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Feasibility and Cost Analysis of Day 4 Granulocyte Colony-Stimulating Factor Mobilized Peripheral Blood Progenitor Cell Collection from HLA-Matched Sibling Donors

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Abstract

Background: Guidelines recommend treatment with 4–5 days of G-CSF for optimal donor peripheral blood progenitor cell (PBPC) mobilization followed by day 5 collection. Given some autologous transplant patients achieve adequate collection by day 4, and possibility that some allogeneic donors may maximally mobilize PBPC before day 5, a feasibility study was performed evaluating day 4 allogeneic PBPC collection.

Methods: HLA-matched sibling donors were collected on day 4 of G-CSF for peripheral blood (PB) CD34⁺ counts $0.04 \times 10^6/\text{ml}$, otherwise they were collected on day 5. Those with inadequate collected CD34⁺ cells/kg recipient weight underwent repeat collection over two-days. Transplant and PBPC characteristics, and cost analysis were compared to a historical cohort collected on day 5 per our prior institutional algorithm.

Results: Of the 101 patient/donor pairs, 50 (49.5%) had adequate PBPC collection on day 4, with median PB CD34⁺ cell count of $0.06 \times 10^6/\text{ml}$. Day 4 donors were more likely to develop bone

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Disclosures of Interest

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pain and require analgesics. Median collected CD34⁺ count was significantly greater, while total nucleated, mononuclear, and CD3⁺ cell counts were significantly lower, at time of transplant infusion for day 4 versus other collection cohorts. There were no significant differences in engraftment or graft-versus-host-disease. Cost analysis revealed 6.7% direct cost savings for day 4 versus historical day 5 collection.

Discussion: Day 4 PB CD34⁺ threshold of $0.04 \times 10^6/\text{ml}$ identified donors with high likelihood of adequate PBPC collection. Day 4 may be the optimal day of collection for healthy donors, without adverse effect on recipient transplant outcomes and with expected cost savings.

Keywords

Hematopoietic Progenitor Cells; Hematopoietic Stem Cell Transplantation; Peripheral Blood Stem Cells; Stem Cell Mobilization

Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) can provide curative potential for patients with high risk malignant hematologic diseases. Over the past decade, allogeneic donor growth factor-mobilized peripheral blood progenitor cells (PBPC) have been used with increasing frequency as the source of hematopoietic stem cells for HSCT, compared to bone marrow-derived stem cells¹⁻⁴. Peripheral blood stem cell transplantation (PBSCT) offers the advantage of shorter time to neutrophil and platelet engraftment and faster hematopoietic recovery after HSCT, as well as facilitates volunteer donor collection with avoidance of donor exposure to general anesthesia and risk of post-harvest musculoskeletal injury. However, compared to bone marrow transplantation (BMT), PBSCT can be associated with an increased risk of acute and chronic graft-versus-host disease (GVHD)⁵⁻⁹. In the allogeneic HSCT setting, PBPC are collected by apheresis procedure from allogeneic donors after high-dose granulocyte colony-stimulating factor (G-CSF) stimulation, though the exact algorithm and timing of donor PBPC mobilization and collection can vary from center to center.

Standard guidelines for the mobilization and collection of autologous PBPCs have been well described¹⁰, with the FDA label for G-CSF mobilization recommending 6–7 days of G-CSF and PBPC collection beginning day 5¹¹. Recently, clinical guidelines for allogeneic PBPC mobilization have been published by the Practice Guidelines Committee of the American Society for Blood and Marrow Transplantation (ASBMT)², with ASBMT and National Marrow Donor Program (NMDP) recommendations for 4 or 5 consecutive days of donor G-CSF administration followed by donor PBPC collection for a target total cell dose for infusion of $4-8 \times 10^6$ CD34⁺ cells/kg recipient weight. These guidelines allow for the collection of PBPC over 1 or 2 days, as needed, to achieve the desired cell dose for infusion.

Given that some autologous PBSCT patients are adequately mobilized by day 4 of G-CSF^{2, 10}, and concern that a subset of allogeneic donors may be maximally mobilized before day 5 of growth factor administration, we performed a feasibility study to evaluate day 4 allogeneic donor PBPC collection. We hypothesized that in a subset of healthy allogeneic donors, peripheral blood CD34⁺ cell counts by day 4 of G-CSF administration would justify

adequate donor mobilization. We quantified peripheral blood CD34⁺ cell counts on day 4 and day 5 of G-CSF in allogeneic HLA-matched sibling donors, and performed PBPC collection for peripheral blood CD34⁺ cell counts $0.04 \times 10^6/\text{ml}$. Patient and donor characteristics, PBPC product composition, and post-HSCT transplant outcomes were compared to a historical cohort of donors collected on day 5 according to our prior algorithm. Cost analysis of the collection procedure was also performed, compared to the historical cohort.

Methods

Patients and Donors

This single-center prospective study included adult patients with malignant diseases who received a first allogeneic HSCT at our center between 7/1/2013 – 6/30/2017. All patients with HLA-matched sibling donors having PBPC collection at Oregon Health & Sciences University (OHSU) were eligible for study inclusion. Donors received 10 µg/kg (actual body weight) of G-CSF subcutaneously once daily prior to PBPC collection, dose banded by oncology pharmacy services to nearest total vial use. All research analyses were performed after approval of the Institutional Review Board at OHSU.

Donor Symptoms

Donors were evaluated for clinical symptoms on day of collection, and within 1-week and again 1-month after PBPC collection. Donor symptoms were retrospectively collected from the electronic medical record, as well as details on any possible donor blood transfusion requirements, hospital admissions, or emergency visits related to the collection procedure.

PBPC Collection Algorithm

Beginning 7/1/2013, HLA-matched allogeneic sibling donor peripheral blood CD34⁺ cell count/ml was determined beginning day 4 of G-CSF administration. In our prior institutional analysis matching autologous circulating CD34⁺ cell numbers with projected CD34⁺ cells/collection, we found the day 4 peripheral blood CD34⁺ cell count/ml to correlate with the collected CD34⁺ cells/kg on day 5 (e.g. >0.015 peripheral blood CD34⁺ cells/ml predicted for the collection of 2×10^6 CD34⁺ cells/kg)¹². Based on this predictive algorithm correlating circulating CD34⁺ cell counts with leukapheresis yields, we proposed to use $0.04 \times 10^6/\text{ml}$ as a predicted target collection. Peripheral blood CD34⁺ cell counts were routinely quantified starting on day 4 of G-CSF for the study cohorts, and beginning on day 5 of G-CSF for the historical cohort, and assessed daily until adequate PBPC collection was obtained. Donor apheresis was subsequently performed on day 4 if the peripheral blood CD34⁺ cell count was $0.04 \times 10^6/\text{ml}$. Donors with a day 4 peripheral blood CD34⁺ cell count of $< 0.04 \times 10^6/\text{ml}$ were collected on day 5, and those donors with inadequate PBPC product CD34⁺ cell collections ($< 4 \times 10^6$ CD34⁺ cells/kg recipient actual body weight) underwent repeat apheresis collection over 2 days. After donor collection, PBPC products were cryopreserved if unable to proceed to PBPC infusion within 24-hours of collection (due to timing of donor collection, patient transplantation). Cryopreserved products were then thawed immediately prior to transplantation. For historical comparison, we retrospectively evaluated a cohort of consecutive allogeneic HLA-matched sibling donor

PBSCT recipients with PBPC collection and transplantation performed immediately prior to the study period.

Peripheral Blood and PBPC Product CD34⁺ Cell Count Enumeration

Donor peripheral blood and PBPC product CD34⁺ cell counts were quantified by flow cytometry (Beckman Coulter Navios and BD FACSCanto II flow cytometers), by the OHSU Flow Cytometry Core Lab. In brief, red cells were lysed using ammonium chloride lysing solution, followed by sample incubation with CD45-FITC/CD34-PE reagent, 7-AAD viability dye, and Stem-Count Fluorospheres (Stem-Kit reagents, Beckman Coulter, Indianapolis, IN), or BD Stem Cell Enumeration kit (BD Biosciences, San Jose, CA). At least 75,000 CD45⁺ leukocyte events, and 1,000 Stem-Count Fluorospheres, were captured per sample. Peripheral blood and PBPC product CD34⁺ cell counts were calculated and reported both as CD34⁺ percentage and as CD34⁺ × 10⁶/ml.

Leukapheresis Procedure

Prior to 1/2017, all PBPC collections were performed using the Cobe Spectra (Terumo BCT, Lakewood, CO). Between 1/2017 and 6/2017, both the Cobe Spectra and the Spectra Optia (Terumo BCT, Lakewood, CO) were utilized during institutional transition to the Spectra Optia. Per our institutional protocol, for both the study and historical cohorts, processed blood volume was 9–15 liters over a 3–4 hour time period daily until the collection goal was met, with a maximum collection amount of 300 mls. Whole blood to anticoagulant ratio was 30:1, using 500 mls anticoagulant citrate dextrose (ACD-A) with 5000 units heparin (Fenwal Inc., Fresenius Kabi, Lake Zurich, IL).

Statistical Analyses

Statistical analyses were performed using one-way ANOVA and Kruskal-Wallis test for non-parametric data. A *p* value of < 0.05 was considered statistically significant. Fine and Gray regression analysis was used to examine the independent effect of PBPC product composition variables, as well as any interactions between significant factors. Time to absolute neutrophil count (ANC) and platelet engraftment were calculated using Kaplan-Meier plots with Log-rank (Mantle-Cox) tests. A test of two proportions was used to evaluate differences in the frequency of donor symptoms.

Cost Analysis of PBPC Product Collection

Cost analysis was performed for the PBPC product collections using the date of collection +/- 6 days for associated costs, and included direct costs (e.g. labor, supplies) associated with donor G-CSF administration, lab testing for peripheral blood CD34⁺ cell count, and for the PBPC product collection procedure. The direct costs per PBPC collection (based on number of collection events per each cohort) were then calculated for each study cohort and compared to the historical cohort, accounting for inflation. Direct costs were available for 48 collection events in the day 4 cohort, for 25 events in the day 5 cohort, for 46 events in the two-day collection cohort, and for 89 events in the historical control cohort.

Results

Patient Characteristics

A total of 101 patient/donor pairs were eligible for inclusion on study, and 75 patient/donor pairs were included in the historical cohort. The majority of patients in the study and historical cohorts underwent HSCT for a diagnosis of acute leukemia (Table 1). Forty-seven of the 101 study patients (46.5%) received myeloablative conditioning, 35 (34.7%) reduced intensity regimens, and 19 (18.8%) received non-myeloablative conditioning regimens [36 (48%), 23 (31%), and 16 (21%) of the 75 patients in the historical cohort, p =not significant]. Most of the study patients received Tacrolimus/Methotrexate for GVHD prophylaxis [62 (61.4%)], with 20 patients (19.8%) receiving Cyclosporine/Methotrexate +/- Prednisone, and 17 (16.8%) receiving Cyclosporine/Mycophenolate. Reflecting a change in institutional practice, 30 (40%) and 32 (43%) of the historical cohort received Tacrolimus/Methotrexate and Cyclosporine/Methotrexate +/- Prednisone, (p =0.044, p =0.009), respectively (Table 1).

Donor Characteristics

Details regarding the donor characteristics are as shown in Table 2. Sixty-two of the 101 donors (61.4%) in the study cohort had adequate peripheral blood CD34⁺ cell counts on day 4 of G-CSF to begin PBPC collection. Of these 62 donors, 50 (80.6%) completed adequate PBPC collection with a single collection on day 4; 12 donors (19.4%) starting collection on day 4 required an additional PBPC collection on day 5 in order to obtain adequate number of CD34⁺ cells in the PBPC product. Thirty-nine of the 101 donors (38.6%) did not meet peripheral blood CD34⁺ cell criteria to initiate PBPC collection on day 4 and thus started collection on day 5. Of the 39 donors beginning collection on day 5, 26 (66.7%) had adequate collection over the single day, while 13 (33.3%) required two-days of collection on days 5 and 6.

The median day 4 donor peripheral blood CD34⁺ cell count was 0.06 (range 0.03–0.13) $\times 10^6$ /ml among donors collecting on day 4, 0.03 (range 0.007–0.09) $\times 10^6$ /ml for donors collecting on day 5, and 0.019 (range 0.004–0.04) $\times 10^6$ /ml for donors collecting over two-days (p <0.001). For donors without a single day 4 collection, the median donor peripheral blood CD34⁺ cell count at PBPC collection was 0.058 (range 0.04–0.13) $\times 10^6$ /ml for donors collecting on day 5, 0.038 (range 0.012–0.08) $\times 10^6$ /ml for donors collecting over two-days, and 0.057 (range 0.004–0.78) $\times 10^6$ /ml for historical cohort donors (p <0.001). Two donors with day 4 peripheral blood CD34⁺ cell counts of 0.03 $\times 10^6$ /ml were collected on day 4, and one donor with a day 4 peripheral blood CD34⁺ cell count of 0.086 $\times 10^6$ /ml was collected on day 5, per the discretion of the attending transplant physician.

Donors collecting over days 4–5 were more likely to be older in age, male, and with a greater median weight, compared to donors collecting over days 5–6 (median age 61 years versus 53 years, median weight 92.4 kg versus 70.5 kg, and 50% male versus 23% male, respectively, Supplementary Table 1); however, these variables failed to reach statistical significance. In contrast, the median day 4 and median day 5 peripheral blood CD34⁺ % and CD34⁺ $\times 10^6$ /ml were significantly greater for donors collecting on days 4–5 compared to days 5–6. In the historical cohort, 60 of the 75 donors (80%) were adequately collected on

day 5, 14 (18.7%) required two-days of collection over days 5 and 6, and 1 donor (1.3%) required collection over three-days (days 5–7).

Donor Symptoms

The most common reported donor symptoms were bone pain, myalgia/malaise, headache, and circumoral paresthesias/electrolyte abnormalities (Figure 1). Compared to the historical cohort, donors with PBPC collection on day 4 were significantly more likely to develop bone pain, require narcotics, and take over-the-counter (OTC) medications. Donors collecting on day 5 were significantly more likely to develop bone pain and take OTC medications, compared to the historical cohort. Donors in the two-day collection cohort were significantly more likely to develop bone pain and circumoral paresthesias/electrolyte abnormalities, compared to the historical donor cohort.

PBPC Product Composition

The median collected PBPC CD34⁺ cell count was significantly greater in products collected on day 4 [7.25 (range 3.06 – 18.79) $\times 10^6$ /kg recipient weight], compared to products collected on day 5 [5.29 (range 3.36 – 11.83) $\times 10^6$ /kg recipient weight], products collected over two-days [2.63 (range 0.63 – 4.47) $\times 10^6$ /kg recipient weight], or products in the historical cohort [4.89 (range 0.42 – 24.04) $\times 10^6$ /ml], $p < 0.001$ (Table 3). For products collected on day 4, the infused PBPC product CD34⁺ cell count [5.67 (range 3.06 – 7.91) $\times 10^6$ /kg recipient weight] was also significantly greater than in the other cohort products ($p = 0.042$). In comparison, the infused PBPC product total nucleated cell (TNC) count [7.13 (range 3.42 – 16.88) $\times 10^8$ /kg recipient weight], mononuclear cell (MNC) count [5.84 (range 3.15 – 14.35) $\times 10^8$ /kg recipient weight], and CD3⁺ cell count [2.14 (range 0.9 – 4.9) $\times 10^8$ /kg recipient weight] were significantly lower in products collected on day 4 compared to other cohorts ($p < 0.001$, $p < 0.001$, and $p = 0.002$, respectively), Table 3. The median and mean PBPC product viabilities were 99–100% and 97.4–99.8%, respectively, among all of the cohorts; while there was a statistical significance for these values ($p < 0.001$), these differences were felt unlikely to be clinically significant and likely related to the different number of thawed PBPC products among the cohorts (6 thawed PBPC products in the day 4 cohort, 0 in the day 5, 2 in the two-day, and 7 thawed products in the historical cohort).

Transplant Outcomes

There were no National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grade III/IV infusion reactions occurring in any of the study cohorts nor among the historical controls (data not shown). We found no significant differences in the number of days to neutrophil engraftment of ANC $500/\mu\text{l}$ (day 13, 13, 14, and 14, for day 4, day 5, two-day, and historical collection cohorts, respectively, $p = 0.544$), to platelet engraftment $>20 \times 10^9/\text{L}$ (day 18, 19, 18, 19, for day 4, day 5, two-day, and historical collection cohorts, respectively, $p = 0.995$), or to platelet engraftment $>50 \times 10^9/\text{L}$ (day 19, 19, 18, 19, for day 4, day 5, two-day, and historical collection cohorts, respectively, $p = 0.913$), based on day of PBPC product collection (Table 4, Figures 2A–2B; Supplementary Figure 1). Additionally, there were no significant differences in the incidence of any acute GVHD ($p = 0.466$), acute GVHD grade II–IV ($p = 0.591$), acute GVHD grade III–IV ($p = 0.122$), nor incidence of chronic GVHD ($p = 0.122$), among the study and historical cohorts.

The number of patients surviving to 1-year post-HSCT was $n=38$ (76%) in the day 4 cohort, 17 (65%) in the day 5, 15 (60%) in the two-day, and 49 (65%) in the historical cohort, though this difference was not significant when comparing across all groups ($p=0.924$), Table 4. The median number of months of follow-up after transplant was significantly greater in the historical cohort compared to the day 4 collection, day 5 collection, and two-day collection cohorts (33.9 months versus 24.4, 19.6, and 14.5 months, respectively, $p=0.007$). However, among the 3 study cohorts, there was no difference in median follow-up (not shown). There were more deaths from any cause in the historical cohort compared to the day 4, day 5, and two-day collection cohorts [46 (61%) versus 20 (40%), 11 (42%), 12 (48%), respectively], though this difference was not statistically significant ($p=0.547$). Numerically there were more deaths from multisystem organ failure ($p=0.046$) and from disease recurrence/persistence ($p=0.059$), and fewer deaths from chronic GVHD ($p=0.069$), in the day 4 collection cohort compared to historical controls, and a trend towards more deaths from acute GVHD in the two-day collection cohort compared to historical controls ($p=0.058$), Figure 3.

Cost Analysis

When evaluating the direct costs per collection procedure, we found a 6.7% cost savings for the day 4 collection compared to the historical cohort. There was a 3.7% cost savings for the day 5 cohort compared to the historical controls. In contrast, among donors in the study cohort requiring two-day collections, we found an 8.5% increase in direct collection costs compared to the historical cohort.

Discussion

Using a peripheral blood CD34⁺ cell threshold of $0.04 \times 10^6/\text{ml}$, we determined that 49.5% of allogeneic HLA-matched peripheral blood stem cell donors underwent adequate mobilization after 4 days of G-CSF administration to allow for a single PBPC collection (Figure 4). The median donor weight was significantly greater among those meeting criteria for day 4 PBPC collection. Whether this collection difference relates to higher G-CSF exposure per kg actual versus ideal body weight is unknown, but may suggest that higher donor G-CSF exposure might result in an even greater number of donors adequately mobilized for single day 4 PBPC collection. Additionally, there were more male donors adequately mobilized by day 4 compared to the other cohorts, however this failed to reach statistical significance in the multivariate analysis. It is possible that with the accrual of additional numbers of donors, a significant gender-based difference in donor mobilization by day 4 may be determined. We also found no evidence of adverse post-HSCT outcomes associated with day 4 PBPC collection, and identified a cost savings benefit for day 4 collection from donors adequately mobilized.

A total of 61.4% of donors in the study cohort met peripheral blood CD34⁺ cell count criteria to initiate PBPC collection on day 4, and of these donors 80.6% collected over one day, while 19.4% required two-days of collection. We thus consider this 19.4% to represent a 'failure of adequate mobilization' according to our proposed collection algorithm. In comparison, we found in our historical cohort that 80% of donors were adequately

mobilized to allow a single PBPC collection on day 5, while 20% required multiple days of collection and thus 'failed adequate mobilization.' In the study cohort, donors collecting over days 4–5 were more likely to be older, male, and of greater weight than those donors collecting over days 5–6. However, these differences were not statistically significant, which may have been due to the small sample number of two-day collection donors. Alternatively, other as yet unknown donor factors may have contributed to the readiness of donors to collect on day 4 versus day 5.

Of interest, we identified significant differences in PBPC product composition based on day of stem cell collection, with higher CD34⁺ cell count and lower TNC, MNC, and CD3⁺ cell counts in products collected on day 4. Others have previously sought to determine the impact of PBPC product composition and specific hematopoietic cell subsets on post-transplant clinical outcomes. Poor quality grafts, defined by post-thaw TNC viability, have been shown to correlate with an increased risk for the development of acute GVHD and transplant-related mortality (TRM)^{13, 14}. An effect of the TNC and CD34⁺ cell doses on neutrophil and platelet engraftment after bone marrow and peripheral blood stem cell transplantation has been demonstrated^{15–17}, as well as a differential impact of high CD34⁺ cell doses on outcomes such as survival, relapse, and GVHD post-HSCT^{16, 18, 19}. The post-HSCT impact of specific cell subsets including CD123⁺ dendritic cells, CD3⁺ effector T-cells, CD8⁺ T-cells, and CD19⁺ B-cells, has also been investigated^{20–26}. Despite our identified differences in PBPC product composition, we found no significant difference in neutrophil and platelet engraftment, nor in acute or chronic GVHD outcomes, among all donors in the multivariate analysis. However, when we compared each of the individual study cohorts to the historical control, a decrease in the incidence of chronic GVHD was observed. It remains unclear if attribution to the graft composition could be the etiology, or linked to change in care algorithms over time (including differences in pre-transplant disease status and treatment, transplant conditioning regimens, GVHD prophylaxis, etc.), versus related to the longer overall post-transplant follow-up in the historical cohort. It is possible that with longer follow-up in the study cohorts and with additional patients/donors, differences in incidence or staging of chronic GVHD may reach significance and may correlate with differences in PBPC product composition. Additionally, it is possible that with more extensive hematopoietic cell subset immunophenotyping, correlation between specific cell subsets and post-HSCT clinical outcomes may be identified.

We observed a higher number of deaths from any cause among patients in the historical controls, which may have been influenced by the longer post-transplant follow-up in this cohort. To attempt to analyze this difference in time from HSCT, we also evaluated 1-year post-HSCT survival among the collection cohorts, and found a clinically relevant increase in the number of patients surviving at 1-year post-HSCT in the day 4 cohort compared to the historical control, though this failed to reach statistical significance, possibly related to the small cohort size. We speculate that there may be early post-HSCT survival differences among the collection cohorts. Longer follow-up post-HSCT and randomized or matched cohort analyses will be necessary to fully determine whether day of stem cell collection has direct impact on overall survival after HSCT, and whether any potential impact is independent of other patient/donor, PBPC graft composition, and transplant variables.

To assess for potential differences in donor risk and experienced side effects, the documented, reported donor symptoms were reviewed during and after the collection procedure(s). The most common donor symptoms found amongst all of our collection cohorts included bone pain, myalgia/malaise, headache, and electrolyte-related symptoms. These findings are in agreement with the published literature, which has described common donor side effects of bone pain, fatigue, myalgia, and malaise and an overall low incidence of serious donor adverse events^{27–33}. In an analysis of 350 donor/recipient pairs enrolled from 42 centers, the majority of peripheral blood stem cell donors reported at least one predominantly G-CSF-related adverse effect, which were mostly mild to moderate in severity³⁴. While several prior analyses compared donor symptoms after peripheral blood versus bone marrow stem cell collection^{31–34}, or focused on patient-reported outcomes³⁵, in this study, donor symptoms based on the day of stem cell collection and number of days of growth factor administration were examined. Compared to our historical cohort, we found that donors collecting on day 4, day 5, or two-day collections were all significantly more likely to report bone pain. With greater programmatic attention to donor management, donor symptoms may have been more likely to be reported and captured in the more recent cohorts versus the historical controls. Those donors collecting on day 4 were also significantly more likely to require narcotics than the historical cohort, perhaps reflecting a more brisk stem cell mobilization and associated bone pain. Donors in the two-day collection cohort were also more likely to have electrolyte-related abnormalities and symptoms, likely related to greater total exposure to anticoagulant (citrate) and leukapheresis times. There was no difference among any of the donor cohorts in the number of required ER visits, and no donors required blood product transfusion.

In our analysis of direct costs associated with the PBPC collection procedure, we identified a total direct cost savings in the study cohort for donors adequately mobilized to allow a single day of collection (6.7% savings for day 4 collection, and 3.7% for day 5 collection), versus the historical control cohort. In comparison, we found an increase in direct costs (8.5% increase) comparing donors in the study cohort requiring two-day collections compared to the historical cohort (in which 20% required two-day collections). We hypothesize that the cost savings in the day 4 and day 5 donor cohorts are likely at least in part related to the decrease in G-CSF related costs required with only one day of collection. The greater costs in the two-day collection cohort likely reflect the increase over time in collection procedure costs. However, additional studies including broader hospital and patient/donor charges, indirect costs, financial burden associated with the requirement for scheduling flexibility in the apheresis unit, hematopoietic cell processing laboratory, and infusion site, as well as the cost of two-day collections for donors inadequately mobilized for a single day 4 collection, are necessary to fully determine the financial impact of the day 4 collection algorithm. Others have performed cost analyses based on the type of HSCT (autologous versus allogeneic), stem cell donor (e.g. PBSCT, BMT, versus alternate donor HSCT), stem cell mobilization protocol (particularly in the autologous HSCT setting), HSCT intensity and conditioning regimen administered, and/or on post-HSCT complications^{36–43}. To our knowledge, our study is the first to evaluate direct PBPC collection costs based on the day of stem cell collection. With increasing numbers of HSCT procedures being performed, we

would anticipate additional total savings over time with day 4 collections, as well as a reduction in utilization of clinical services (e.g. pharmacy services, G-CSF, etc.).

In conclusion, our data suggest that day 4 should be the optimal day of PBPC collection for a population of healthy allogeneic HLA-matched peripheral blood stem cell donors, reducing G-CSF exposure and leading to expected cost savings (6.7%) compared to our historical PBPC collection algorithm. Whether our day 4 collection algorithm would be feasible, and these results similar, in the related HLA-mismatched, unrelated donor, and alternative donor (e.g. haploidentical) HSCT setting remains to be determined and merits further investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

HSCT	Hematopoietic stem cell transplantation
PB	Peripheral blood
PBPC	Peripheral blood progenitor cells
PBSCT	Peripheral blood stem cell transplantation
BMT	Bone marrow transplantation
GVHD	Graft-versus-host disease
G-CSF	Granulocyte colony-stimulating factor
ASBMT	American Society for Blood and Marrow Transplantation
NMDP	National Marrow Donor Program
ANC	Absolute neutrophil count
OTC	Over-the-counter
TNC	Total nucleated cell
MNC	Mononuclear cell
TRM	Transplant-related mortality

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Highlights:

- A population of matched related donors are adequately mobilized by day 4 of G-CSF.
- Differences in PBPC composition and donor symptoms were based on day of collection.
- Day 4 PBPC collection led to significant cost savings versus a historical cohort.

Figure 1:

Donor symptoms and pain medication use among the collection cohorts.

Frequency of donor symptoms in the study collection cohorts were compared to historical control cohort.

Figure 2A:

Cumulative incidence of neutrophil engraftment (ANC >500/μl). Two patients that died prior to achieving ANC >500/μl were excluded from analysis (one allograft recipient from day 4 collection, one from historical cohort).

Figure 2B:

Cumulative incidence of platelet engraftment $>20 \times 10^9/L$. Ten patients that died prior to achieving platelet engraftment $>20 \times 10^9/L$ were excluded from analysis (four allograft recipients from day 4 collection, one from day 5 collection, one from two-day collection, and four from historical cohort).

Figure 3:

Cause of death among the collection cohorts. * In the two-day collection cohort, one patient died of gastrointestinal hemorrhage on day +35 after HSCT. In the historical cohort, one patient died of failure to thrive on day +428 after HSCT, two patients died of non-infectious interstitial pneumonia on day +299 and day +1615.

Figure 4:
Feasibility of Day 4 G-CSF Mobilized PBPC Collection.

Table 1:

Patient Characteristics

Characteristic	Day 4 Collection N= 50	Day 5 Collection N= 26	Two-Day Collection N= 25	Historical Cohort N= 75	P-value
Recipient age in years, median (range)	55 (18–68)	52 (23–76)	56 (25–71)	56 (22–74)	0.545
Recipient weight in kg, median (range)	84.2 (45.6–129.7)	79.3 (47.5–105)	91.4 (56–157)	79.8 (45–148.3)	0.056
Recipient Gender, No. (%)					0.357
Male	24 (48%)	12 (46%)	17 (68%)	39 (52%)	
Female	26 (52%)	14 (54%)	8 (32%)	36 (48%)	
Recipient diagnosis at transplant, No. (%)					
AML	22 (44%)	7 (27%)	13 (52%)	30 (40%)	0.308
ALL	11 (22%)	5 (19%)	4 (16%)	12 (16%)	0.842
MDS/MPD	11 (22%)	6 (23%)	5 (20%)	17 (23%)	0.993
NHL	2 (4%)	4 (15%)	1 (4%)	10 (13%)	0.180
CML	2 (4%)	0	1 (4%)	3 (4%)	0.783
Other	2 (4%) [†]	4 (14%) ^{††}	1 (4%) ^{†††}	3 (4%) ^{††††}	0.147
Graft source					
HLA-matched sibling donor PBPC	50 (100%)	26 (100%)	25 (100%)	75 (100%)	n/a
Conditioning regimen, No. (%)					
Myeloablative	21 (42%)	13 (50%)	13 (52%)	36 (48%)	0.832
Reduced intensity	18 (36%)	8 (31%)	9 (36%)	23 (31%)	0.908
Non-myeloablative	11 (22%)	5 (19%)	3 (12%)	16 (21%)	0.748
GVHD prophylaxis, No. (%)					
Tacrolimus/Methotrexate	31 (62%)	15 (58%)	16 (64%)	30 (40%)	0.044
Cyclosporine/Methotrexate ± Prednisone	8 (16%)	6 (23%)	6 (24%)	32 (43%)	0.009
Cyclosporine/Mycophenolate	10 (20%)	4 (15%)	3 (12%)	12 (16%)	0.837
Other	1 (2%)*	1 (4%)*	0	1 (1%)*	0.745
Year of transplant					
7/2010 – 6/2013	0	0	0	75 (100%)	n/a
7/2013 – 6/2017	50 (100%)	26 (100%)	25 (100%)	0	<0.0001

Abbreviations: AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; MDS, myelodysplastic syndrome; MPD, myeloproliferative disease; NHL, non-Hodgkin lymphoma; CML, chronic myelogenous leukemia; PBSC, peripheral blood progenitor cells.

[†] Severe aplastic anemia (n=1); Hodgkin lymphoma (n=1)

^{††} Biphenotypic leukemia (n=1); Fanconi anemia (n=1), plasma cell disorder (n=2)

^{†††} Plasma cell disorder (n=1)

^{††††} Biphenotypic leukemia (n=2); Hodgkin lymphoma (n=1)

* Cyclosporine, Alemtuzumab

**
Cyclosporine, with CD34-selected product, and ATG.

***
Tacrolimus, Sirolimus, Methotrexate

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Table 2:

Donor Characteristics

Characteristic	Day 4 Collection N= 50 (49.5%)	Day 5 Collection N= 26 (25.7%)	Two-Day Collection N= 25* (24.8%)	Historical Cohort N= 75**	P-value
Donor age in years, median (range)	52 (18–68)	53 (40–65)	56 (20–68)	56 (13–70)	0.604
Donor weight in kg, median (range)	88.8 (53–225)	75.8 (52–117)	75.6 (48.9–171)	83.9 (43.5–142.8)	0.020
Donor Gender, No. (%)					0.134
Male	33 (66%)	13 (50%)	10 (40%)	37 (49%)	
Female	17 (34%)	13 (50%)	15 (60%)	38 (51%)	
Day 4 donor peripheral blood CD34 ⁺ %, median (range)	0.14 (0.06–0.4)	0.08 (0.03–0.18)	0.05 (0.01–0.08)	n/a	<0.001
Day 4 donor peripheral blood CD34 ⁺ × 10 ⁶ /ml, median (range)	0.06 (0.03–0.13) [‡]	0.03 (0.007–0.086) ^{‡‡}	0.019 (0.004–0.04)	n/a	<0.001
Donor peripheral blood CD34 ⁺ % at collection, median (range)	n/a	0.16 (0.08–0.26)	0.09 (0.03–0.25)	0.13 (0.01–0.37)	<0.001
Donor peripheral blood CD34 ⁺ × 10 ⁶ /ml at collection, median (range)	n/a	0.058 (0.04–0.13)	0.038 (0.012–0.08)	0.057 (0.004–0.78)	<0.001

Abbreviations: Kg, kilogram.

* Twelve donors collected on days 4 and 5; thirteen donors collected on days 5 and 6.

** In the historical cohort, fourteen donors required 2-day collections (days 5, 6); one donor required 3-days of collection (days 5, 6, 7).

[‡] Two donors with day 4 peripheral blood CD34⁺ cell counts of $0.03 \times 10^6/\text{ml}$ were collected on day 4, per discretion of the attending transplant physician.

^{‡‡} One donor with a day 4 peripheral blood CD34⁺ cell count of $0.086 \times 10^6/\text{ml}$ was collected on day 5, per discretion of the attending transplant physician.

Table 3:

Product Composition

Characteristic	Day 4 Collection N= 50	Day 5 Collection N= 26	Two-Day Collection N= 25	Historical Cohort N= 75	P-Value
Collected CD34 ⁺ × 10 ⁶ /kg recipient weight, median (range)	7.25 (3.06–18.79)	5.29 (3.36–11.83)	2.63 (0.63–4.47)	4.89 (0.42–24.04)	<0.001
Infused CD34 ⁺ × 10 ⁶ /kg recipient weight, median (range)	5.67 (3.06–7.91) *	5.25 (3.36–7.74)	4.89 (2.3–7.82)	5.02 (1.3–7.92)	0.042
Infused TNC × 10 ⁸ /kg recipient weight, median (range)	7.13 (3.42–16.88)	8.15 (0.07–20.91)	13.38 (5.04–25.52)	8.03 (3.07–23.05)	<0.001
Infused MNC × 10 ⁸ /kg recipient weight, median (range)	5.84 (3.15–14.35)	6.82 (0.06–17.67)	10.73 (3.46–16.64)	6.06 (2.43–16.16)	<0.001
Infused CD3 ⁺ × 10 ⁸ /kg recipient weight, median (range)	2.14 (0.9–4.9)	2.5 (0.96–7.05)	3.84 (0.96–6.37)	2.31 (0.83–7.23)	0.002
Product viability, median (range)	99% (77–100%)	100% (98–100%)	100% (78–100%)	100% (70–100%)	<0.001

Abbreviations: TNC, total nucleated cells; MNC, mononuclear cells.

* One donor collected a total of 3.06×10^6 CD34⁺ cells/kg recipient weight, which was deemed adequate for transplantation and infusion per discretion of the attending transplant physician.

Table 4:

Transplantation Outcomes

Characteristic	Day 4 Collection N= 50	Day 5 Collection N= 26	Two-Day Collection N= 25	Historical Cohort N= 75	P-Value
Days to ANC $\geq 500/\mu\text{L}$, median	13 (0–34) [*]	13 (8–22)	14 (0–21)	14 (0–27) ^{**}	0.544
Days to platelets $\geq 20 \times 10^9/\text{L}$, median (range)	18 (0–306) [†]	19 (0–129) ^{††}	18 (0–41) ^{†††}	19 (0–48) ^{††††}	0.995
Days to platelets $\geq 50 \times 10^9/\text{L}$, median (range)	19 (0–415) [†]	19 (0–314) ^{††}	18 (0–133) ^{†††}	19 (0–88) ^{††††}	0.913
Any grade acute GVHD, No. (%)	21 (44%) [†]	11 (42%)	11 (44%)	41 (55%) ^{††}	0.466
Acute GVHD grade II–IV	16 (33%)	10 (39%)	9 (36%)	33 (45%)	0.591
Acute GVHD grade III–IV	9 (19%)	1 (4%)	7 (28%)	17 (23%)	0.122
Chronic GVHD	11 (28%) ^φ	8 (42%) ^{φφ}	3 (17%) ^{φφφ}	46 (71%) ^{φφφφ}	0.122
1-year overall survival, No. (%)	38 (76%)	17 (65%)	15 (60%)	49 (65%)	0.924
Death from any cause, No. (%)	20 (40%)	11 (42%)	12 (48%)	46 (61%)	0.547
Median follow-up from transplant, months (range)	24.4 (0.6–57.1)	19.6 (0.9–49.2)	14.5 (1.2–52.7)	33.9 (0.4–93.9)	0.007

Abbreviations: ANC, absolute neutrophil count.

^{*} One patient died prior to ANC engraftment.

^{**} One patient died prior to ANC engraftment.

[†] Four patients died prior to platelet engraftment $\geq 20 \times 10^9/\text{L}$.

^{††} One patient died prior to platelet engraftment $\geq 20 \times 10^9/\text{L}$; two patients died prior to platelet engraftment $\geq 50 \times 10^9/\text{L}$.

^{†††} One patient died prior to platelet engraftment $\geq 20 \times 10^9/\text{L}$; two patients died prior to platelet engraftment $\geq 50 \times 10^9/\text{L}$.

^{††††} Four patients died prior to platelet engraftment $\geq 20 \times 10^9/\text{L}$; seven patients died prior to platelet engraftment $\geq 50 \times 10^9/\text{L}$.

[†] Forty-eight patients evaluable for acute GVHD; 3 patients with suspected but not biopsy-proven acute GVHD.

^{††} Seventy-four patients evaluable for acute GVHD.

^φ Forty patients alive beyond day 100 and evaluable for chronic GVHD.

^{φφ} Nineteen patients alive beyond day 100 and evaluable for chronic GVHD.

^{φφφ} Eighteen patients alive beyond day 100 and evaluable for chronic GVHD.

^{φφφφ} Sixty-five patients alive beyond day 100 and evaluable for chronic GVHD.