemotherapy alone. This increase was markedly enhanced by treatment with G-CSF after chemotherapy.

Like others,\textsuperscript{28,29} we have found that there is greater mobilization of progenitors into the circulation when a more myelosuppressive stimulus is used: AE at cycles 7 and 11 was more myelosuppressive and a better priming treatment than AC at cycle 1. Interestingly, a low-nadir absolute neutrophil count (ANC) is not a prerequisite for the release of primitive cells. Patients receiving chemotherapy with G-CSF were both protected from neutropenia and had enhanced primitive hemopoietic cell release. Corticosteroids have been suggested to contribute to hematopoietic progenitor release, but this has been controlled for in this study, as prednisolone, 25 mg, daily was administered to both groups.

To date, multiple apheresis procedures have been required to obtain enough primitive blood cells for transplantation even in patients with little prior treatment.\textsuperscript{20,23,30} This has resulted in considerable patient morbidity, expense, and delays in initiating treatment that could prove harmful to patients with rapidly growing tumors. The 400-fold increase in GM-CFC after priming with VAPEC-B and G-CSF (Table 1) indicates that it will usually be possible to harvest sufficient PB stem cells at a single apheresis and that the toxicity of more myelosuppressive chemotherapy is not justified. A minimum of 5 x 10\textsuperscript{5} GM-CFC/kg body weight are recommended for BM transplantation. Based on the GM-CFC yields from patients primed with chemotherapy and G-CSF in this study, we predict that mononuclear cells from 5 mL/kg body weight PB will be sufficient for successful engraftment. These results have led us to use G-CSF priming for apheresis after AE in 7-cycle VAPEC-B in 13 patients with high-grade NHL of poor prognosis.\textsuperscript{31} In each case, adequate numbers of PB progenitor cells for transplantation were obtained at a single apheresis. Median (range) yields were mononuclear cells 3.8 x 10\textsuperscript{9}/kg (0.2 to 9.7); GM-CFC 8.3 x 10\textsuperscript{9}/kg (5.2 to 22.0); CD34\textsuperscript{+} cells 2.8 x 10\textsuperscript{5}/kg (6.8 to 41.0). We have also successfully used this method to mobilize hematopoietic progenitor cells for transplantation in heavily pretreated patients with acute lymphoblastic leukemia and relapsed Hodgkin's disease.\textsuperscript{32}

Despite variability between patients, we have found that the magnitude and timing of primitive cell release are reproducible following an identical stimulus in individual patients unless infection supervenes. It is possible to predict the time of peak release and optimize cell collection (Fig 2). In any individual, the WBC count was as useful for predicting the day of peak primitive cell release as CFU-GM numbers. In all patients, the increase in circulating WBC after myelosuppressive chemotherapy with or without G-CSF parallels the release of primitive hematopoietic cells but lags
24 hours behind it (Fig 2). The optimal time for primitive blood cell collection is when the WBC is increasing exponentially after the chemotherapy-induced nadir. In patients receiving VAPEC-B and G-CSF, this occurs when the WBC is 5 to 10 x 10^9/L.

The advantages of early collection, before irreversible cytotoxic damage to BM tissue has occurred, must be weighed against the disadvantages, such as increased risk of malignant contamination. Using VAPEC-B chemotherapy, there is no difference in primitive blood cell release at cycle 7 over cycle 11 nor in the ability of these cells to initiate and sustain long-term hematopoiesis in vitro, which indicates that in the short term there is no measurable damage to the BM.

There are many descriptive reports of PB stem cell transplantation in humans, but the source of the cells effecting long-term engraftment has not been determined, and therefore it is unclear if long-term hematopoiesis originates from the graft or from the surviving host cells. Studies of sex-mismatched syngeneic transplants in mice show that the same minimum number of cells are required for in vivo engraftment using PB mononuclear cells from mice treated with G-CSF or normal BM. This study also showed that the transplanted PB cells are able to reconstitute long-term hematopoiesis of donor origin. In our in vitro transplantation model, primed human PB mononuclear cells are similarly comparable with BM indicating that they also have the potential to contribute to long-term hematopoiesis. To establish this unequivocally will require gene-marking studies.

Therefore, transplantation with primitive hematopoietic cells from the PB after myeloablative therapy could be a safe alternative to BM.

In conclusion, we have shown that chemotherapy with G-CSF is a better priming regimen than chemotherapy alone in patients with high-grade NHL. VAPEC-B and G-CSF increase the number of circulating progenitors to levels comparable with normal BM. Therefore, it is feasible to collect sufficient cells for autologous transplantation at a single apheresis and without delay or disruption to routine chemotherapy. The blood contains both committed progenitors and cells with an in vitro BM-repopulating capacity (long-term culture-initiating cells). The release of primitive cells parallels the increase in WBC with a set lag. Therefore, an increasing WBC can be used as a guide to when to harvest.

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