Kinetics of Committed and Primitive Blood Progenitor Mobilization After Chemotherapy and Growth Factor Treatment and Their Use in Autotransplants

By H.J. Sutherland, C.J. Eaves, P.M. Lansdorp, G.L. Phillips, and D.E. Hogge

Peripheral blood cells (PBCs) collected by leukapheresis after progenitor mobilization with chemotherapy and growth factors have been used successfully to replace marrow autografts in protocols requiring stem-cell support. Moreover, such transplants are often associated with more rapid recovery of blood cell counts than is routinely achieved with bone marrow. While conditions that mobilize colony-forming cells (CFCs) into the circulation are becoming increasingly well characterized, little information is available as to how these or other mobilizing treatments may influence the release of more primitive cells into the peripheral blood. To quantitate the peripheral blood content of such cells, we used the long-term culture-initiating cell (LTC-IC) assay, which detects a cell type that is able to produce progeny CFCs after a minimum of 5 weeks in cultures containing marrow fibroblasts. In this report, we present the findings on 21 patients who were transplanted over a 7-year period at our institution with PBCs alone. PBCs were collected in steady-state (n = 6) or during the recovery phase after high-dose cyclophosphamide (Cy; n = 15, nine with and six without additional growth factor administration). PBCs collected from another 11 patients given granulocyte colony-stimulating factor (G-CSF) were transplanted together with autologous marrow. Time-course studies of nine patients after Cy ± granulocyte-macrophage CSF (GM-CSF) showed that CD34+ cells, CFCs, and LTC-ICs fell from normal to undetectable levels after Cy, and increased at the time of white blood cell (WBC) recovery.

LTC-ICs to a mean of sixfold and CFCs to a mean of 26-fold higher after mobilization than in steady-state collections; however, more than 2-log interpatient variability was observed. After PBC transplantation, the median time to a WBC count more than 10^9/L was 12 days; polymorphonuclear leucocyte (PMN) count more than 0.5 x 10^9/L, 15 days; and platelet count more than 20 x 10^9/L, 17 days, although patients who received fewer than 1.5 x 10^6 CFCs/kg had a more than 50% chance of delayed count recovery (>28 days). Patients who received Cy + GM-CSF-stimulated PBCs had more rapid and consistent platelet recoveries as compared with other groups receiving Cy mobilized or steady-state PBCs alone, and a rapid WBC recovery after Cy predicted a rapid WBC recovery after transplantation. Numbers of LTC-ICs in the graft did not correlate with numbers of CFC or CD34+ cells, or with the speed of engraftment. The proliferative potential of LTC-ICs collected during mobilization in this patient population was found to be significantly lower than that of LTC-ICs from normal-donor blood or bone marrow samples. These studies provide evidence that LTC-ICs can be mobilized into the blood by treatments used to transiently increase numbers of CFC in the circulation, but to a more limited extent.

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However, in humans, the influence of high doses of chemotherapy or growth factors before leukapheresis on the blood levels of more primitive cells with long-term repopulating ability is not yet established. Long-term culture-initiating cells (LTC-ICs) are primitive hematopoietic cells that are able to produce clonogenic progenitors (burst forming unit-erythocyte [BFU-E], CFU-granulocyte, macrophage-[CFU-GM], and CFU-granulocytes, erythrocyte, monocyte, macrophage [CFU-GEMM]) after a minimum of 5 weeks of culture in the presence of irradiated human marrow fibroblasts (or functionally analogous cells from other sources). The purpose of the present study was to examine the levels of LTC-ICs and CFCs in human blood before and after various mobilizing treatments, including high-dose cyclophosphamide (Cy) with and without granulocyte-macrophage CSF (GM-CSF) ± interleukin-3 (IL-3) administered after Cy, and G-CSF alone. Posttransplant recovery and cell-collection parameters were compared for those patients transplanted with autologous blood cells without the addition of bone marrow.

MATERIALS AND METHODS

Patients. Between July 1, 1986 and April 1, 1993, 21 patients at our institution were selected for transplantation using PBCs alone. Fourteen patients with Hodgkin’s disease (HD) received PBC transplants because of bone marrow involvement with their malignancy or previous pelvic irradiation, or as part of our planned protocol for induction-failure HD. One additional patient was considered to have high-risk HD; however, on subsequent relapse, his pretransplant pathology was reviewed and he was reclassified as a non-Hodgkin’s lymphoma (NHL) (UPN 586). The remaining patients with a variety of malignancies (Table 1) were candidates for high-dose therapy, but could not undergo marrow transplant due to either marrow involvement with malignancy or previous pelvic irradiation. All patients with HD had received mechlorethamine, vincristine, prednisone, and procarbazine (MOPP) and doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD), or a hybrid of these regimens before transplantation. After analysis of PBC collections, it was decided to transplant bone marrow in addition to PBCs for one patient (UPN 597) due to the low number of CFCs in the PBC collections. Six patients were transplanted with PBCs collected in steady-state hematopoiesis. The remaining patients were transplanted with PBCs collected during the increase in white blood cell (WBC) count after the nadir induced by Cy alone (n = 6), Cy + GM-CSF (n = 7), or Cy + GM-CSF and IL-3 (n = 2). In another series of 11 patients, PBCs were collected following treatment with G-CSF and used to supplement purged autologous bone marrow in an attempt to speed count recovery in these patients. These latter patients had a variety of diagnoses (acute myelogenous leukemia [AML], seven; myeloma, two; HD, one; NHL, one) and are included only for analysis of progenitor content of the PBC collections. PBC collection, analysis, and transplantation were performed on patients after informed consent and with the approval of the Clinical Screening Committee for Research Involving Human Subjects of the University of British Columbia Vancouver, Canada.

PBC collections. Collections were performed using CS3000 (Baxter Fenwal Division, Deerfield, IL) or Spectra (Cobe Laboratories, Lakewood, CO) cell-separator machines. Nine liters of blood was processed over a period of 2 to 3 hours per collection. Some patients required indwelling hemodialysis catheters for this procedure. All collections were frozen in a controlled-rate freezer and stored in liquid nitrogen. Collections continued until approximately more than 6.0 \times 10^7 mononuclear cells (MNCs)/kg had been collected for patients receiving PBC autografts alone. Steady-state collections were scheduled two to three times per week. Fifteen patients had PBCs collected during the period of blood count recovery after priming with Cy (7 g/m²) administered in divided daily doses over 4 days. Nine of these patients additionally received 5 \mu g/kg/d of GM-CSF by subcutaneous injection or continuous intravenous infusion and, in two of these patients, this dose of GM-CSF was combined with IL-3 at 2.5 \mu g/kg/d administered subcutaneously. Injection of growth factors was begun on the day after the last dose of Cy and continued until after completion of the PBC collections, with the exception of two patients whose GM-CSF injections were stopped before the PBC collections (UPN 805 and UPN 597), one due to GM-CSF toxicity. Daily collections began on the day after Cy when the total WBC count first reached 10^9/L. Eleven patients had PBC collections on days 5, 6, and 7 of treatment with G-CSF at 12 \mu g/kg/d administered subcutaneously. The number of progenitors collected per leukapheresis for each mobilization strategy was compared by an analysis of variance on log-transformed data.

Peripheral blood stem-cell transplantation. After complete recovery from high-dose Cy, patients were readmitted to the hospital for autologous transplantation. Patients with HD were conditioned with etoposide (2.4 g/m²), cisplatin (50 mg/m² \times 3), Cy (1.8 g/m² \times 4), and carmustine (500 mg/m²) as previously described. Patients with multiple myeloma received busulfan (4 mg/kg \times 4), Cy (60 mg/kg \times 2), and melphalan (90 mg/m²) as described previously. LTC-IC assays. LTC-IC numbers were determined for each leukapheresis in all patients and also in the peripheral blood of nine patients twice per week starting before Cy and continuing until the PBC collections ended. Thawed, cryopreserved MNCs (2 \times 10^7) from each apheresis collection or MNCs recovered from approximately 20 mL of Ficol peripheral blood (maximum, 2 \times 10^7/mL dish) were seeded onto preestablished irradiated human marrow feeders as previously described. After 5 weeks in culture, nonadherent and adherent cells were pooled, washed, and plated together in methylcellulose for determination of the total CFC content (BFU-E, CFU-GM, and CFU-GEMM). The number of LTC-ICs in starting cell suspensions of both normal peripheral blood and bone marrow has been previously shown to be equal to the total CFC content of 5-week-old assay LTC dissociated by 4. This value was therefore used to calculate the LTC-IC numbers shown, although during the course of these experiments the proliferative potential of LTC-IC in some of these patients was found to be lower (mean 1.5 LTC-IC/CFU) than shown. Limiting dilution analysis was also performed on seven patients who had received priming as described previously.

Quantitation of CFCs and CD34+ cells. CFCs and CD34+ cell numbers were measured on each leukapheresis collection and on blood samples in nine patients before Cy and twice weekly after Cy until the leukaphereses were completed. CD34+ cell numbers were determined by 8G12-fluorescein isothiocyanate (FITC) staining by comparison to unstained controls and analysis on a FACScan or FACStar™ (Becton Dickinson, Mountain View, CA). CFC numbers were determined by plating cells in a methylcellulose medium containing 10% agar leukocyte-conditioned medium and 5 U/mL erythropoietin (StemCell Technologies, Vancouver, Canada), and incubating the assay cultures at 37°C in a 5% CO₂ humidified incubator for 18 days. Total BFU-E, CFU-GM, and CFU-GEMM were calculated from assessment in situ of colonies of erythroid, granulocyte-macrophage, and multiple lineages of cells using standard scoring criteria as described previously.

RESULTS

LTC-IC kinetics after mobilization. Kinetic evaluations were performed twice weekly on the peripheral blood of...
nine patients recovering from Cy, five of whom received GM-CSF after Cy and four of whom did not. Before Cy, both CFC and LTC-IC levels were not different from those previously measured at our center for a series of normal individuals (mean ± SEM: CFC, 137 ± 35/mL [patients] vs 153 ± 15/mL [controls, n = 109]; LTC-IC, 3.3 ± 1.2/mL [patients] vs 2.7 ± 0.5/mL [controls n = 21]; P > .05). The kinetics of CFC and LTC-IC changes observed in the individual patients described in this study are presented in Fig 1. After Cy, both CFCs and LTC-ICs fell to undetectable levels. The subsequent peaks of CD34+ cell, CFC, and LTC-IC numbers are generally coincident with the beginning of the rise of the WBC count, although marked interpatient variability was observed. Overall, LTC-IC numbers peaked slightly earlier as compared with CFCs (mean, 26 days vs 28 days, after Cy, UPN 564 being excluded as no peak was achieved in this case). The mean WBC counts at the time of the beginning (±1 LTC-IC/mL) and at the peak of the LTC-IC rebound were 0.9 × 10^9/L and 2.4 × 10^9/L, respectively. This suggests that our current policy of performing daily leukapheresis beginning on the day that the WBC count reaches 10^9/L spans the period of both CFC and LTC-IC rebound after Cy with or without GM-CSF. The height of the LTC-IC peak was a mean of 5.6-fold increased above mean steady-state values (range, <1 to 26×), while the CFC concentration in peripheral blood was increased, on average, 26-fold in the same patients (range, <1 to 106×).

**Limiting dilution studies of mobilized peripheral blood LTC-ICs.** We have previously used limiting dilution techniques to determine the proliferative capabilities of LTC-ICs in normal blood and bone marrow. LTC-ICs from both sources display a wide range of proliferative capabilities; however, on average, both produce four (range, one to 32) CFCs detectable at the end of a 5-week period in long-term culture. To determine if Cy and GM-CSF resulted in mobilization of a qualitatively different population of circulating LTC-ICs, cells from the leukapheresis collections of seven patients treated in this way were plated at limiting numbers into mini–long-term culture. The number of negative assay cultures was analyzed using Poisson statistics and the weighted-mean method to derive the frequency of LTC-ICs in the starting populations. The average proliferative potential of LTC-ICs from each patient was then calculated by dividing the total number of CFCs present in all of the 5-week mini–long-term cultures by the number of the derived LTC-ICs in the same cultures. The mean number of CFCs...
Fig 1. Kinetics of total WBC count, CFC (CFU-GM, BFU-E, and CFU-GEMM), and LTC-IC recovery in nine patients who received Cy chemotherapy, five of whom also received GM-CSF. Values below the level of detection of the assay (ie, no events observed) were assigned .01 for the purposes of presentation. (□) CD34+ (× 10⁸/mL); (■) WBC (× 10⁹/mL); (□) CFC (× 10⁵/mL); (●) LTC-IC (per milliliter).

per LTC-IC from these patients was 1.6 ± 0.2 (Table 2). This is significantly lower than the proliferative potential determined for LTC-ICs in normal blood (3.7 ± 1.2, n = 3; P ≤ .05) and in unseparated or partially purified normal bone marrow (4.3 ± 0.3, n = 19; P ≤ .05) (Mann-Whitney test).

PBC collections. The mean number of MNCs, CD34+ cells, CFCs, and LTC-ICs collected per 9-L leukapheresis procedure is presented in Table 3. The actual WBC count on the day of first leukapheresis was 1.5 ± 0.1 × 10⁹/L, and the absolute neutrophil count (ANC), 0.9 ± 0.1 × 10⁹/L (mean ± SEM; range, 0.03 to 1.1 × 10⁹/L). There was no correlation between the ANC and frequency of CFUs and LTC-ICs per 10⁵ cells in the first leukapheresis collection (n = 11). MNC numbers were, as expected, lower in patients whose PBC were collected at the time they were just beginning to recover their counts after Cy and higher in patients who received G-CSF alone. CFC numbers per 9-L leukapheresis (Table 3) were increased by mobilization with Cy and/or growth factors as compared with steady-state collections (P ≤ .05), and a trend toward increased LTC-IC numbers with mobilization (P = .07) was also observed. There were no significant differences between the numbers of CD34+ cells, CFCs, or LTC-ICs collected per leukapheresis between any of the mobilization techniques (P > .05). However, there was a trend toward higher numbers of CD34+ cells and CFCs in collections obtained following growth factors. This trend was not observed for LTC-ICs, for which numbers were lower in collections after GM-CSF + Cy than in collections mobilized by Cy alone.

Table 2. Limiting Dilution Analysis of Mobilized PBCs

<table>
<thead>
<tr>
<th>UPN</th>
<th>Priming Strategy</th>
<th>LTC-ICs/10⁵ (95% CI)</th>
<th>CD34+/LTC-IC</th>
</tr>
</thead>
<tbody>
<tr>
<td>565</td>
<td>Cy</td>
<td>3.3 (2.1-5.2)</td>
<td>1.3</td>
</tr>
<tr>
<td>663</td>
<td>Cy + GM-CSF</td>
<td>45 (27-74)</td>
<td>2.7</td>
</tr>
<tr>
<td>670</td>
<td>Cy + GM-CSF</td>
<td>166 (97-283)</td>
<td>1.8</td>
</tr>
<tr>
<td>586</td>
<td>Cy + GM-CSF</td>
<td>4.6 (2.3-6.6)</td>
<td>1.6</td>
</tr>
<tr>
<td>873</td>
<td>G-CSF</td>
<td>2.3 (1.5-3.6)</td>
<td>1.7</td>
</tr>
<tr>
<td>867</td>
<td>G-CSF</td>
<td>3.9 (2.6-6.0)</td>
<td>1.1</td>
</tr>
<tr>
<td>883</td>
<td>G-CSF</td>
<td>1.8 (1.2-2.8)</td>
<td>1.3</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.

Engraftment characteristics. Most of the patients who received only PBCs as their transplant achieved prompt recovery
of WBCs and neutrophils. However, platelet recovery was delayed beyond 28 days in six patients. Median days to neutrophil recovery (>0.5 × 10^9/L) was 15 days and did not change with the use of the different mobilization strategies. The median day to achieve a self-sustained platelet count of 20 × 10^9/L was 13 days in those patients who received GM-CSF ± IL-3 before PBC harvesting, as compared with 34 days in those patients who received PBCs collected in steady-state and 31 days in patients whose PBCs were collected after Cy alone. These differences were significant (P = .05) in a log-rank analysis.

The parameter most predictive for rapid WBC and neutrophil recovery was rapid recovery of total WBC count after Cy (r = .9, P = .05). No correlation was found between the number of CFCs transplanted and the speed of recovery of any type of PBC; however, a threshold appeared to exist at approximately 1.5 × 10^5 CFCs infused/kg body weight. Of the six patients who received less than this number of CFCs, two had delayed (>day 28) WBC recovery, three had delayed neutrophil recovery, and four had delayed platelet recovery. None of the 15 patients who received this number of PBC CFCs or more had delayed WBC or neutrophil recovery, although two patients, who did not receive growth factor for the mobilization of their PBCs, showed delayed platelet recovery. This resulted in significant differences in the platelet and ANC recoveries between these two groups (P = .05). On the basis of these findings, we now aim to transplant at least this number of CFCs, i.e., ≥1.5 × 10^5 CFCs/kg body weight.

Substitution of CD34+ cell numbers for CFC quantitation in assessing the quality of leukapheresis collections would be of practical importance, since it would allow much more rapid clinical decision-making. Unfortunately, in this series of patients, although a general correlation between numbers of CD34+ cells and CFCs was present, a threshold cell dose above which rapid count recovery occurred posttransplant, which was detected for CFC, was not apparent in the subset of patients in which CD34+ cells were enumerated. Similarly, the number of LTC-ICs transplanted did not predict the speed of recovery of any type of PBC. No evidence of late graft failure has been observed in these patients, with a follow-up duration in excess of 7 months for all surviving patients.

**DISCUSSION**

Cells with long-term bone marrow—repopulating ability have been shown to circulate in murine peripheral blood, and prompt and sustained count recovery is seen in the majority of patients who receive autologous marrow and PBPCs. Nevertheless, little is known about the mobilization of cells analogous to those that reconstitute murine hematopoiesis into human peripheral blood. Human LTC-ICs share many characteristics with murine-repopulating stem cells. In murine experiments where direct comparisons are possible, LTC-ICs have been shown to be more primitive than many CFU-S and to copurify with long-term in vivo repopulating cells. In normal humans, LTC-ICs have been shown to circulate in the peripheral blood at a frequency of approximately 3/mL, and to have the same cell-surface phenotype and proliferative capabilities as bone marrow LTC-IC. The peripheral blood LTC-ICs obtained after priming in the patients in this study had a lower proliferative potential as compared with normal blood or bone marrow LTC-ICs; however, it is impossible to know from these studies whether this reduction is due to the effect of priming or to the previous chemoradiotherapy to which these patients were exposed, since marrow LTC-ICs were not analyzed.

Functional end points that might measure LTC-IC proliferation in vivo are unknown. By analogy with murine studies, it seems unlikely that LTC-ICs are primarily responsible for the initial rapid recovery of WBC and platelet counts that can occur in transplant recipients. However, they may be important in preventing the transient decrease in blood counts following initial count recovery, which has been reported to occur in some patients transplanted with peripheral blood.

The ideal minimum number of LTC-ICs that should be transplanted is unknown. The concentration of these cells in normal bone marrow is one per 2 × 10^5 cells. Thus, an allogeneic graft of 3 × 10^8 cells/kg recipient weight would provide approximately 15,000 LTC-ICs/kg. In the autologous setting, bone marrow grafts containing 1,500 LTC-ICs/kg have consistently allowed reconstitution of hematopoiesis within 3 to 4 weeks, which was subsequently sustained. In this study, PBC autografts contained 60 to 9,600 LTC-ICs/kg. The graft containing the lowest number of LTC-ICs also had a low number of CFCs, and this patient did show a delayed count recovery. However, successful and sustained engraftment was achieved with some PBC grafts containing as few as 500 LTC-ICs/kg.

While CFCs and LTC-ICs are present in the blood in steady-state, their frequency relative to other nucleated cells is approximately 100 times lower than their frequency in the bone marrow. During the period after intensive chemotherapy, when the blood counts are recovering, and/or after exogenous growth factors are administered, the levels of LTC-ICs, CFCs, and CD34+ cells in the blood increase. In our series, two patients primed with G-CSF alone had a bone marrow evaluation during the time of PBC leukapheresis. CFC content per 10^6 cells was higher in the PBC leukapheresis product (113% and 308% as compared with the bone marrow sample), and LTC-IC frequencies were equivalent (132% and 73% of bone marrow). Transplantation of PBCs collected at this time can result in rapid WBC count recovery following high-dose chemoradiotherapy as compared with autologous marrow grafts. G-CSF administration has been shown to mobilize cells with a capacity for also enhancing platelet recovery. Whether these effects are explained solely by quantitative changes in the numbers of different

| Table 3. Progenitor Cells Collected per 9-L Leukapheresis (Mean ± SEM) |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Mobilization Technique | MNCs/kg (10^6) | CD34+ Cells/kg (10^6) | CFCs/kg (10^5) | LTC-ICs/kg (10^4) |
| None (n = 6) | 1.5 ± 0.3 | — | 1.6 ± 0.5 | 1.0 ± 0.3 |
| Cy (n = 6) | 0.9 ± 0.1 | 1.1 ± 0.3 | 5.2 ± 1.4 | 6.0 ± 2.2 |
| Cy + GM-CSF | — | — | — | — |
| ± IL-3 (n = 9) | 1.4 ± 0.4 | 4.2 ± 1.6 | 22.9 ± 9.7 | 2.6 ± 1.2 |
| G-CSF (n = 11) | 3.1 ± 0.6 | 4.7 ± 1.0 | 13.1 ± 3.2 | 6.7 ± 3.0 |

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types of progenitors infused with mobilized PBC autografts or whether the mobilization procedure also induces relevant qualitative changes in progenitor homing or their subsequent proliferative and differentiative behavior is not known. It is interesting that, thus far, it has not been possible to reduce to less than 8 to 10 days the initial period of neutropenia and thrombocytopenia that follows autologous transplantation, even when very large numbers of committed progenitors are infused.

In this study, we have demonstrated that LTC-ICs, as well as CFCs, are mobilized by Cy and rebound simultaneously with or even slightly before the CFCs as the blood cell count is also rapidly increasing. The magnitude of the peak increase in LTC-ICs was, on average, fivefold lower than the magnitude of the peak increase in CFCs (5.6-fold vs 26-fold). Higher numbers of CFCs and LTC-ICs were collected when leukapheresis was performed daily starting when the WBC count reached 10^9/L after Cy with or without GM-CSF and continuing until 6 × 10^9 cells/kg were harvested, as compared with steady-state collections. Interestingly, the administration of GM-CSF after Cy increased the yield of CFCs during the rebound phase. But did not further augment the number of LTC-ICs that could be collected. G-CSF alone was also capable of increasing the numbers of both CFCs and LTC-ICs that could be collected to a similar degree. A dose of 1.5 × 10^5 CFCs/kg seems to be sufficient to ensure rapid count recovery after transplantation. Although this number of cells could be readily harvested with one to four 9-L leukaphereses from most of the patients receiving Cy and/or growth factor mobilization in this series, occasionally this was not achieved even after nine or 10 collections. Indeed, in excess of 100 collections would have been necessary to harvest this number of CFCs from the steady-state peripheral blood of some of these individuals. These low progenitor yields likely reflect the large amount of previous chemotherapy that all of these patients had received before PBC harvest. Nevertheless, it is gratifying to note that since we have begun using hematopoietic growth factors ± Cy as part of our mobilization strategy, satisfactory progenitor yields are more routinely obtained and rapid recovery of both neutrophil and platelet counts has been seen in all of these latter patients posttransplant. Thus, even heavily pretreated cancer patients can be considered candidates for high-dose therapy regimens supported by growth factor–mobilized PBCs.

Transplantation of pluripotential and self-renewing repopulating stem cells, at least in the allogeneic setting, is considered to be essential for long-term survival. In murine experiments, it has been possible to separate populations with immediate and long-term repopulating potential and demonstrate a separate role for the latter population at least under certain experimental conditions.8,26-28 With increasingly sophisticated in vivo and in vitro procedures for augmenting and activating human cells able to give rapid count recovery after myeloablative therapy, it will be important to ensure that sufficient cells with long-term repopulating ability are also infused. This consideration assumes even greater significance for protocols that envisage transplanting genetically modified hematopoietic stem cells for long-term therapeutic benefit. However, the definition of what constitutes a sufficient number of such cells remains a challenge that continuing careful analysis of manipulated grafts may help to clarify.

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