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# Impact of Mobilization and Remobilization Strategies on Achieving Sufficient Stem Cell Yields for Autologous Transplantation

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## ABSTRACT

**The purpose of this article was to examine historic institutional autologous stem cell mobilization practices and evaluate factors influencing mobilization failure and kinetics. In this retrospective study we analyzed clinical records of 1834 patients who underwent stem cell mobilization for autologous transplantation from November 1995 to October 2006 at the Washington University in St. Louis. Successful mobilization was defined as collection of $\geq 2 \times 10^6$ $CD34^+$ cells/kg. From 1834 consecutive patients, 1040 met our inclusion criteria (502 non-Hodgkin's lymphoma [NHL], 137 Hodgkin's lymphoma, and 401 multiple myeloma [MM]). A total of 976 patients received granulocyte colony-stimulating factor (G-CSF) and 64 received G-CSF plus chemotherapy (G/C) for the initial mobilization. Although the median $CD34^+$ cell yield was higher in G/C group than in G-CSF alone group, the failure rates were similar: 18.8% and 18.6%, respectively. Overall, 53% of patients collected $\geq 2 \times 10^6$ $CD34^+$ cells/kg during the first apheresis with either mobilization regimen. Regardless of mobilization regimen used, MM patients had the highest total $CD34^+$ cell yield and required less aphereses to collect $\geq 2 \times 10^6$ $CD34^+$ cells/kg. Mobilized, preapheresis, peripheral blood $CD34^+$ count correlated with first day apheresis yield ($r = .877$, $P < .001$) and 20 cells/$\mu$L was the minimum threshold needed for a successful day 1 collection. For the remobilization analysis we included patients from the whole database. A total of 269 of 1834 patients underwent remobilization using G/C, G-CSF, and/or GM-CSF, and G-CSF plus plerixafor. Only 23% of remobilized patients achieved $\geq 2 \times 10^6$ $CD34^+$ cells/kg and 29.7% failed to pool sufficient number of stem cells from both collections. Patients receiving G-CSF plus plerixafor had lowest failure rates, $P = .03$. NHL patients remobilized with G-CSF who waited $\geq 25$ days before remobilization had lower $CD34^+$ cell yield than those who waited $\leq 16$ days, $P = .023$. Current mobilization regimens are associated with a substantial failure rate irrespective of underlying disease. Patients who fail initial mobilization are more likely to fail remobilization. These findings suggest that there is a need for more effective first-line mobilization agents.**
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## KEY WORDS

Stem cell transplantation • Stem cell mobilization • Growth factors

## INTRODUCTION

High-dose chemotherapy, in conjunction with autologous stem cell transplantation (ASCT), has emerged as a preferred treatment modality for a variety of hematologic malignancies including multiple myeloma (MM), non-Hodgkin's lymphoma (NHL), and Hodgkin's lymphoma (HL) [1-3]. Multiple randomized trials have demonstrated the advantage of mobilized peripheral blood stem cells (PBSC) over the bone marrow for ASCT [4-6]. The collection of adequate number of $CD34^+$ cells, a surrogate marker of hematopoietic stem cells, is paramount because the

dose of infused $CD34^+$ cells influences the success and rate of hematopoietic recovery [7-10]. There is evidence to support that a "minimum" dose of $2 \times 10^6$ $CD34^+$ cells/kg is needed to ensure successful hematopoietic recovery and sustained engraftment [11-14]. Recent studies have suggested that the "optimal" dose, $\geq 5 \times 10^6$ $CD34^+$ cells/kg, results in more rapid and predictable hematopoietic and, especially, platelet recovery [15-18]. However, it may be difficult to collect this yield in older and heavily pretreated patients.

The 2 most commonly used mobilization regimens are the cytokine granulocyte colony-stimulating factor (G-CSF) and G-CSF plus chemotherapy (G/C). G-CSF induces marrow hyperplasia and subsequent release of stem cells into the circulation. Mobilization is mediated in part through proteases that disrupt interactions between adhesion molecules expressed on stem cell surface and their ligands on bone marrow stroma, and in part by nonproteolytic mechanisms regulating molecular expression of stromal cell-derived factor-1 (SDF-1) at the mRNA level [19-24]. A significant proportion of patients mobilized with G-CSF alone fail to collect the minimum number of $CD34^+$ cells to support ASCT, largely because of prior cytotoxic chemotherapy and advanced age [25,26]. Addition of chemotherapy to G-CSF is thought to induce marrow aplasia, which subsequently stimulates hematopoietic recovery. It is speculated that the concomitant use of chemotherapy and G-CSF might have a synergistic effect on protease release in the bone marrow [27]. A novel small molecule, chemokine receptor-4 (CXCR4) antagonist, AMD3100 (Plerixafor), has been tested in the clinic and found to enhance mobilization when administered with G-CSF [28-33].

Failure rates with current mobilization regimens are estimated to be between 5% and 30% [15,34,35]. An unsuccessful initial mobilization attempt results in additional mobilizations, which negatively impact patients' outcomes and significantly increase health care utilization. The purpose of this retrospective analysis is to examine the efficacy of mobilization with G-CSF alone and in combination with chemotherapy in achieving minimal and optimal stem cell targets, and to evaluate mobilization kinetics. We further correlate peripheral blood $CD34^+$ cell count/μL before mobilization and immediately prior to the first apheresis with mobilized $CD34^+$ cell/kg yield. Finally, we evaluate the impact of various mobilization regimens on the success of remobilization.

## PATIENTS AND METHODS

### Patient Population

This is a single-center retrospective analysis of the clinical records in the ASCT database at Washington University in St. Louis from November 1995 through October 2006. Patient records were included if patients had MM, NHL, or HL, and had at least 1 PBSC mobilization attempt using G-CSF alone or G/C. Patient records were excluded if patients had solid tumors or leukemia, and first mobilization using agents other than G-CSF or G/C. However, when evaluating remobilization results we included patient records from the whole database.

### Mobilization Regimens

Initial mobilization regimens included G-CSF and G/C. Patients mobilized with G-CSF alone received G-CSF at 10 μg/kg/day subcutaneously (s.c.) for 4 days prior to apheresis. Aphereses and G-CSF were continued daily for up to 5 consecutive days or until $\geq 2 \times 10^6$ $CD34^+$ cells/kg were collected. The use and selection of chemotherapy, as part of mobilization regimen, depended on the patient's diagnosis, clinical status, and the preference of the treating physician. Patients mobilized with G/C started G-CSF at 10 μq/kg/day s.c. on day 4 after chemotherapy and continued until aphereses were completed. Apheresis started based on the total white blood cell count $>5000 \times 10^6$/L. First mobilization was defined as no prior mobilization attempt within 1 year. Mobilization failure was defined as $<2 \times 10^6$ $CD34^+$ cells/kg obtained within 5 apheresis days. Patients who failed initial mobilization were remobilized after 10-30 days. Remobilization regimens included G-CSF and/or granulocyte-macrophage colony-stimulating factor (GM-CSF), G/C, and G-CSF plus plerixafor (G/P). When used in combination with G-CSF, the dose of GM-CSF was 5 μg/kg/day s.c. GM-CSF was started 5 days prior to apheresis (1 day prior to G-CSF) and continued daily, 30 min to 1 hour after G-CSF, until target goal $CD34^+$ was met or total of 5 aphereses. Patients mobilized with G/P received G-CSF at 10 μg/kg/day s.c. every morning for 4 days and on the evening of the fourth day they received plerixafor at 240 μg/kg s.c. The aphereses were started on day 5, after the morning dose of G-CSF. Patients continued receiving their morning dose of G-CSF and evening dose of plerixafor until collected $CD34^+$ cell count was $\geq 2 \times 10^6$/kg or total of 5 aphereses.

### Apheresis and $CD34^+$ Cell Enumeration

Aphereses were performed using continuous-flow blood cells separator (COBE Spectra, Lakewood, CO) processing 18 to 20 L of blood during each procedure. Estimation of $CD34^+$ cell content in peripheral blood and in the apheresis product was performed by flow cytometry using fluorescein-conjugated antihuman CD34 monoclonal antibody (anti-HPCA-2, Becton Dickinson, San Jose, CA) [36,37]. The harvested product was cryporeserved in 10% DMSO and Plasma-Lyte-A (Baxter, Deerfield, IL).

### Engraftment

Neutrophil engraftment was defined as the first of 3 consecutive days with absolute neutrophil count $\geq 0.5 \times 10^9$/L without growth factor support, and platelet engraftment as the first of 7 consecutive days with platelet count $\geq 20 \times 10^9$/L without transfusions.

### Statistical Analysis

Descriptive statistics were used to identify the proportion of patients achieving minimal and optimal $CD34^+$ cell collection, and mobilization failure by disease and mobilization regimen. Inferential statistical testing was performed on the median total apheresis yield between diseases using Kruskal-Wallis with Dunn's posttest. Chi-square test or Fisher's exact test when appropriate was used to compare mobilization failure between different regimens. Time to hematopoietic recovery was estimated using the Kaplan-Meier product-limit method and the log-rank test. The Spearman rank correlation was used to test the association of first-day apheresis $CD34^+$ cell yield with resting and mobilized peripheral blood $CD34^+$ cell count. Statistical significance was set at $P < .05$. Descriptive and inferential statistics were performed using GraphPad Prism.

## RESULTS

### Patient Populations and Demographics

The Washington University ASCT database contained 2132 mobilization cases including 1834 cases of first mobilization and 298 of remobilization. An overview of the database is provided in Figure 1. Among 1834 first mobilizers, 1040 patients (56.7%) met our inclusion criteria: 502 cases of NHL, 137 cases of HL, and 401 cases of MM. 976 (93.8%) patients were initially mobilized with G-CSF and 64 (6.2%) patients with G/C. Patient characteristics are presented in Table 1. NHL and HL were analyzed together because these patients have similar previous treatments. The only significant difference within the disease groups was that MM patients with more advanced disease and a longer period from last treatment to first mobilization were more likely to receive G/C. For the remobilization analysis we included patients from the whole database. The database contained 298 cases of remobilization for 269 patients (29 patients were mobilized a third time).

### $CD34^+$ Cell Yield and Failure Rates

Overall 81.3% (846 of 1040) of patients collected $\geq 2 \times 10^6$ $CD34^+$ cells/kg after a maximum of 5 aphereses, 52.7% (548 of 1040) collected 2-5 $\times 10^6$ $CD34^+$ cells/kg, and 28.7% (298 of 1040) collected $>5 \times 10^6$ $CD34^+$ cells/kg (Figure 2A). When cell collection outcomes were compared by mobilization regimens, the failure rate with G-CSF alone was 18.6% (182 of 976) and with G/C was 18.8% (12 of 64), $P = .984$. Despite similar failure rates, more patients receiving G/C collected $>5 \times 10^6$ $CD34^+$ cells/kg than patients receiving G-CSF alone (56.3% versus 26.8%, respectively, $P < .001$). The median $CD34^+$ cell yield was higher in patients receiving G/C than those receiving G-CSF alone ($5.43 \times 10^6$ and $3.36 \times 10^6$, respectively). In addition, there was no difference in failure rates within each disease group with either mobilization regimen (Figure 2B and Table 2). Using G/C, more patients collected the optimal count in all 3 diseases. Patients with MM had the highest total $CD34^+$ cell yield regardless of mobilization regimen.

### Apheresis Kinetics

Among the patients who were successfully mobilized, approximately 53% collected $\geq 2 \times 10^6$ $CD34^+$ cells/kg on the first apheresis day. A total of 77.7% of patients mobilized with G-CSF reached

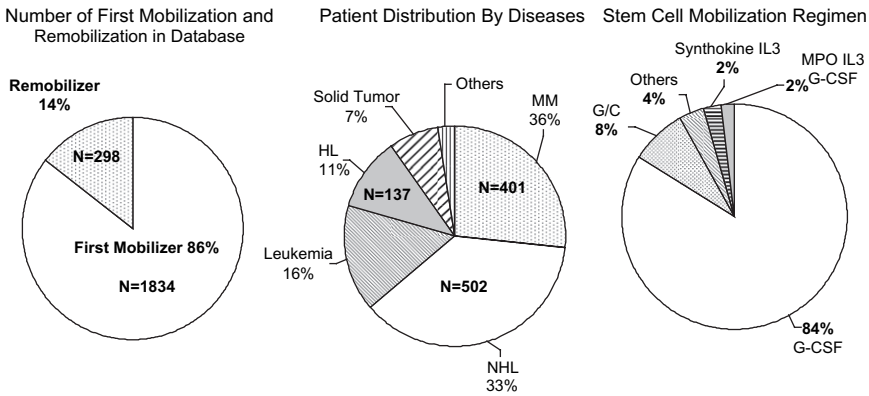


**Figure 1.** Overview of autologous stem cell transplantation database by disease and by mobilization regimens; first mobilization (N = 1834), remobilization (N = 298). NHL (non-Hodgkin's lymphoma), HL (Hodgkin's lymphoma), G-CSF (granulocyte colony-stimulating factor); GM-CSF (granulocyte-macrophage colony-stimulating factor), Synthokine (modified human Interleukin-3/IL-3), MPO (Myelopoietin, a G-CSF-IL-3 fusion protein).

**Table 1.** *Patient Characteristics by Mobilization Regimens and by Disease*

| | NHL/HL | | | MM | | |
|---|---|---|---|---|---|---|
| | G/C | G-CSF | *P*-value | G/C | G-CSF | *P*-value |
| **Number of Patients** | 47 | 592 | | 17 | 384 | |
| **Median Age (years)** | 51 | 53 | | 56 | 57 | |
| **Gender, n (%)** | | | | | | |
| **Male** | 28 (59.6) | 354 (59.8) | .9761 | 12 (70.5) | 231 (60.2) | .3890 |
| **Female** | 19 (40.4) | 238 (40.2) | | 5 (29.5) | 153 (39.8) | |
| **Disease Status, n (%)** | | | | | | |
| **CR/ PR ≤ 1** | 14 (29.8) | 223 (37.7) | .5488 | 13 (76.5) | 346 (90.1) | .0004 |
| **CR/ PR = 2** | 24 (51.1) | 274 (46.3) | | 3 (17.6) | 38 (9.9) | |
| **CR/ PR ≥ 3** | 9 (19.1) | 95 (16.0) | | 1 (5.9) | 0 | |
| **Prior radiotherapy** | 14 (29.8) | 97 (16.4) | .0196 | 7 (41.2) | 192 (50.0) | .5697 |
| **Number of prior chemotherapy regimens*** | | | | | | |
| **1** | 17 (37.0) | 130 (22.0) | .0659 | 13 (76.4) | 230 (59.8) | .3379 |
| **2** | 22 (47.8) | 357 (60.3) | | 3 (17.6) | 134 (35.0) | |
| **≥ 3** | 7 (15.2) | 105 (17.7) | | 1 (6.0) | 20 (5.2) | |
| **Time from last chemotherapy to mobilization** | | | | | | |
| **1 to 2 months** | 40 (87.0) | 531 (89.7) | .4056 | 9 (53.0) | 346 (90.2) | <.001 |
| **2 to 3 months** | 5 (10.9) | 37 (6.2) | | 4 (23.5) | 19 (4.9) | |
| **>3 months** | 1 (2.1) | 24 (4.1) | | 4 (23.5) | 19 (4.9) | |
| **Chemomobilization** | | | | | | |
| **Cyclophosphamide** | 3 (6.4) | — | | 17 (100%) | — | |
| **Ara-C + Etoposide** | 12 (25.5) | — | | 0 | — | |
| **ESHAP/ DSHAP** | 14 (29.8) | — | | 0 | — | |
| **ICE/ RICE** | 13 (27.6) | — | | 0 | — | |
| **Others** | 5 (10.6) | — | | 0 | — | |

NHL indicates non-Hodgkin's lymphoma; HL, Hodgkin's lymphoma; MM, multiple myeloma; G-CSF, granulocytecolony-stimulating factor; G/C, G-CSF + chemotherapy; CR, complete remission; PR, partial remission; ICE, ifosfamide, carboplatin, etoposide; ESHAP/DHAP, etoposide, cytarabine, methylprednisolone, cisplatine/cytarabine, dexamethasone, cisplatin.

*One NHL patient in the G-CSF and chemotherapy mobilization group did not receive any therapy prior to mobilization and was not included in the disease status evaluation and prior chemotherapy evaluation.

this minimum target within the first 2 days, compared with 75.0% mobilized with G/C ($P$ = NS; Figure 2C). This pattern of apheresis was observed across all 3 diseases (Figure 2D). G/C significantly increased the percentage of patients reaching the minimum $CD34^+$ cell count on the first apheresis day only in MM (63.6% with G-CSF and 93.8% with G/C, $P = .013$). The median number of aphereses to achieve $\geq 2 \times 10^6$ $CD34^+$ cells/kg was significantly greater among NHL and HL patients than MM (2 and 1, respectively, $P < .01$).

## Peripheral $CD34^+$ Cell Counts

Mobilized, preapheresis, peripheral blood $CD34^+$ cell count was found to be a significant predictor of day 1 $CD34^+$ cell collection regardless of the underlying disease or mobilization regimen ($P < .0001$, $r > .899$; Figure 3A). Additionally, we identified the minimum of 20 mobilized peripheral blood $CD34^+$ cells/μL required for a successful day 1 collection. 54.2% (529 of 976) of G-CSF mobilized patients and 58.1% (36 of 62) of G/C mobilized patients had peripheral blood $CD34^+$ cells count >20 cells/μL on day 1 immediately prior to the first apheresis. This is consistent with percentage of patients collecting $\geq 2 \times 10^6$ $CD34^+$ on the first apheresis day (53.1% for G-CSF and 54.7% for G/C; Figure 2C). Premobilization, steady-state peripheral blood $CD34^+$ cell count correlated poorly with the first day apheresis yield for all 3 diseases ($r < .54$; Figure 3B).

## Engraftment

The relationship between the dose of infused $CD34^+$ cells and engraftment was analyzed. Infusion of $>10 \times 10^6$ $CD34^+$ cells/kg was associated with a shorter time to neutrophil and platelet engraftment than was a cell dose of $<2 \times 10^6$ $CD34^+$ cells/kg ($P < .01$). There were no differences in time to either platelet or neutrophil recovery among the different mobilization regimens used.

## Remobilization

A total of 350 of 1834 patients failed initial mobilization but only 269 of 350 patients were remobilized. Following remobilization, only 62 (23.0%) patients achieved $\geq 2 \times 10^6$ $CD34^+$ cells/kg. The failure rates following remobilization with G-CSF and/or GM-CSF, G/C, and G/P were 81.6%, 73.5%, and 27.8%, respectively, $P < .001$ (Table 3).

We further examined the impact of wait time between first mobilization and remobilization on the remobilization failure rate. The time between the first and second mobilization was segregated into quartiles.

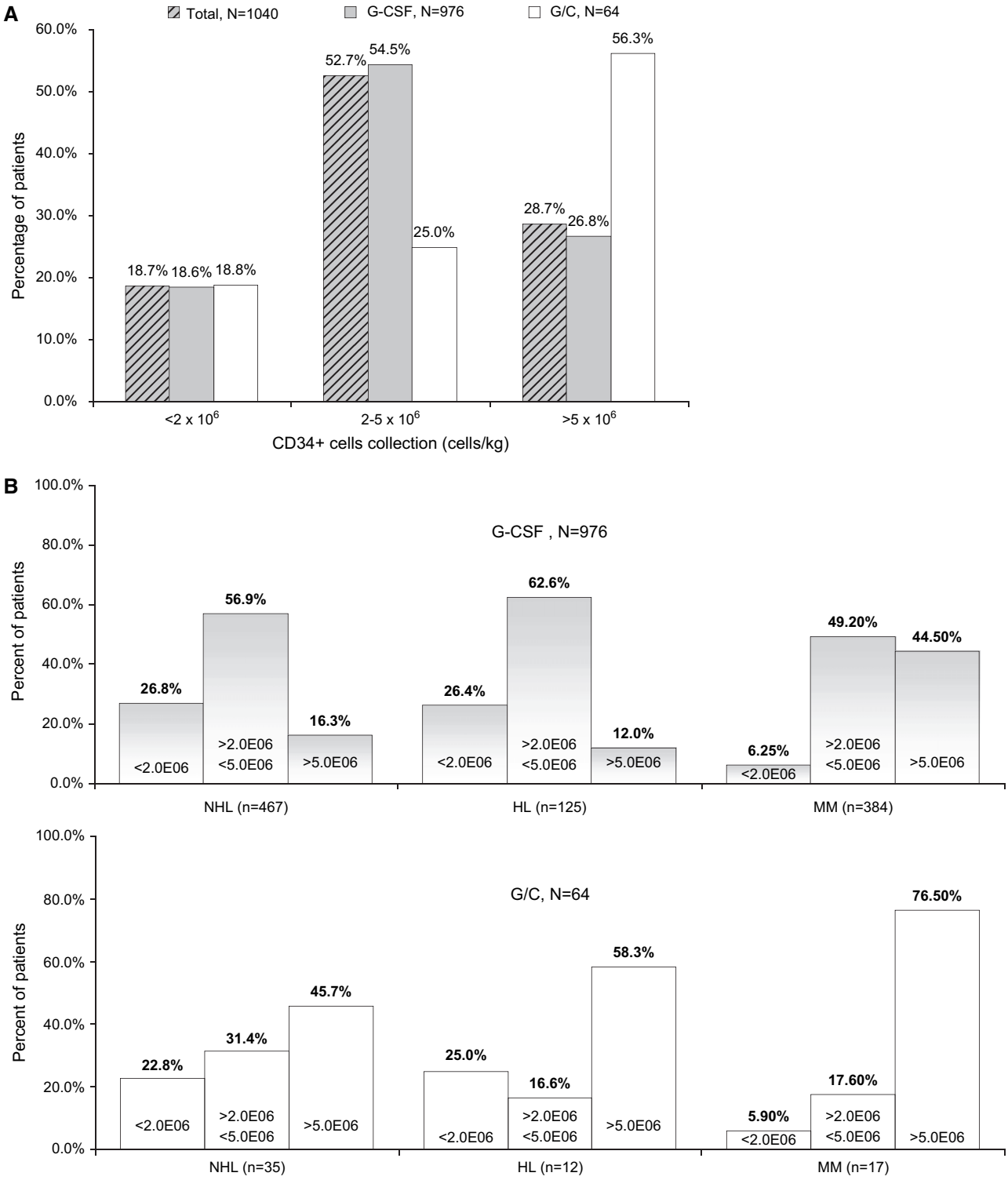


**Figure 2.** (A) Distribution of total $CD34^+$ cells/kg yield within 5 apheresis days after the first mobilization. Total number of patients analyzed was 1040; 976 mobilized with G-CSF and 64 with G/C. (B) $CD34^+$ cell/kg yield by disease and by mobilization regimens. (C) Duration of apheresis to collect $\geq 2 \times 10^6$ $CD34^+$ cells/kg for successfully mobilized patients. Total number of successfully mobilized patients was 846; 794 mobilized with G-CSF and 52 with G/C. (D) Duration of apheresis to collect $\geq 2 \times 10^6$ $CD34^+$ cells/kg in different diseases for successfully mobilized patients. Total number of successfully mobilized patients was 846; 794 mobilized with G-CSF and 52 with G/C. NHL (non-Hodgkin's lymphoma), HL (Hodgkin's lymphoma), MM (multiple myeloma), G-CSF (granulocyte colony-stimulating factor), G/C (G-CSF + chemotherapy).

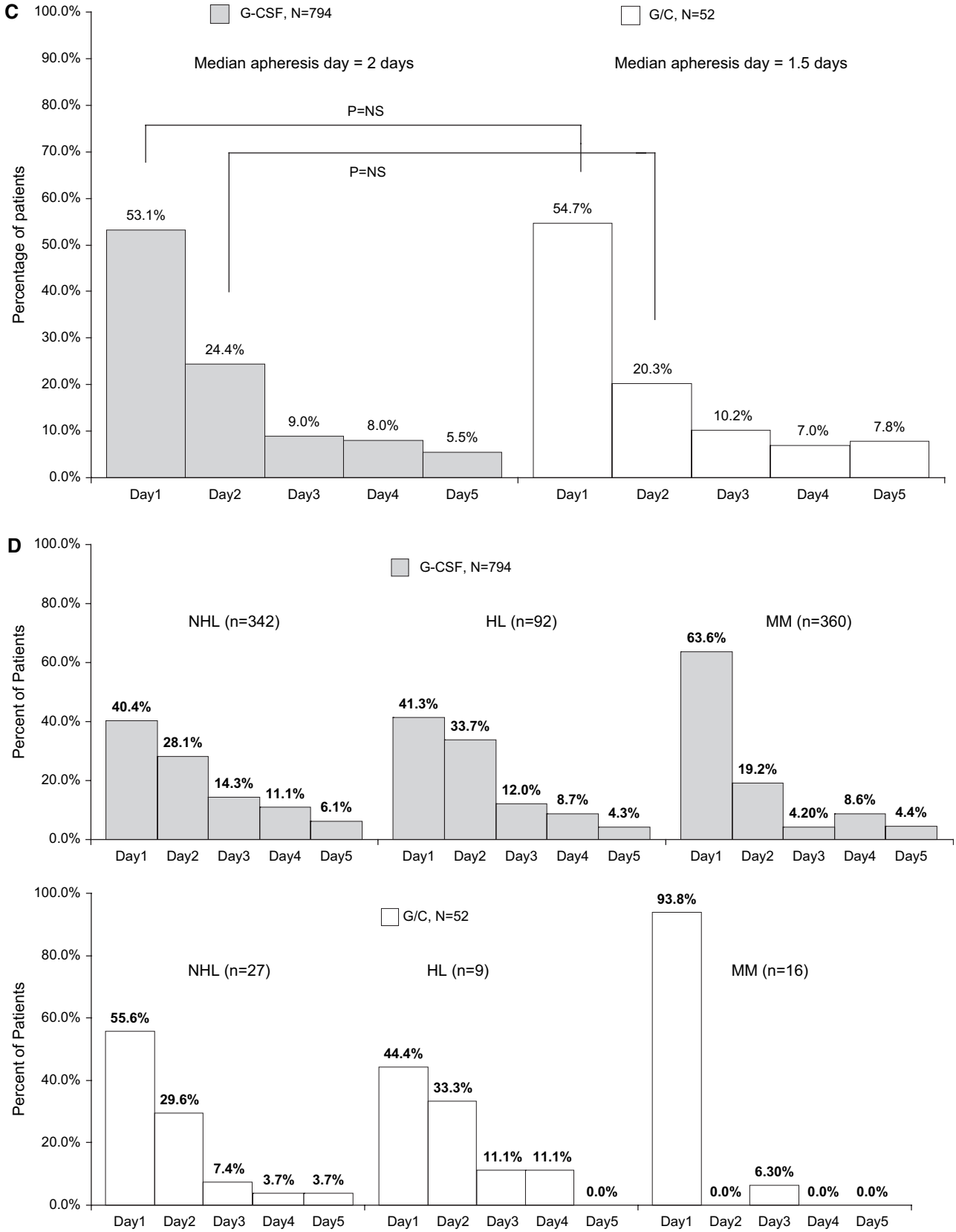


**Figure 2.** (*Continued*)

**Table 2.** *First Mobilization Failure Rates and CD34$^+$ Cell Yields by Disease and by Regimen*

| Disease | Mobilization | N | Failure* (%) | CD34$^+$ Cell Yield† ($\times 10^6$ cells/kg) Median (range) |
|---|---|---|---|---|
| NHL (n = 502) | G-CSF | 467 | 26.8% | 2.9 (2.8-3.0) |
| | G/C | 35 | 22.9% | 4.7 (2.8-8.5) |
| HL (n = 137) | G-CSF | 125 | 26.4% | 3.0 (2.8-3.4) |
| | G/C | 12 | 25.0% | 4.7 (1.0-9.5) |
| MM (n = 401) | G-CSF | 384 | 6.3% | 4.6 (4.2-5.0) |
| | G/C | 17 | 5.9% | 8.5 (4.5-16.3) |

NHL indicates non-Hodgkin's lymphoma; HL, Hodgkin's lymphoma; MM, multiple myeloma; G-CSF, granulocytecolony-stimulating factor; G/C, G-CSF + chemotherapy.

*NHL: $P = .61$; HL: $P = .92$; MM: $P = .95$.

†$P < .01$ compared between G-CSF and G/C for all diseases.

The lowest wait time quartile was ≤16 days and the longest was ≥25 days. NHL patients remobilized with G-CSF who waited ≥25 days before remobilization had lower CD34$^+$ cell yield than those who waited ≤16 days, ($P = .023$; Figure 4).

When cells from the first and second mobilization were pooled, 169 patients (62.8%) collected 2-5 $\times$ $10^6$ CD34$^+$ cells/kg and 20 patients (7.4%) collected >5 $\times$ $10^6$ CD34$^+$ cells/kg. Importantly, 80 patients (29.7%) failed to pool sufficient number of cells from the first and second mobilization to proceed to transplantation. Among remobilization regimens, G/C had the highest pooled failure rates (47.1%) compared to G-CSF ± GM-CSF (28.1%) and G/P (16.7%) ($P = .03$; Table 3). Remobilization with G/P had the lowest failure rate, both after second mobilization alone and after pooling the cells from the first and second collections.

## DISCUSSION

An ideal mobilization regimen should allow for predictable and reliable collection of sufficient CD34$^+$ cells for transplantation, have limited toxicity, and result in prompt and durable engraftment. The findings from this retrospective study, however, demonstrate that our current mobilization regimens are far from ideal. Although mobilization regimens containing G/C resulted in significantly higher CD34$^+$ cell yield and higher percentage of patients reaching the optimal CD34$^+$ cell count than regimens using G-CSF alone, the failure rates for initial mobilization were not different between the 2 mobilization groups. In addition, the failure rates with either mobilization regimen were nearly identical within each disease group. When failure rates were compared among different diseases, patients with NHL and HL had approximately 4-fold higher failure rates, with either mobilization regimen, than patients with MM. Both mobilization regimens had a similar collection pattern, with over 75% of successfully mobilized patients collecting the minimum CD34$^+$ dose within the first 2 apheresis days. CD34$^+$ cell yield declined significantly after second collection, suggesting that there is little benefit in extending apheresis beyond the first 2 days.

In our study, only 56.3% of patients in G/C group and 26.8% in G-CSF group achieved the optimal CD34$^+$ cells target of 5 $\times$ $10^6$ cells/kg after 5 apheresis days. When the total CD34$^+$ cell yields were compared among different disease groups, MM patients had higher yield compared to NHL and HL regardless of the mobilization regimens, likely because of the fact that NHL and HL patients are frequently more heavily pretreated with cytotoxic chemotherapy than patients with MM. Recent data suggests that this may not be the case in MM patients treated prior to stem cell harvest with lenalidomide containing therapy [38]. It should be noted that none of the MM patients in our database received lenalidomide prior to mobilization. Because of the higher yield of CD34$^+$ cells collected per apheresis in MM patients mobilized with G/C, such regimens might be useful in preparation for tandem ASCT.

It was initially thought that chemotherapy as a part of mobilization regimen might reduce tumor contamination in the apheresis product. Although tumor contamination might be reduced by the addition of chemotherapy, it does not appear to have any effect on relapse rate or survival [39,40]. Chemotherapy containing mobilization regimens are associated with increased risk for secondary malignances, impaired fertility, cardiac toxicity, risk of cytopenias and infections, resulting in increased resource use and cost [41-44]. In addition, such regimens have a less predictable collection schedule; thus, the potential to delay the transplant, resulting in increased morbidity and mortality. Because of these potential risks, the routine addition of chemotherapy to G-CSF for mobilization may not be justified. Several randomized studies compared mobilization using G-CSF alone with G/C [42,45,46]. Although these studies were relatively small, they showed that despite the higher yield of CD34$^+$ cells collected in G/C groups, mobilization with G-CSF alone resulted in adequate CD34$^+$ cell collections with lower toxicity and cost.

Many variables have been previously reported to be associated with successful mobilization including peripheral blood white cell count, platelet count, peripheral blood CD34$^+$ cell count prior to mobilization, the number of days after chemotherapy administration, and other patient factors [26,47-50]. However, none of these factors alone are predictive of CD34$^+$ cell collection. We observed that mobilized, preapheresis, peripheral blood CD34$^+$ cell count is strongly associated with day 1 CD34$^+$ cell yield regardless of underlying disease or mobilization regimen. Until

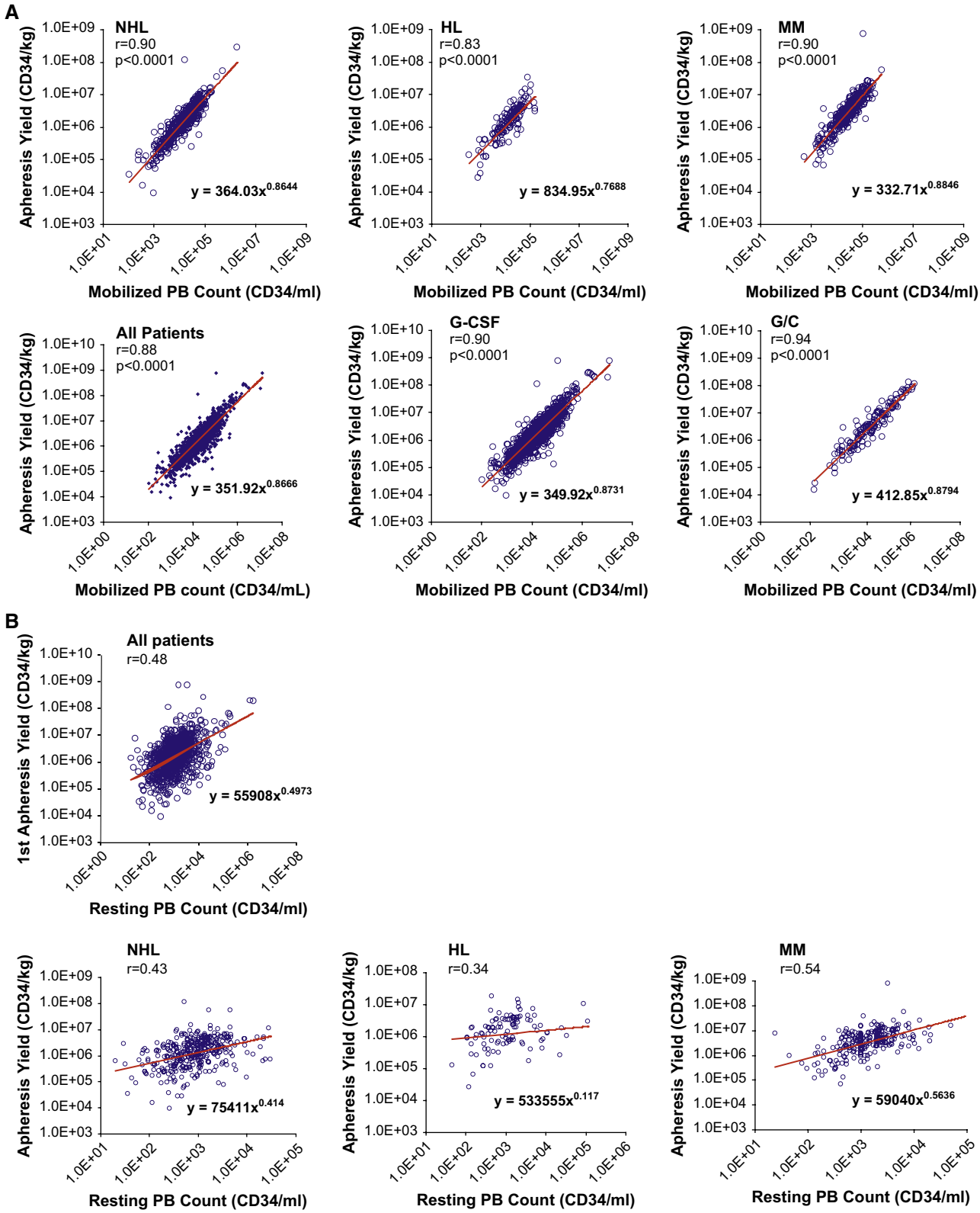


**Figure 3.** (A) Correlation between mobilized preapheresis peripheral blood CD34$^+$ cell count with day 1 apheresis yield. (B) Correlation of pre-mobilization peripheral blood CD34$^+$ cell count with day 1 apheresis yield. NHL (non-Hodgkin's lymphoma), HL (Hodgkin's lymphoma), MM (multiple myeloma), G-CSF (granulocyte colony-stimulating factor), G/C (G-CSF + chemotherapy).

**Table 3.** *Outcomes of Remobilization*

| | G-CSF / GM-CSF | G/C | G/P |
|---|---|---|---|
| **Remobilization regimen used** | **N = 217** | **N = 34** | **N = 18** |
| **First mobilization with G-CSF** | | | |
| **Median $CD34^+$ cell/kg yield** | **$1.1 \times 10^6$** | **$0.8 \times 10^6$** | **$1.0 \times 10^6$** |
| **Median apheresis days** | **4 days** | **3 days** | **2.5 days** |
| **Remobilization** | | | |
| **Median $CD34^+$ cell/kg yield** | **$1.2 \times 10^6$** | **$0.9 \times 10^6$** | **$4.6 \times 10^6$** |
| **Median apheresis days** | **3 days** | **2 days** | **2.5 days** |
| **Failure rate*** | **81.6%** | **73.5%** | **27.8%** |
| **Pooled cells (first and second mobilization)** | | | |
| **Median $CD34^+$ cell/kg yield** | **$2.5 \times 10^6$** | **$2.1 \times 10^6$** | **$5.5 \times 10^6$** |
| **Median apheresis days** | **6** | **7** | **6** |
| **Overall failure rate†** | **28.1%** | **47.1%** | **16.7%** |

G-CSF indicates granulocytecolony-stimulating factor; G/C, G-CSF + chemotherapy.
*$P \leq .001$ comparison among all 3 groups.
†$P = .03$ comparison among all 3 groups.

there are other reliable and predictable markers for successful collection, mobilized peripheral blood $CD34^+$ cell count may be the only reliable way of determining if the patient should undergo apheresis.

In our database 350 patients failed initial mobilization but only 269 (77%) of those were remobilized.

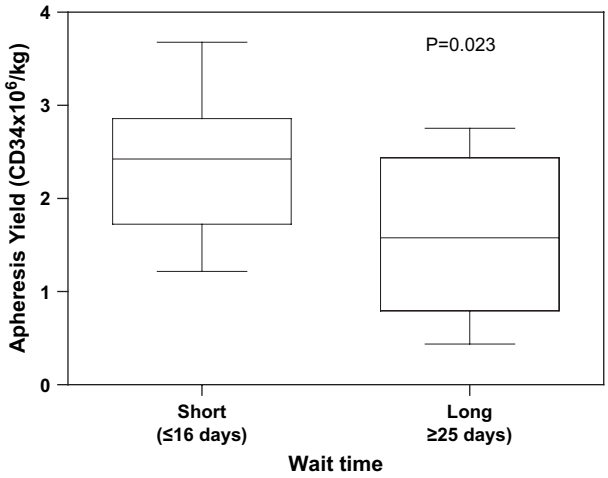


**Figure 4.** Impact of wait time between first and second mobilization on apheresis yield in NHL (non-Hodgkin's lymphoma) patients remobilized with G-CSF (granulocyte colony-stimulating factor); Box-Whiskers graphs compares the median CD34/kg yields from the lowest wait time quartile (<16 days) to the quartile with the longest wait time to remobilization (>25 days).

The remaining 23% of patients were never mobilized again, progressed, and were not candidates for ASCT, or proceeded to allogeneic stem cell transplantation. When collections from the first and second mobilizations were pooled, approximately 30% of patients failed to collect sufficient cells for transplantation, and this was universal across all diseases. This represents another 80 patients who either progressed or were exposed to the risks of allogeneic transplantation. All of these alternatives dramatically increase the risk of early morbidity and mortality, emphasizing again the need to achieve a minimum yield of $2 \times 10^6$ $CD34^+$ cells /kg during the first mobilization attempt. We observed that patients who failed initial mobilization were likely to fail remobilization regardless of mobilization regimen and underlying disease.

The timing between first and second mobilization influenced remobilization outcomes in NHL patients mobilized with G-CSF. Surprisingly, a longer wait time between the first and second mobilization was associated with a worse mobilization outcome. This was an unexpected finding which was not seen in "good mobilizing" myeloma group where early or delayed remobilization resulted in similar stem cell yields (data not shown). These data demonstrate the lack of an advantage of waiting to remobilize versus proceeding as early as possible in both NHL and MM patients. The benefit of early remobilization seen in NHL patients may be because of multiple factors including less infection, less disease progression, reduced exposure to marrow suppressing drugs, and changing dynamics of bone marrow recovery after initial mobilization attempt.

Plerixafor, a direct inhibitor of the interaction between the chemokine SDF-1 and its receptor CXCR4, is a new and promising agent being studied alone or in the conjunction with G-CSF for stem cell mobilization [28-33,51,52] Flomenberg et al. [33] compared mobilization with G-CSF and G/P in patients with MM and NHL. All patients underwent 2 mobilizations, 1 using G-CSF as a single agent and another using G/P. For all patients, G/P mobilized more $CD34^+$ cells per apheresis, required fewer aphereses and mobilized a higher total yield of $CD34^+$ cells/kg. Cashen et al. [29] reported successful mobilization of stem cells using G/P in heavily pretreated HL patients. In our retrospective analysis remobilization with G/P had the lowest failure rate, both after second mobilization alone and after pooling the cells from the first and second collections. This is similar to the compassionate use program experience where G/P was successfully used in patients who failed initial mobilization attempts using different mobilization regimens [28]. Two phase III, multicenter, randomized, double-blind, placebo-controlled studies comparing G/P with G-CSF for mobilization of stem cells in patients with MM and

NHL have shown that patients mobilized with G/P were significantly more likely to achieve the target $CD34^+$ cell count with fewer aphereses [51,52].

Consistent with other studies [15-18], we found that patients transplanted with $>10 \times 10^6$ $CD34^+$ cells/kg had faster neutrophil and platelet recovery than patients receiving $<2 \times 10^6$ $CD34^+$ cells. This target of $CD34^+$ cells might be difficult to achieve with current mobilization regimens. In addition, we found no significant difference in platelet or neutrophil engraftment among groups receiving G-CSF alone versus G/C, similar to randomized studies comparing those 2 mobilization regimens [42,45,46,53].

In summary, this study shows that current mobilization regimens are far from optimal. It is to our knowledge the largest retrospective study comparing success of initial mobilization with G-CSF versus G/C and analyzing remobilization strategies on achieving minimum stem cell yields for autologous transplantation. Although the number of patients who received G/C was limited, it still represents a significant number of patients studied and provides an insight into current clinical practices. A better understanding of variables associated with mobilization success and kinetics may further optimize stem cell collection and reduce complications associated with ASCT. It is clear that addition of chemotherapy to G-CSF does not have a significant impact on reaching the minimum target necessary for proceeding to ASCT in patients with MM, NHL, and HL. Although optimal yields occur more often, G/C has no advantage over G-CSF alone to reduce failure rates for stem cell mobilization. Ironically, there appears to be no benefit in adding chemotherapy to G-CSF for remobilization. New strategies are needed to minimize initial mobilization failure rates, especially in patients at high risk for failure, and allow collection of adequate number of stem cells in a timely and predictable manner.

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