# A prospective randomized trial of two popular mononuclear cell collection sets for autologous peripheral blood stem cell collection in multiple myeloma

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**BACKGROUND:** The COBE Spectra AutoPBSC collection set (AUTO-kit; CaridianBCT) is a popular dual-stage collection set for peripheral blood progenitor (PBPC) collection. Although the AUTO-kit is purportedly equivalent to the white blood cell (WBC) collection set (WBC-kit) for PBPC collection, improved CD34 yields after switching from the AUTO-kit to the WBC-kit were anecdotally observed, particularly in patients with higher WBC counts. A prospective, randomized trial of the AUTO- and WBC-kits for PBPC collection in multiple myeloma (MM) patients was therefore designed.

**STUDY DESIGN AND METHODS:** Sixty-eight MM patients were prospectively randomly assigned to either the WBC-kit or the AUTO-kit for PBPC collection. Primary study variables included the number of leukapheresis procedures per transplant, CD34/kg yield per procedure, and cumulative CD34/kg yield per mobilization cycle. Results were compared relative to collection kit and mobilization regimen. Statistics and graphics were performed with commercial software.

**RESULTS:** CD34/kg yields were higher with the WBC-kit, with 94% of chemotherapy-mobilized MM patients collecting 6 million CD34/kg in a single mobilization ($p = 0.06$). The WBC-kit also had a faster CD34 collection rate relative to peripheral CD34 counts. The AUTO-kit was significantly sensitive to high WBC counts, with a 50% decrease in CD34 collection efficiency and CD34 collection rate. This effect was specific to MM and not observed in lymphoma patients. Granulocyte–colony-stimulating factor mobilization and the AUTO-kit were associated with an increased incidence and severity of infusion reactions.

**CONCLUSIONS:** The WBC-kit performed consistently better than the AUTO-kit for PBPC collection in chemotherapy-mobilized MM patients, with fewer procedures per mobilization, superior collection rates, and a decreased incidence of infusion reactions.

High-dose chemotherapy, followed by autologous peripheral blood progenitor cell transplantation (APBPCT), has become an accepted treatment for many hematologic malignancies, including multiple myeloma (MM).[1,2] Although not curative, APBPCT can double disease-free survival in MM, with 40% of patients surviving 7 years in some studies.[2,3] More recent strategies to improve long-term survival include retransplantation,[4,5] planned tandem APBPCT,[6-8] allogeneic transplantation,[9] and post-transplant therapy with thalidomide.[10,11] MM is now the most common indication for APBPCT,[12] with many transplant centers requiring the collection of 6 to 20 million CD34/kg, or sufficient cells to support two to three APBPCTs.[11,13,14] At the University of Michigan, MM patients now comprise 52% of all patients and 54% of all PBPC collections.

**ABBREVIATIONS:** APBPCT(s) = autologous PBPC transplant(s); AUTO-kit = AutoPBSC collection set; CBC = complete blood count; CE = collection efficiency; chemo + GF = chemotherapy and growth factor mobilization; DT-PACE = 10 mg/m$^2$ cisplatin, 10 mg/m$^2$ doxorubicin, 400 mg/m$^2$ cyclophosphamide, 40 mg/m$^2$ etoposide, 40 mg oral dexamethasone, 200 mg thalidomide; GF-only = growth factor only mobilization; MM = multiple myeloma; NHL = non-Hodgkin's lymphoma; TBV(s) = total blood volume(s); WBC-kit = WBC collection set.

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The rising clinical demand for leukopheresis services has stimulated intense interest in identifying patient, treatment, and technical factors that will improve PBPC mobilization and collection. Factors favoring mobilization are a diagnosis of MM,[15,16] mobilization with chemotherapy,[17-20] growth factor dose,[13,16,19,21] the premobilization platelet (PLT) count,[17,22,23] and peripheral blood counts (white blood cells [WBCs], CD34 > 20/μL, PLTs) at the time of leukapheresis.[24-26] Poor prognostic factors are an older age, female sex, a diagnosis of non-Hodgkin's lymphoma (NHL), extensive prior chemotherapy, and a history of radiation therapy.[17,18,27] Although frequently overlooked, procedure-related factors can also impact collection. These include patient vascular access and flow rate,[28-31] total blood volume (TBV) processed,[15,27] operator experience, and the specific apheresis device used.[24,32-44]

At the University of Michigan, we have historically used the COBE Spectra blood separator (CaridianBCT, Lakewood, CO) with the AutoPBSC collection set (AUTO-kit) and automated mononuclear cell (MNC) software (Version 6.1) for adult collections. The latter is a fully automated program and dual-stage collection set that requires minimal operator intervention, decreased citrate toxicity, less PLT contamination, and reportedly, equivalent or superior collection efficiencies (CEs) to other collection platforms.[40-44] In 2005, we noted an increase in the number of leukapheresis procedures required for APBPCT, particularly in MM patients with high peripheral WBC counts. In many of these patients, we anecdotally observed improved CD34 collection yields after switching to the WBC collection set (WBC-kit). We therefore designed a prospective randomized trial comparing the performance of the AUTO-kit and WBC-kit in MM patients. We demonstrate that the WBC-kit and chemotherapy mobilization resulted in higher CD34 collection yields, fewer total procedures, and decreased infusion toxicity.

## MATERIALS AND METHODS

### Patient criteria

All adult MM patients referred for autologous PBPC collection between December 2005 and July 2007 were enrolled. All patients were evaluated and medically cleared for APBPCT according to institutional guidelines before their first leukapheresis procedure. The target yield for all MM patients was $6 \times 10^6$ CD34 cells/kg or two APBPCTs ($3 \times 10^6$/kg per transplant). Informed consent for leukapheresis and infectious disease testing was obtained from all patients on the first day of collection. All protocols and consent for PBPC mobilization, collection, and transplantation, including this study, were approved by the institutional review board of the University of Michigan.

### Study design

Patients were alternately assigned to either the WBC-kit or AUTO-kit on the first day of apheresis, and all subsequent collections, until the designated target yield of $6 \times 10^6$ CD34/kg was achieved.[42] During the course of the study, eight patients were randomly assigned to the incorrect group (six to AUTO, two to WBC). Ten patients with poor collection yields ($<0.5 \times 10^6$ CD34/kg/day; CD34/μL > 20) on 2 successive days were switched to the alternate collection kit at the discretion of the apheresis attending physician ("Mixed," Fig. 1). Patients failing to collect $6 \times 10^6$ CD34 cells were remobilized and collected at a later date. In remobilized patients, each mobilization cycle was considered a separate event for postcollection analysis. Only patients collecting at least $3 \times 10^6$ CD34/kg in a single mobilization cycle were included in postcollection analysis: Mobilization cycles collecting less than $3 \times 10^6$

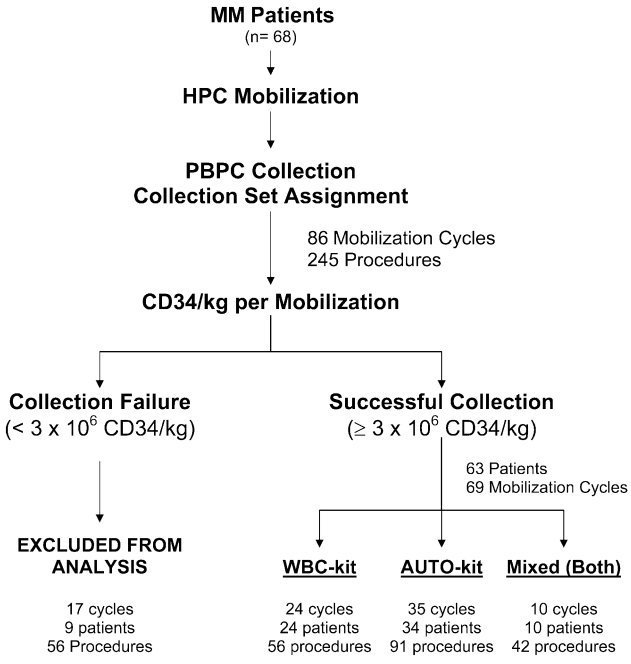


**Fig. 1. Study schematic. Sixty-eight MM patients were randomly assigned to either the WBC-kit or AUTO-kit. Each mobilization cycle was considered a separate event for analysis. Altogether, 69 cycles from 63 patients successfully collected at least $3 \times 10^6$ CD34/kg in a single mobilization. Seventeen cycles were excluded from analysis due to poor collection yields. 63 cycles represent a primary mobilization. Six patients were remobilized to collect sufficient cells for a second APBPCT. All successful mobilizations, including remobilizations, were categorized in postcollection analysis by collection kit used: AUTO-kit, WBC-kit, and mixed, in which both AUTO- and WBC-kits were used during the course of a single mobilization. Most remobilized patients (five of six) were collected in a different treatment arm for the first and second mobilization.**

**TABLE 1. Excluded mobilization cycles**

| Patient characteristics | Number (%) |
|---|---|
| Number of patients (%) | 9 |
| Age (years), mean ± SD | 56.7 ± 6.8 |
| Male/female | 6/3 |
| IgG/IgA | 7/1 |
| Peripheral blood counts, mean ± SD | |
| WBCs ($\times 10^9$/L) | 26.5 ± 15.9 |
| CD34/μL | 19.5 ± 15.0 |
| Prior therapy (%) | |
| Radiation | 3 (30) |
| ≥5 courses anthracyclines | 5 (55) |
| ≥3 courses alkylating agents | 4 (30) |
| Second-line therapy | 4 (44) |
| Prior APBPCT | 1 (11) |
| Other cancer | 1 (11) |
| >70 years of age | 0 |
| >6 months of lenolamide | 0 |
| PBPC collection (AUTO-kit/WBC-kit) | |
| Total number of procedures | 56 (25/31) |
| Total mobilizations | 17 (9/8) |
| First mobilization | 7 (3/4) |
| Remobilization | 10 (6/4) |
| GF-only mobilization (%) | 12 (70) |
| CD34/kg yield ($\times 10^6$), mean ± SD | |
| Per procedure | 0.45 ± 0.27 |
| Per cycle | 1.49 ± 0.77 |

CD34/kg were excluded. A total of 17 mobilization cycles, involving nine patients and 57 procedures, were excluded due to poor collection yields (Fig. 1, Table 1).

Patient demographic data included patient age, sex, weight, MM subtype, CD34 mobilization regimen, and number of mobilization cycles (Table 2). Patient laboratory studies included baseline and Day 1 preapheresis complete blood count (CBC), manual WBC differential, peripheral CD34 count (%CD34, CD34/μL), and total protein and albumin. A daily preapheresis CBC and WBC differential were recorded for all patients requiring more than one procedure. When available, preapheresis quantitative serum immunoglobulin and whole blood viscosity were recorded. Procedure-related data included collection kit (AUTO, WBC), nurse operator, TBV, TBV per body weight (100 mL/kg), cumulative CD34/kg yield, and number of procedures per mobilization cycle (Table 3). TBV was not corrected for anticoagulant volume.

### Mobilization regimens

CD34 mobilization was determined by the patient's attending transplant physician. The majority of patients (70%, Table 2) enrolled were collected after chemotherapy, followed by daily granulocyte–colony-stimulating factor (G-CSF; 10 μg/kg/day). For chemotherapy, patients were treated with either cyclophosphamide (2-4 g/m$^2$) or DT-PACE (10 mg/m$^2$ cisplatin, 10 mg/m$^2$ doxorubicin, 400 mg/m$^2$ cyclophosphamide, 40 mg/m$^2$ etoposide, 40 mg oral dexamethasone, 200 mg thalidomide).[14,45,46] Leukapheresis was initiated between 11 and 14 days after chemotherapy when the peripheral WBC count exceeded $5.0 \times 10^9$/L.[34,47] Patients collected after chemotherapy, regardless of specific chemotherapy regimen, were classified as "chemotherapy + growth factor" mobilization (chemo + GF; Table 2) for subsequent analysis.

Approximately 30% of patients were mobilized with G-CSF only (10-16 μg/kg/day), starting 4 days before the first leukapheresis procedure (Table 2). A minority of these patients were mobilized with G-CSF (10 μg/kg) and granulocyte-macrophage–CSF (GM-CSF; 500 μg/day). Patients mobilized with either G-CSF or G-CSF plus GM-CSF were classified as "growth factor only" (GF-only) for purposes of analysis.

### Apheresis collections

All leukapheresis procedures were performed on a COBE Spectra blood separator. Venous access was established using a central venous catheter. For patients randomly assigned to the WBC-kit (Software Version 4.7), MNCs were collected by continuous-flow centrifugation, with the blood-plasma interface manually adjusted to a 1% to 2% hematocrit (Hct) using a WBC colorgram (COBE Spectra), a maximum flow rate of 80 mL/min, a whole blood:ACDA ratio of 12:1, and collect volume rate of 1.0 mL per minute. For the AUTO-kit, MNCs were collected using the manufacturer's default software settings (Version 6.1). Harvest volume (5.0 mL), chase volume (5.0 mL), whole blood flow rates, and harvest frequency were determined by the system based on patient size, MNC concentration, and inlet flow rate.[42] Approximately 200 mL of PLT-depleted plasma was collected concurrently. For AUTO- and WBC-kits, three TBVs were processed, averaging 13 L or 162 mL/kg per procedure (Table 3). To prevent citrate toxicity, all patients received prophylactic calcium gluconate replacement throughout the procedure.[48]

### PLT analysis

The impact of leukapheresis on peripheral PLT counts was monitored by daily preapheresis PLT counts. The transfusion records for all patients were also reviewed for any PLT or RBC transfusion support during the week of PBPC collection.

### Product analysis

Volume and WBC count were determined on all products immediately after collection. For units requiring volume reduction, the initial and final volume, WBC count, and percentage of cell loss were recorded (Table 2). The final %MNC and MNCs/kg were determined on all products before freezing. CD34 yields and cell viability were

**TABLE 2. Patient demographics**

| Demographic | All patients* | PBPC collection set† | | |
|---|---|---|---|---|
| | | WBC-kit | AUTO-kit | p Value† |
| Number collection cycles | 69 | 24 | 35 | |
| Donor characteristics | | | | |
| Number of patients | 63 | 24 | 34 | |
| Age (years)‡ | 56.9 ± 7.9 | 57.5 ± 7.4 | 57.6 ± 7.8 | NS |
| Male/female | 38/25 | 14/10 | 23/12 | NS |
| Weight (kg)‡ | 84.3 ± 21.4 | 86.7 ± 22.7 | 83.1 ± 19.7 | NS |
| Myeloma subtype (%)§ | | | | |
| IgG | 33 (52) | 9 (37.5) | 21 (61) | 0.07§ |
| IgA | 17 (27) | 9 (37.5) | 8 (23) | NS |
| IgD | 3 (5) | 0 | 2 (6) | NS |
| Light chain only | 10 (16) | 6 (25) | 3 (9) | NS |
| Total protein (g/dL)‡ | 6.4 ± 1.1 | 6.3 ± 1.1 | 6.4 ± 1.1 | NS |
| Albumin (g/dL)‡ | 3.6 ± 0.4 | 3.6 ± 0.5 | 3.6 ± 0.5 | NS |
| Immunoglobulin (mg/dL)¶ | | | | |
| IgG (range) | 596 (124-4940) | 627 (139-4940) | 449 (137-4440) | NS |
| IgA (range) | 47 (6-1380) | 67 (6-1380) | 37 (6-478) | 0.05§ |
| IgM (range) | 21 (5-137) | 26 (5-137) | 21 (5-137) | NS |
| Total immunoglobulin (range) | 800 (195-4960) | 877 (246-4960) | 733 (195-4473) | NS |
| Mobilization regimen | | | | |
| Chemo + GF (%)** | 48 (70) | 18 (75) | 25 (71) | NS |
| Cyclophosphamide + G-CSF | 28 | 14 | 12 | NS |
| DT-PACE + G-CSF | 20 | 4 | 13 | NS |
| Premobilization PLT count ($\times 10^9$/L)‡,†† | 273.1 ± 109.4 | 276.9 ± 78.2 | 269.9 ± 132.2 | NS |
| GF-only (%)** | 21 (30) | 6 (25) | 10 (29) | NS |
| G-CSF | 17 | 4 | 8 | NS |
| G-CSF + GM-CSF | 4 | 2 | 2 | NS |
| Premobilization PLT count ($\times 10^9$/L)†† | 256.9 ± 85.5 | 248.8 ± 68.7 | 261 ± 96 | NS |

* Includes all patients, including patients collected with both AUTO- and WBC-kits (mixed).
† Statistical comparison of WBC-kit and AUTO-kit using t test unless indicated otherwise. Mixed collections not included. A p value of less than 0.05 was considered significant.
‡ Data reported as mean ± SD.
§ Chi-square test.
¶ Quantitative immunoglobulin levels at time of PBPC mobilization. Data reported as median (range). Total immunoglobulin (IgG + IgA + IgM).
** GF = growth factor.
†† Baseline PLT count immediately before initiating PBPC mobilization.[17,22,23]
NS = not significant.

determined by flow cytometry as recommended by the International Society of Hematology and Graft Engineering (ISHAGE).[47,49] Hematopoietic colony-forming assays were not performed per institutional policy. Cells were volume-adjusted and frozen in 10% dimethyl sulfoxide (DMSO) and stored in the vapor phase of liquid nitrogen.[47]

### Infusion reactions

PBPC infusion records and patient medical records were reviewed for adverse reactions during PBPC infusion. Reactions limited to nausea, vomiting, or fever were labeled as mild. Infusion reactions that included dyspnea, chest tightness, significant hypotension, or hypertension were considered severe.

### Engraftment data

Patient medical records were reviewed for WBC and PLT engraftment. WBC, early PLT, and late PLT engraftment were determined as previously described.[47]

### Collection in lymphoma patients

As a nonmyeloma control, a retrospective analysis was performed for all adult lymphoma patients undergoing autologous PBPC collection between January 2006 and June 2008. PBPC collections were performed using the AUTO-kit (70%) or mix of AUTO- and WBC-kits (Mixed) between January 2006 and December 2007. Beginning January 2008, the WBC-kit was used for all PBPC collections in our facility. Patients underwent daily leukapheresis for a target yield of $3 \times 10^6$ CD34/kg. Patient demographic, laboratory data, and product characteristics were collected as described for MM patients. All procedures, including failed mobilizations, were included in the final analysis.

### Statistical analysis

Analysis was restricted to successful mobilizations in which at least $3 \times 10^6$ CD34/kg were collected after a single mobilization. Primary performance measures were the CD34/kg yield and success rate for one and two APBPCTs. Direct comparisons of AUTO- and WBC-kit performance

**TABLE 3. PBPC collection and yields by collection set**

| Measure | All collections* | PBPC collection set† | | |
|---|---|---|---|---|
| | | WBC-kit | AUTO-kit | p Value† |
| Peripheral blood counts‡ | | | | |
| WBCs count ($\times 10^9$/L) | 31.3 ± 19.9 | 28.1 ± 17.7 | 29.2 ± 18.4 | NS |
| WBCs, Day 1 | 26.6 ± 21.8 | 25.7 ± 19.3 | 23.7 ± 17.4 | NS |
| %MNCs | 14.8 ± 13.5 | 12.4 ± 7.3 | 12.4 ± 11.5 | NS |
| %Hct | 31.5 ± 4.9 | 30.6 ± 4.9 | 31.9 ± 4.4 | NS |
| Hct, Day 1 | 32.5 ± 5.1 | 32.4 ± 4.7 | 32.1 ± 4.6 | NS |
| PLT count ($\times 10^9$/L) | 140.7 ± 81.9 | 127.7 ± 71.8 | 131.0 ± 73.9 | NS |
| PLTs, Day 1 | 157.6 ± 103.8 | 146.7 ± 94.5 | 145.9 ± 92.1 | NS |
| PLT count > 200 ($\times 10^9$/L), Day 1 (%)§ | 20/69 (29) | 6/24 (25) | 9/34 (26) | NS |
| %CD34, Day 1 (range) | 0.62 ± 0.88 (0.02-4.68) | 0.65 ± 0.62 (0.04-2.38) | 0.81 ± 1.00 (0.05-4.68) | NS |
| CD34/μL, Day 1 | 125.2 ± 184.2 | 153.2 ± 200.5 | 142.3 ± 193.3 | NS |
| Median (range) | 56 (0.16-80.0) | 70.3 (3.4-800) | 64.2 (3.7-777) | |
| Collection | | | | |
| Total number of procedures | 189 | 57 | 91 | — |
| Procedures per mobilization | 2.8 ± 1.5 | 2.3 ± 1.3 | 2.6 ± 1.4 | NS |
| TBV processed (L) | 13.7 ± 3.6 | 13.3 ± 3.4 | 13.5 ± 3.6 | NS |
| TBV (100 mL)/kg | 161.8 ± 31.8 | 169.8 ± 35.2 | 160.8 ± 31.5 | NS |
| Percentage decrease in PLT count per day¶ (range) | 12.5 ± 13.6 (0-53) | 13.3 ± 15.5 (0-43) | 10.5 ± 10.9 (0-46) | NS |
| Number of PLT transfusions** | 1 | 1 | 0 | NS |
| Number of RBC transfusions** | 0 | 0 | 0 | NS |
| Product characteristics | | | | |
| Volume (mL) | | | | |
| Initial volume | 145.1 ± 82.0 | 180.9 ± 75.1 | 111.6 ± 70.4 | <0.0001 |
| Final volume | 102.1 ± 37.1 | 99.5 ± 37.4 | 93.8 ± 33.3 | NS |
| Number of units processed (%) | 110 (58) | 44 (77) | 41 (45) | 0.0006 |
| WBCs ($\times 10^9$/L) | | | | |
| Initial WBC count (range) | 255.6 ± 887.8 (15.8-943.7) | 340.5 ± 1405 (15.8-943.7) | 207.1 ± 83.4 (53.5-315.5) | NS |
| Final WBC count (range) | 246.9 ± 95.6 (27-684) | 233.1 ± 104.5 (27-547.8) | 246.5 ± 86.7 (77.1-684) | NS |
| Number of units with cell loss | 58/110 | 22/44 | 23/41 | NS |
| Median cell loss | 5% | 5% | 4% | NS |
| Total MNC yield ($\times 10^{10}$) | 1.41 ± 0.87 | 1.48 ± 0.92 | 1.36 ± 0.84 | NS |
| %MNCs | 56.3 ± 21.4 | 59.3 ± 25.1 | 54.5 ± 18.6 | NS |
| %MNC-CE | 39.4 ± 20.6 | 40.4 ± 16.2 | 38.7 ± 18.9 | NS |
| %CD34 (range) | 1.25 ± 2.10 (0.04-22.23) | 1.60 ± 1.75 (0.1-8.3) | 1.42 ± 2.62 (0.4-22.23) | NS |
| %CD34-CE | 32.6 ± 31.4 | 31.3 ± 19 | 33.6 ± 37.0 | NS |
| Collection yields/kg | | | | |
| MNCs/kg per unit ($\times 10^8$) | 1.61 ± 0.88 | 1.66 ± 0.94 | 1.55 ± 0.83 | NS |
| CD34/kg per unit ($\times 10^6$) (range) | 3.25 ± 5.19 (0.1-41.2) | 4.67 ± 7.11 (0.3-41.2) | 3.26 ± 4.67 (0.1-33.4) | NS |
| CD34/kg per mobilization | 9.54 ± 7.08 | 11.08 ± 8.67 | 8.48 ± 5.63 | 0.048 |

* All collections regardless of collection kit, including mixed collections. Most results reported as mean ± SD unless otherwise indicated.
† Comparison (t test) of WBC-kit and AUTO-kit: mixed collections not included.
‡ Mean preleukapheresis peripheral blood count for all procedures. Blood counts before the first procedure (Day 1) also included.
§ Number and percentage of patients with a PLT count of more than $200 \times 10^9$/L on the first day of leukapheresis.[23] PLT counts of greater than $200 \times 10^9$/L were strongly associated with GF-only mobilization (14/20; p = 0.00005).
¶ Mean percentage change in daily PLT count per procedure.
** Number of patients requiring either PLT or RBC transfusion during leukapheresis. Only one patient required a PLT transfusion the day before starting PBPC collection for a PLT count of $12 \times 10^9$/L.
NS = not significant.

in MM patients were restricted to patients collected solely with the AUTO- or WBC-kit for the entire mobilization cycle: "mixed" collections were excluded. Mixed collections were only included in the aggregate data of all collections.

Patient demographic, laboratory, and collection results were reported as the mean ± standard deviation (SD), percentage, median, and range as indicated. The MNC and CD34 CEs (%CE) were calculated as described by Dzieczkowski and coworkers[33] and Ford and coworkers,[31] respectively. Categorical variables were compared primarily by t test unless otherwise indicated. Proportional variables were examined by chi-square (EpiInform, CDC, Atlanta, GA). To determine the significance of individual CD34 collection rates (slope, b), the confidence interval (CI) for each slope was calculated using the appropriate critical t values (t*) at t(n – 2) distribution, where

$$CI = b \pm b_{SE}(t^*).^{50}$$

Univariate statistics (t test, paired t test, Mann-Whitney U test), correlation coefficient (R), correlation probabilities,

linear regression including t-probabilities and standard error, and graphics were performed with commercial software (Kaleidograph, Synergy Software, Reading, PA). A p value of less than 0.05 was considered significant.

## RESULTS

### Patient demographics

Between December 2005 and July 2007, a total of 68 MM patients underwent autologous PBPC collection at our facility. Sixty-three patients (93%), who successfully collected at least $3 \times 10^6$ CD34 cells/kg in a single mobilization, were included in the final analysis. Six patients required a second mobilization to reach $6 \times 10^6$ CD34/kg or two APBPCTs. Altogether, 69 mobilization cycles and 189 procedures were available for analysis.

Seventeen mobilizations were excluded from the final analysis, including 14 cycles from six patients with multiple poor mobilizations and three cycles from three patients who had one prior successful collection but failed to remobilize after additional chemotherapy and GF-only mobilization (Fig. 1). Excluded cycles were associated with GF-only mobilization ($p = 0.002$), low CD34/μL ($p < 0.0001$), and poor CD34/kg yields ($p < 0.001$). Many patients had risk factors for poor mobilization including prior radiotherapy and extensive chemotherapy (Table 1).[17,18,27]

For analysis, each successful collection was classified by the type of kit used, WBC-kit or AUTO-kit, during the entire mobilization collection cycle. Mixed collections, in which patients were switched to the alternate collection set, were only included in the aggregate data of all collections (All), regardless of collection set. As shown in Tables 2 and 3, there was no significant difference in patient age, sex, weight, or TBV processed between collection kits. Approximately 70% of all patients, regardless of kit, were collected after chemotherapy (chemo + GF) while the remaining 30% were mobilized with GF-only. The AUTO-kit group had a higher percentage of patients mobilized with DT-PACE (52%), which we have shown to be equivalent to cyclophosphamide for PBPC mobilization in MM.[46]

### Peripheral blood counts

The CBC, %MNCs, and CD34 counts on the first day of collection, and for all procedures in aggregate, were compared by kit (Table 3) and mobilization regimen (Table 4). There was no significant difference in peripheral WBC, %MNC, %Hct, and PLT and CD34 counts between kits, although AUTO-kit patients had a higher mean %CD34 (Table 3). Patients mobilized with GF-only had a higher mean WBC count whereas chemo + GF patients had significantly higher peripheral CD34 counts (Table 4).

### Product characteristics

PBPC products collected with the WBC-kit had a greater initial volume and WBC count, on average, than the AUTO-kit (Table 3).[40-43] Volume reduction was performed on 45% of AUTO-kit and 77% of WBC-kit products before freezing. After processing, there was no significant difference in volume or WBC count between collection kits although some degree of cell loss (1%-29%) was documented in 25% of AUTO- and 51% of WBC-kit units. Seven patients had greater than 10% cell loss in multiple successive collections. There was no correlation between cell loss, collection kit, MM subtype, laboratory studies, or mobilization regimen in these patients (data not shown).

An initial analysis of CD34 yield by collection kit suggested improved performance with the WBC-kit (Table 3). The WBC-kit had a higher mean %CD34 and CD34/kg yield per unit and a 23% higher CD34/kg yield per mobilization cycle ($p = 0.048$) than the AUTO-kit.

### CD34/kg yield by day and collection kit

We initially examined the CD34/kg yield per procedure by mobilization regimen, collection kit, and collection day (Fig. 2A). Without exception, patients mobilized with chemo + GF collected 40% to 60% more CD34 cells per collection day ($p = 0.016$-$0.044$), and per cycle (Table 4), over GF-only patients. When subanalyzed by collection kit, mean CD34/kg yields tended to be higher with chemo + GF mobilization and WBC-kit, particularly on Day 3 (CD34/kg = 2.35 vs. 1, $p = 0.02$). Similar findings were observed when mixed collections (Fig. 1) were included in the analysis ($p = 0.0019$, not shown). The mean CD34/kg yield per cycle was also higher in chemo + GF patients using the WBC-kit (CD34/kg 13.4 vs. 9.6, $p = 0.09$). In GF-only patients, the total CD34/kg yield was slightly better with the AUTO-kit ($p = 0.03$) although there was no significant difference per collection day between kits (Fig. 2A).

### Number of procedures for one APBPCT

The minimum number of procedures required to collect $3 \times 10^6$ CD34/kg or one APBPCT, and the total number of procedures per cycle, were compared by mobilization regimen and kit (Fig. 2, Table 4). As expected, patients mobilized with chemo + GF underwent fewer procedures than GF-only patients, with 46% to 67% collecting one APBPCT in one procedure (Fig. 2B, $p = 0.0003$; odds ratio [OR], 13.07; 95% CI, 2.32-96.48). Most GF-only patients required at least 2 days to collect one APBPCT. Altogether, 84% of chemo + GF and 75% of GF-only patients collected one APBPCT within 2 days. Although not significant, approximately 10% to 15% more chemo + GF patients

**TABLE 4. Comparison by mobilization regimen***

| Measure | All | Chemo + GF | | GF-only | | | p Value† |
|---|---|---|---|---|---|---|---|
| | | WBC-kit | AUTO-kit | All | WBC-kit | AUTO-kit | |
| Peripheral blood counts‡ | | | | | | | |
| WBC count ($\times 10^9$/L) | 24.1 ± 15.8 | 25.5 ± 18.6 | 23.0 ± 13.5 | 42.2 ± 20.9 | 41.5 ± 18.0 | 42.7 ± 22.7 | <0.0001 |
| WBCs, Day 1 | 20.8 ± 16.2 | 22.6 ± 20.6 | 19.5 ± 12.4 | 39.8 ± 27.2 | 33.5 ± 7.1 | 43.0 ± 32.9 | 0.006 |
| %MNCs | 14.5 ± 10.2 | 16.2 ± 9.9 | 13.3 ± 10.5 | 13.1 ± 5.0 | 12.0 ± 4.7 | 13.7 ± 5.3 | NS |
| %Hct | 30.2 ± 4.69 | 31.9 ± 4.9 | 31.2 ± 4.4 | 33.5 ± 4.6 | 34.2 ± 3.7 | 35.2 ± 6.4 | <0.0001 |
| PLT count, Day 1 ($\times 10^9$/L) | 114 ± 68 | 107 ± 57 | 119 ± 74 | 253 ± 107 | 263 ± 76 | 212 ± 107 | <0.0001 |
| %CD34 | 0.85 ± 1.00 | 0.81 ± 0.63 | 1.04 ± 1.24 | 0.18 ± 0.24 | 0.13 ± 0.07 | 0.25 ± 0.11 | 0.0038 |
| CD34/μL | 171.9 ± 208.8 | 189.3 ± 226.3 | 178.1 ± 220.6 | 55.9 ± 34.7 | 44.9 ± 25.3 | 56.5 ± 38.2 | 0.032 |
| Median (range) | 77.4 (3.7-800.2) | 115.3 (3.4-800.2) | 74.4 (3.7-777.2) | 56.0 (2.5-146.5) | 46.1 (9.2-76) | 53 (17.6-146.5) | |
| Collection results | | | | | | | |
| Total number of procedures | 114 | 38 | 56 | 75 | 18 | 35 | NS |
| Procedures/mobilization | 2.4 ± 1.5 | 2.1 ± 1.3 | 2.2 ± 1.4 | 3.6 ± 1.5 | 3.0 ± 1.3 | 3.5 ± 1.3 | 0.002 |
| Number of procedures for one APBPCT | 1.7 ± 1.1 | 1.4 ± 0.7 | 1.7 ± 1.1 | 2.4 ± 0.9 | 2.3 ± 1.4 | 2.2 ± 0.6 | 0.019 |
| Number collecting one APBPCT in one procedure (%) | 28 (46) | 12 (67) | 16 (64) | 2 (12) | 1 (17) | 1 (10) | 0.0003§ |
| Number collecting two APBPCTs in one mobilization (%) | 27 (56) | 17 (94)¶ | 18 (72) | 9 (43) | 1 (17) | 5 (50) | 0.001§ |
| Total CD34/kg per cycle ($\times 10^6$) | 10.48 ± 7.50 | 13.41 ± 8.83 | 9.57 ± 6.37 | 5.55 + 1.78 | 4.08 ± 1.56 | 6.01 ± 1.54 | <0.0001 |
| CD34/kg per unit ($\times 10^6$) | 4.40 ± 6.41 | 5.53 ± 7.87 | 3.77 ± 5.37 | 1.54 ± 0.99 | 1.46 ± 0.89 | 1.66 ± 1.13 | <0.0001 |
| MNCs/kg per unit ($\times 10^8$) | 1.28 ± 0.65 | 1.38 ± 0.08 | 1.20 ± 0.53 | 2.10 ± 0.96 | 2.16 ± 1.02 | 2.07 ± 0.93 | <0.0001 |
| Granulocytes/kg per unit ($\times 10^7$) | 1.23 ± 1.10 | 1.30 ± 1.45 | 1.19 ± 0.79 | 1.45 ± 1.12 | 1.62 ± 1.56 | 1.36 ± 0.84 | NS |

* Results reported as mean ± SD unless otherwise indicated.
† p Values comparing chemo + GF and GF-only mobilization in all patients, regardless of collection set. Similar results were observed in subanalysis of AUTO- and WBC-kit. A p value of less than 0.05 was considered significant.
‡ No significant differences in peripheral blood counts between AUTO-kit and WBC-kit by mobilization regimen.
§ Chi-square comparing percentage collecting one or two APBPCTs in all patients by mobilization regimen.
¶ WBC-kit versus AUTO-kit, p = 0.06.
NS = not significant.

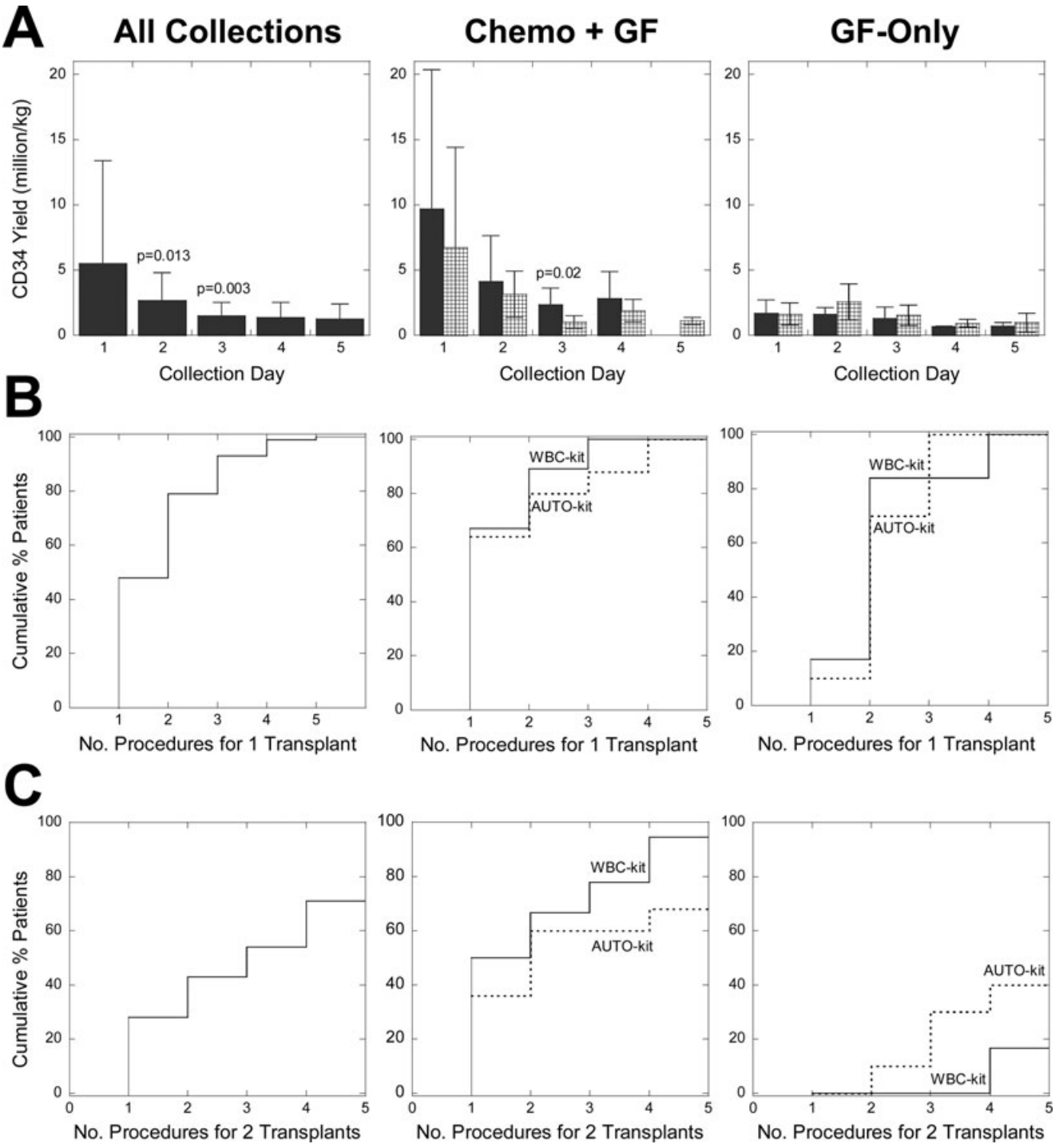


**Fig. 2. CD34 yields and collection success rate by mobilization regimen and collection kit. (Row A) CD34/kg yield per day (mean ± SD) in all collections, regardless of mobilization or kit. Also shown are the CD34/kg yields in chemo + GF–mobilized and GF-only–mobilized patients collected with the WBC-kit (■) and AUTO-kit (▦). (Row B) Cumulative percentage of patients successfully collecting at least $3 \times 10^6$ CD34/kg or one APBPCT per leukapheresis procedure in all patients, chemo + GF–mobilized patients, and GF-only–mobilized patients. Results for WBC-kit (—) and AUTO-kit (- - -) are also shown. (Row C) Cumulative percentage of patients collecting at least $6 \times 10^6$ CD34/kg or two APBPCTs by mobilization regimen and collection kit.**

successfully collected for one APBPCT with the WBC-kit per procedure (Fig. 2B).

### Number of procedures for two APBPCTs

We also examined the success rate to collect $6 \times 10^6$ CD34/kg in a single mobilization cycle (Fig. 2C, Table 3). Overall, 82% of chemo + GF– versus 37% of GF-only–mobilized patients collected two APBPCT in a single mobilization cycle ($p = 0.001$; OR, 7.29; 95% CI, 1.75-32.22). In chemo + GF patients, more patients collected for two APBPCTs with the WBC-kit (94% vs. 72%, $p = 0.06$), with 50% collecting in one procedure.

### CD34 collection rate

Despite equivalent peripheral CD34 counts and MNC-CE (Table 3), CD34/kg yields tended to be consistently higher with the WBC-kit in chemo + GF–mobilized patients. To explain the latter, we plotted the CD34/kg yield per peripheral CD34 count by kit and mobilization regimen (Figs. 3A and 3B). As reported, there was a linear correlation between CD34 count (CD34/μL) and CD34/kg yield when all collections were examined (Fig. 3A).[24] When examined by kit and mobilization regimen, the fastest CD34 collection rate (slope) was observed using chemo + GF mobilization and WBC-kit. The results were more dramatic when CD34/kg yields were plotted by %CD34 cells (Fig. 3B, $p < 0.05$). In chemo + GF patients, a nonlinear relationship was noted with the WBC-kit, resulting in high CD34/kg yields despite low circulating %CD34 cells.

### Comparison of CD34 collection in individual patients

A few patients were remobilized and collected using the alternate collection set, including two patients excluded from the final analysis due to poor collection yields (Figs. 3C through 3E). In all patients, the WBC-kit collected more CD34 cells than the AUTO-kit in the first 2 days of collection, regardless of mobilization regimen used ($p = 0.003$, paired t test). The improved collection with the WBC-kit was particularly noteworthy in patients 55 and 128, in which two different mobilization regimens were used.

### Effect of peripheral WBC count on CD34 collection

Five prior studies have reported a decrease in MNC-CE and CD34-CE at elevated peripheral WBC and CD34 counts, particularly at WBC counts greater than $20 \times 10^9$/L.[26,30-31,38,51] Similarly, we had observed decreased CD34/kg yields and CD34 collection rates in GF-only patients (Fig. 3), who typically had higher peripheral WBC counts (Table 4). To explore whether WBC count impacted CD34 collection, the mean CD34/kg yield and CD34 collection rate were compared at "high" ($>20 \times 10^9$/L) and "low" ($<20 \times 10^9$/L) WBC counts as defined by Gidron and colleagues.[51]

In general, the mean CD34/kg yield decreased with increasing peripheral WBC count (Fig. 4A). We also observed a drop in MNC-CE and CD34-CE at high WBC counts with both kits, with a 50% decrease in CD34-CE with the AUTO-kit (Table 5). The impact of WBC count on CD34 collection was also evident when CD34 collection rate was plotted at high and low WBC counts. Specifically, high WBC counts were associated with a 50% decrease in CD34 collection rate or slope using the AUTO-kit (Fig. 4B, $p < 0.01$). In contrast, high WBC counts had no apparent effect on CD34 collection rates with the WBC-kit (Fig. 4C, p = NS).

We examined several factors that could potentially impact blood viscosity, laminar flow, and MNC collection in the AUTO-kit design (Table 5).[52] As expected, high WBC counts were associated with GF-only mobilization. Higher WBC counts were accompanied by higher PLT and RBC counts, particularly in GF-only patients who typically displayed a parallel increase between WBC counts, Hct levels ($R = 0.36$, $p = 0.0014$; Fig. 4C), and PLT counts ($R = 0.49$, $p = 0.03$; not shown). In GF-only patients, there was an inverse relationship between Hct and %MNC-CE with the AUTO-kit (Fig. 4D). Hct, however, had no independent effect on CD34 collection rates (Fig. 4E). There was no correlation between %MNC-CE, %CD34-CE, CD34 yield, and CD34 collection rates with either premobilization or daily PLT counts (not shown),[17,22,23] serum protein, albumin,[31] or immunoglobulin levels. A recent fibrinogen, C-reactive protein, or whole blood viscosity was not available for analysis in most patients.[52]

### CD34 collection in lymphoma patients by collection set

To test whether our observations were unique to MM patients, we performed a retrospective analysis of PBPC collection in adult autologous lymphoma patients. Unlike MM patients, lymphoma patients were a very heterogenous population with a wide range in patient age, prior treatment (not shown), chemotherapy-associated mobilization, and mobilization failures[53,54] (Table 6). In general, slightly more lymphoma patients collected in one procedure with the WBC-kit (Fig. 5A). When normalized for peripheral CD34 counts, the WBC-kit performed slightly better than the AUTO-kit (Fig. 5B). In Hodgkin's lymphoma, a nonlinear relationship was again observed between CD34 yields and %CD34 cells (Fig. 5C, $p < 0.01$). In contrast to MM, the peripheral WBC count had no impact on CD34 collection rates in lymphoma patients (Fig. 5D, p = NS).

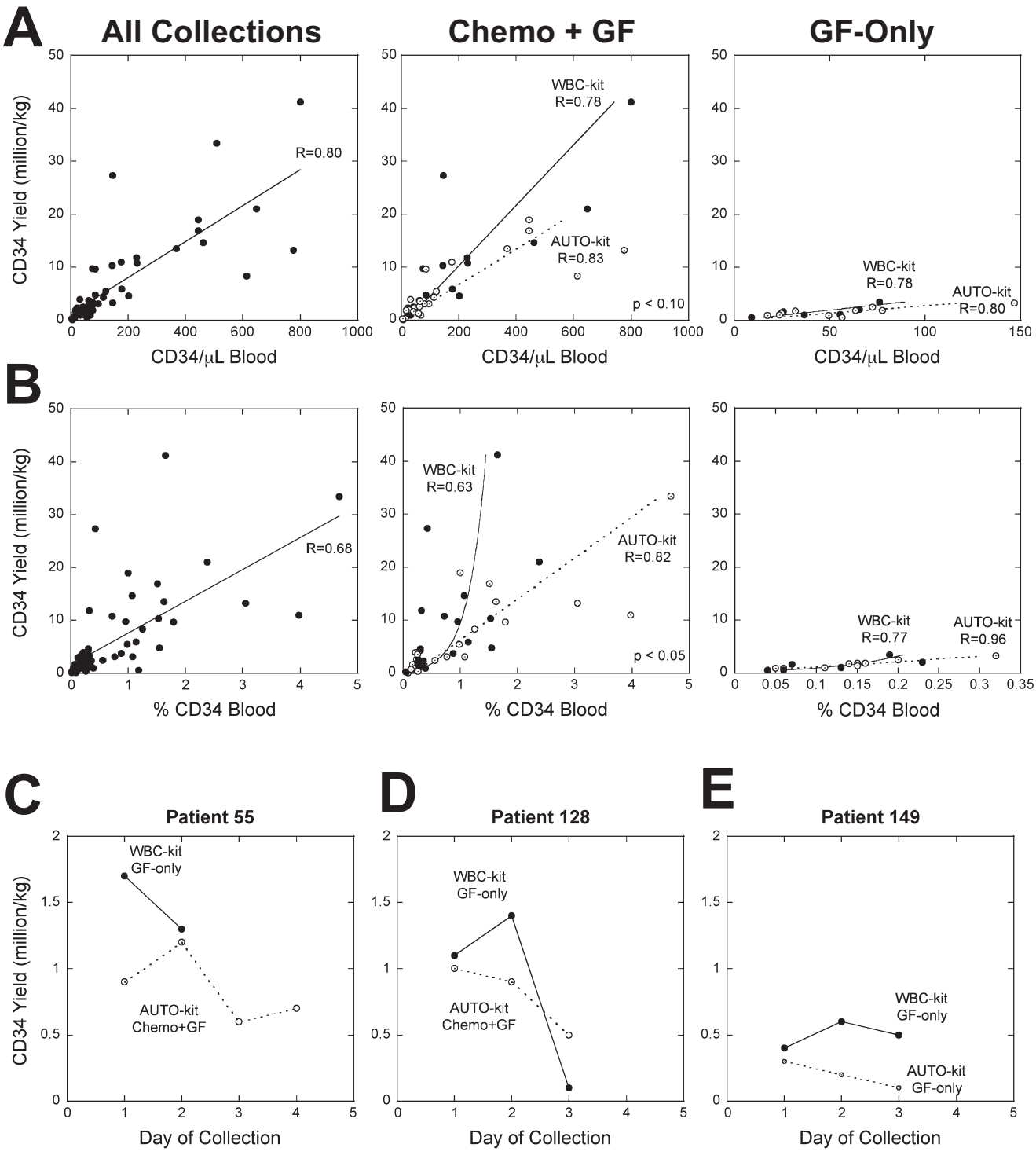


**Fig. 3. CD34 collection rate relative to peripheral CD34 counts. (Row A) CD34/kg yield per peripheral CD34/μL in all patients, chemo + GF patients, and GF-only–mobilized patients. The collection rate and correlation coefficients for all collections, WBC-kit (—), and AUTO-kit only (- - -) were determined by linear regression (correlation probabilities p = 0.05 to p < 0.0001). A difference in collection rate (slope) was observed at 90% CI between AUTO-kit (90% CI, 12.48-21.06) and WBC-kit (90% CI, 22.58-39.04).[50] (Row B) CD34/kg yield per procedure by peripheral %CD34 cells in all patients, chemo + GF patients (correlation p = 0.02 – 0.0001), and GF-only–mobilized patients (p = 0.15 – 0.54) by collection kit. The collection rate or slope between AUTO-kit (95% CI, 0.09-0.17) and WBC-kit (95% CI, 0.68-0.73) was significant. (C-E) Direct comparison of CD34/kg yield per procedure in three remobilized patients by collection kit and mobilization regimen, including two poor mobilizers that were excluded from postcollection analysis.**

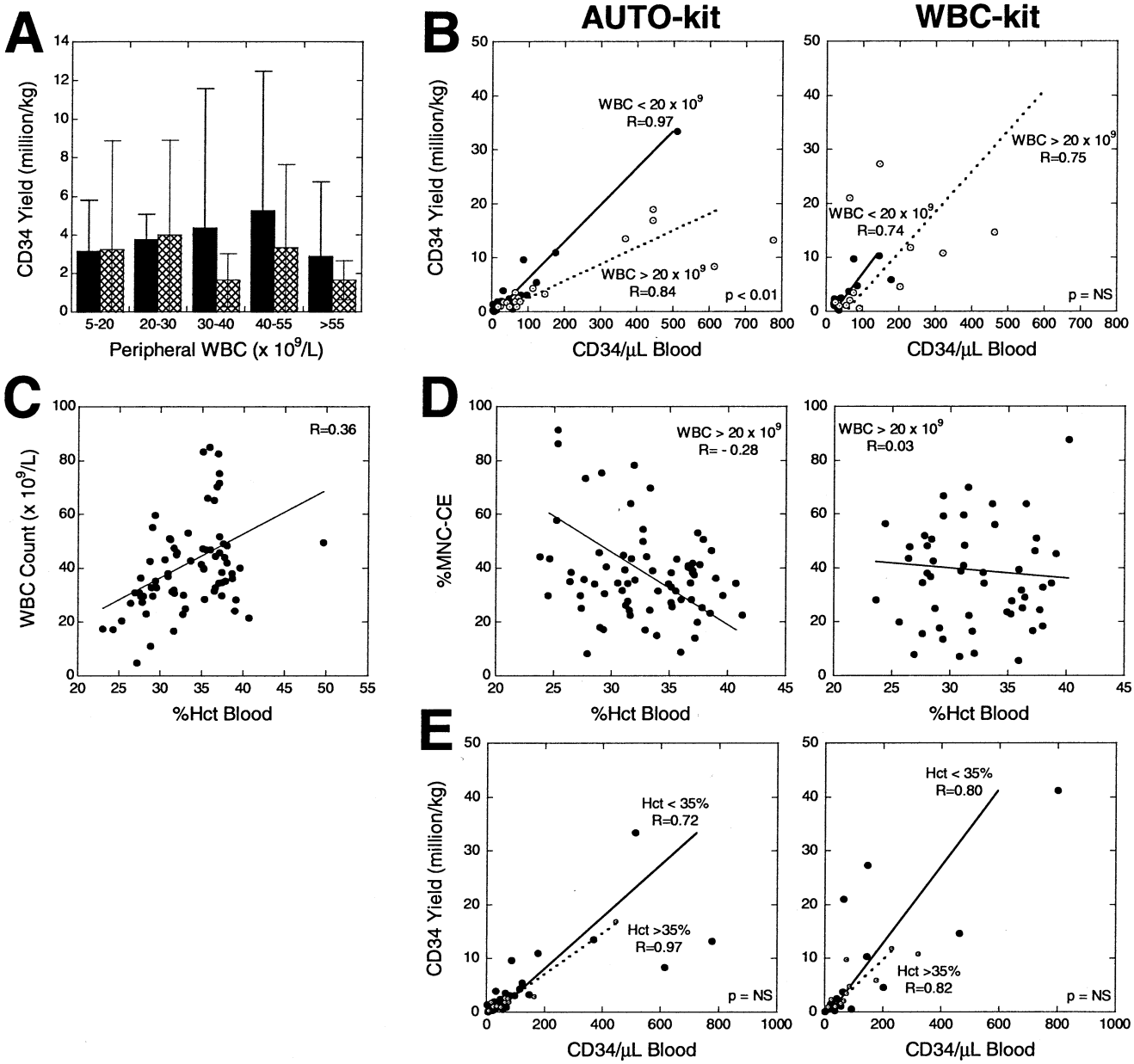


**Fig. 4. Effect of peripheral WBC count and Hct on CD34 collection. (A) CD34/kg yield (mean ± SD) relative to peripheral WBC count using the WBC-kit (■) or AUTO-kit (▩). (B) CD34 collection rate in the AUTO-kit and WBC-kit at low WBC (<20 × $10^9$/L, —) and high peripheral WBC counts (>20 × $10^9$/L, - - -; correlation probabilities p < 0.001 – 0.0001). p Values refer to the collection rate or slope at high and low WBC counts, as calculated from 95% and 99% CI.[50] (C) Correlation between peripheral Hct (%) and the WBC count in GF-only–mobilized patients (correlation p = 0.002 to p < 0.0001). (D) Correlation between Hct (%) and %MNC-CE in GF-only–mobilized patients using the AUTO-kit or WBC-kit. (E) CD34 collection rate by %Hct using the AUTO-kit and WBC-kit in GF-only–mobilized patients.**

### Effect of collection kit on PLT counts

One stated disadvantage of the WBC-kit for PBPC collection is the risk of procedure-related thrombocytopenia, with some studies reporting a 30% to 43% decrease in PLT count per procedure.[40-42,55,56] To examine the latter, we calculated the absolute and percentage change in daily PLT count. The mean decrease in daily PLT count was 12% (range, 0% to 53%) with no significant difference between kits (Table 3). The AUTO-kit, however, had the greatest intrapatient change in PLT count (p = 0.0005 vs. WBC-kit, p = 0.05; paired t test).

We also reviewed the transfusion record of each patient for any PLT or RBC transfusions during the course

**TABLE 5. PBPC collection relative to peripheral blood WBC count***

| Measure | Peripheral WBC count ($\times 10^9$/L) Low | High | p Value* |
|---|---|---|---|
| Peripheral blood counts† | | | |
| WBC count ($\times 10^9$/L) | 11.8 ± 4.6 | 39.4 ± 15.0 | <0.0001 |
| %MNCs | 15.1 ± 8.3 | 9.4 ± 4.5 | <0.0001 |
| MNCs ($\times 10^9$/L) | 1.76 ± 0.9 | 3.7 ± 1.6 | <0.0001 |
| %Hct | 29.5 ± 4.9 | 32.6 ± 4.1 | 0.00013 |
| PLT count ($\times 10^9$/L) | 86.2 ± 38.9 | 157.0 ± 76.0 | <0.0001 |
| CD34/μL | 73.7 ± 98.7 | 190.0 ± 221.9 | 0.01 |
| Median (range) | 44.7 (2.5-510.1) | 74.3 (16.3-800.2) | |
| Serum protein† | | | |
| Total protein (g/dL) | 6.5 ± 1.3 | 6.2 ± 0.9 | NS |
| Albumin (g/dL) | 3.4 ± 0.4 | 3.7 ± 0.6 | 0.06 |
| Immunoglobulin (mg/dL) | | | |
| IgG, median | 614 | 572 | NS |
| IgA, median | 47 | 32 | NS |
| IgM, median | 23 | 27 | NS |
| Mobilization | | | |
| Chemo + GF | 25 | 18 | 0.0019 |
| GF-only | 2 | 14 | 0.0019 |
| Collection yield† | | | |
| MNCs/kg ($\times 10^8$) | 1.03 ± 0.47 | 1.69 ± 0.82 | <0.0001 |
| WBC-kit | 1.08 ± 0.45 | 1.78 ± 0.79 | 0.002 |
| AUTO-kit | 1.10 ± 0.48 | 1.83 ± 1.13 | <0.0001 |
| CD34/kg ($\times 10^6$) | 3.40 ± 4.77 | 4.05 ± 6.23 | NS |
| Median | 2.1 | 1.9 | |
| WBC-kit | 3.44 ± 2.62 | 5.43 ± 8.89 | NS |
| AUTO-kit | 3.37 ± 5.76 | 3.19 ± 3.90 | NS |
| CE† | | | |
| %MNC-CE | 43.3 ± 21.4 | 35.1 ± 17.3 | 0.07 |
| WBC-kit | 40.0 ± 19.7 | 35.9 ± 22.8 | NS |
| AUTO-kit | 45.4 ± 37.0 | 34.5 ± 12.9 | 0.10 |
| %CD34-CE | 44.6 ± 4.4 | 23.8 ± 13.6 | 0.017 |
| WBC-kit | 37.5 ± 20.0 | 25.9 ± 18.2 | NS |
| AUTO-kit | 49.2 ± 5.5 | 22.3 ± 9.3 | 0.05 |

* Comparison of peripheral WBC in patients collected with either the WBC-kit or AUTO-kit only. Results reported as mean ± SD unless otherwise indicated. A p value of less than 0.05 was considered significant. NS = not significant and p > 0.10.
† No significant difference between AUTO- and WBC-kit by peripheral WBC count.

of PBPC collection (Table 3). Only one patient required a PLT transfusion. This patient received a PLT transfusion the day before starting PBPC collection for a PLT count of $12 \times 10^9$/L. This patient underwent four procedures using the WBC-kit without additional transfusion support. No patient studied required a RBC transfusion during the course of PBPC collection.

### Infusion reaction rate by kit and mobilization

Most patients underwent at least one APBPCT and 30% received two APBPCTs, for a total of 88 infusions (Table 7). The mean reaction rate for all infusions was 26%, with a higher reaction rate with AUTO-kit units (33%). Most reactions were mild and included nausea and vomiting (83%), cough (17%), cramps (9%), fever, and rigors (4%). Five reactions were relatively severe with cardiopulmonary symptoms. Reactions were significantly associated with GF-only mobilization ($p < 0.0001$; relative risk, 4.1; OR, 8.1; 95% CI, 2.4-27.9). Although GF-only patients accounted for only 25% of all APBPCTs, they comprised nearly 60% (13/23) of all infusion reactions.

Prior studies have reported a link between PBPC infusion reactions, DMSO dose, and the number of contaminating granulocytes.[57-60] In general, the total granulocyte yield ($3.61 \times 10^9$; $p = 0.0001$), granulocytes/kg ($4.07 \times 10^7$; $p = 0.0001$), and volume infused (417 mL) were higher in units associated with infusion reactions (Fig. 6). When reactions were examined by mobilization regimen, the granulocyte dose and volume were significantly higher in GF-only units ($p < 0.00001$), particularly when collected with the AUTO-kit ($5.19 \times 10^7$ granulocytes/kg, $p = 0.0006$). Among severe reactions, granulocyte doses averaged $6.31 \times 10^7$/kg for GF-only units collected with the AUTO-kit.

### Engraftment

All patients received an equivalent CD34/kg dose per transplant, regardless of collection kit or mobilization regimen. There was no significant difference in time to WBC or PLT engraftment. Engraftment times were consistent with previously published studies from our institution.[47]

## DISCUSSION

Several semi- and fully automated apheresis platforms are available for the collection of peripheral CD34 cells.[32-44] Since its introduction in 1998, the AUTO-kit has been broadly implemented at many institutions. Among the cited advantages of the AUTO-kit are an automated interface and anticoagulant management, increased interface stability, decreased operator oversight, decreased citrate reaction rates, a smaller product volume, and increased product purity with reductions in PLT and granulocyte contamination.[40-42] Observed disadvantages of the AUTO-kit are an increase in collection time, technical difficulties leading to skipped MNC harvests, and inferior collection yields at low peripheral CD34 counts.[39,40,42]

Although we had routinely used the AUTO-kit in adult patients since January 1998, we used the WBC-kit for PBPC collection in children, in remobilized patients, and in adults with falling collection yields. Because the WBC-kit was anecdotally associated with improved collection yields in many patients, we designed a prospective randomized trial using the WBC-kit or AUTO-kit in MM

**TABLE 6. Lymphoma patient demographics and PBPC collection results**

| Measure | Lymphoma type | | p Value* |
|---|---|---|---|
| | Hodgkin's | Non-Hodgkin's | |
| Patient demographics | | | |
| Number of patients | 29 | 69 | — |
| Age, years (range) | 38.1 ± 15.2 (20-67) | 52.4 ± 12.4 (19-69) | <0.0001 |
| Male/female | 13/16 | 43/26 | NS |
| Weight, kg | 80.5 ± 27.5 | 81.1 ± 18.2 | NS |
| TBV, L | 12.1 ± 12.6 | 13.2 ± 3.4 | NS |
| WBC count, Day 1 ($\times 10^9$/L)† (range) | 28.7 ± 23.5 (4.5-91.6) | 24.5 ± 20.1 (4.5-88.5) | NS |
| CD34/μL, Day 1† | 97.0 ± 158.0 | 38.8 ± 67.5 | 0.06 |
| Median (range) | 39.8 (0.8-715.3) | 8.9 (0-415.0) | |
| Mobilization regimen | | | |
| Chemo + GF (%)†,‡ | 31 (94) | 65 (71) | 0.007§ |
| Cyclophosphamide | 13 | 33 | NS |
| ICE/R-ICE | 14 | 20 | NS |
| ESHAP/R-ESHAP | 2 | 5 | NS |
| Other | 2 | 7 | NS |
| GF-only (%)† | 2 (6) | 27 (29) | 0.007§ |
| Collection kit (%)† | | | |
| AUTO-kit only | 23 (70) | 52 (56) | NS§ |
| WBC-kit only | 7 (21) | 19 (21) | NS |
| Mixed | 3 (9) | 21 (23) | NS |
| Mobilization | | | |
| Total number of mobilizations | 33 | 92 | — |
| Number of patients remobilized (%) | 3 (10) | 18 (26) | 0.08§ |
| Failure to collect after two or more mobilizations (%)¶ | 1 (3) | 10 (14) | 0.11§ |
| CD34/kg yield/mobilization** | 6.53 ± 9.08 | 2.99 ± 3.83 | 0.05 |
| Median (range) | 4.3 (0.2-42.9) | 2.4 (0-30.3) | |
| WBC-kit† | 8.15 ± 9.53 | 4.45 ± 6.27 | NS |
| AUTO-kit† | 5.88 ± 9.07 | 2.51 ± 2.50 | 0.11 |

* Comparison of Hodgkin's and NHL patients. A p value of less than 0.05 was considered clinically significant. NS = not significant and $p > 0.12$.
† No significant difference by collection set.
‡ Chemotherapy abbreviations: ICE/R-ICE = ifosfamide, carboplatin, etoposide ± rituximab (R); ESHAP/R-ESHAP = etoposide, methylprednisolone, high-dose cytarabine, cisplatin ± rituximab; other = R-CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone ± rituximab), EPOCH (etoposide, vincristine, doxorubicin, cyclophosphamide, prednisone), HCVAD (cyclophosphamide, doxorubicin, vincristine, dexamethasone, methotrexate, cytarabine, prednisone), or gemcitibine.
§ Chi-square.
¶ Number and percentage of patients who failed to collect at least $3 \times 10^6$ CD34/kg (one APBPCT) after two separate PBPC mobilization cycles.
** Mean CD34/kg yield per mobilization cycle for all collections, including remobilizations and mobilization failures. There was no significant difference in CD34/kg per mobilization for all patients and those patients mobilized with chemo + GF ($p = 0.9$).

**Fig. 5. CD34 collection in lymphoma patients by collection set. (Row A) Cumulative percentage of patients successfully collecting at least $3 \times 10^6$ CD34/kg or one APBPCT per leukapheresis procedure using the WBC-kit (—) or AUTO-kit (- - -) in Hodgkin's and NHL patients. (Row B) CD34/kg collection rate per peripheral CD34/μL concentration and collection kit in all lymphoma patients, Hodgkin's patients, and NHL. (Row C) CD34/kg collection per peripheral %CD34 concentration by lymphoma subtype and collection kit. (Row D) CD34/kg collection rate per peripheral CD34/μL concentration relative to peripheral WBC count and collection set in lymphoma patients. Fewer than $20 \times 10^9$/L WBCs (- - -); more than $20 \times 10^9$/L WBCs (—). p Values refer to comparison of CD34 collection rates (slope) at 95% and 99% CI.[50]**

patients undergoing autologous PBPC collection. MM patients were chosen because they have a low rate of mobilization failure and represent a relatively homogenous patient population with regard to age, pretreatment chemotherapy, and mobilization regimens. In addition, MM represents the majority (52%) of all adult APBPCT patients at our institution. Finally, MM may represent a technically unique patient population due to circulating paraprotein, which could impact blood viscosity, cell separation, and elutriation.[52] Because of the impact of mobilization regimen on CD34 mobilization,[17-20] results were analyzed by both collection kit and mobilization. We also performed a retrospective review of AUTO- and WBC-kit performance in adult lymphoma patients as a non-myeloma control.

As expected, mobilization regimen was the single greatest factor affecting CD34 collection. Patients collected with chemo + GF had significantly higher CD34 counts, higher CD34 yields, and fewer total procedures than patients mobilized with GF-only (Table 4).

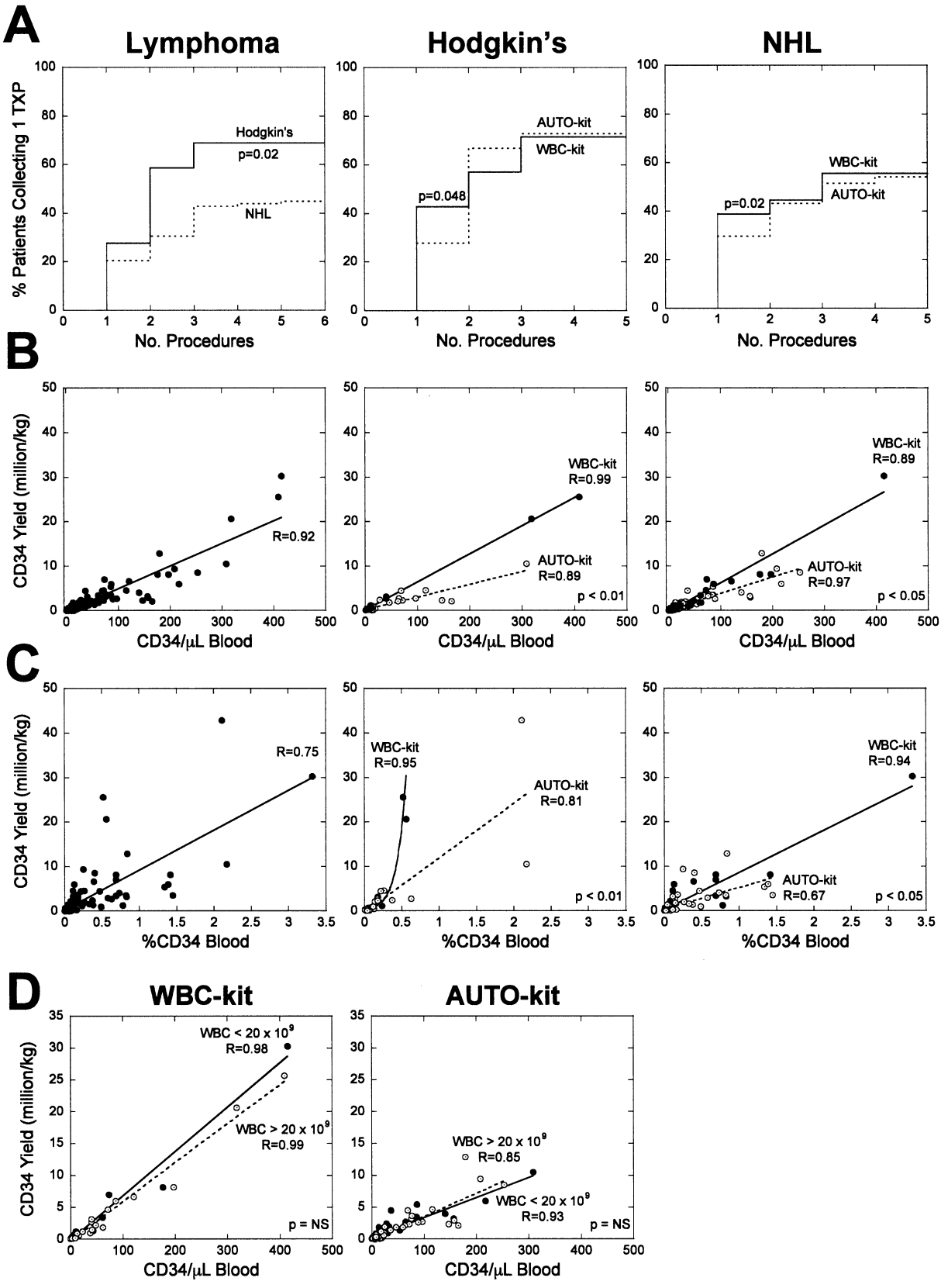
A
Lymphoma
Hodgkin's
NHL
% Patients Collecting 1 TXP
Hodgkin's
p=0.02
NHL
AUTO-kit
WBC-kit
p=0.048
WBC-kit
AUTO-kit
p=0.02
No. Procedures
B
CD34 Yield (million/kg)
R=0.92
WBC-kit
R=0.99
AUTO-kit
R=0.89
p < 0.01
WBC-kit
R=0.89
AUTO-kit
R=0.97
p < 0.05
CD34/μL Blood
C
CD34 Yield (million/kg)
R=0.75
WBC-kit
R=0.95
AUTO-kit
R=0.81
p < 0.01
WBC-kit
R=0.94
AUTO-kit
R=0.67
p < 0.05
%CD34 Blood
D
WBC-kit
AUTO-kit
CD34 Yield (million/kg)
WBC < 20 x 10^9
R=0.98
WBC > 20 x 10^9
R=0.99
p = NS
WBC > 20 x 10^9
R=0.85
WBC < 20 x 10^9
R=0.93
p = NS
CD34/μL Blood

**TABLE 7. Infusion toxicity and marrow engraftment in MM patients**

| Measure | All patients | Collection set | | p Value* |
|---|---|---|---|---|
| | | WBC-kit | AUTO-kit | |
| Transplant | | | | |
| Number of transplants | 88 | 35 | 45 | — |
| Number of patients receiving transplants | 63 | 24 | 33 | — |
| Number of patients with two APBPCTs | 25 | 11 | 12 | — |
| CD34/kg per APBPCT† | 4.22 ± 1.81 | 4.52 ± 2.64 | 4.0 ± 1.53 | NS |
| Infusion reaction (%)‡ | | | | |
| No reaction | 65 (73) | 28 (80) | 30 (67) | NS |
| Infusion reaction | 23 (26) | 7 (20) | 15 (33) | 0.18‡ |
| Mild | 18 (20) | 6 (17) | 11 (24) | NS |
| Severe | 5 (6) | 1 (3) | 4 (9) | 0.18‡ |
| Engraftment (days)† | | | | |
| ANC > $500 \times 10^9$/L§ | 11.5 ± 0.8 | 11.7 ± 1.0 | 11.6 ± 0.7 | NS |
| PLT > $20 \times 10^9$/L¶ | 12.5 ± 3.3 | 13.1 ± 4.9 | 12.6 ± 2.3 | NS |
| PLT > $50 \times 10^9$/L¶ | 17.9 ± 6.5 | 18.0 ± 8.0 | 18.1 ± 6.0 | NS |

* Comparison by PBPC collection kit using two-tailed t-test unless indicated otherwise. A p value of less than 0.05 was considered significant.
† Results reported as mean ± SD.
‡ Chi-square.
§ Sustained absolute neutrophil count (ANC) of more than $0.5 \times 10^9$/L.[47]
¶ Sustained PLT count of more than $20 \times 10^9$/L or more than $50 \times 10^9$/L in the absence of PLT transfusion for 72 hours.[47]
NS = not significant.

Chemo + GF patients were also more likely to collect sufficient CD34+ cells for two transplants (Fig. 2, Table 4). Although some authors have claimed equivalent CD34 collections with GF-only,[61-63] our results agree with more recent studies showing improved mobilization with chemo + GF in MM.[18,19] Contrary to recent reports,[17,22,23] neither premobilization nor Day 1 PLT counts were helpful in predicting successful CD34 collection, probably because the highest PLT counts were associated with GF-only mobilization ($p = 0.0005$, Table 3).

We also observed a higher daily success rates with the WBC-kit in chemo + GF–mobilized patients. Overall, 10% to 15% more patients successfully collected per procedure with the WBC-kit, with more than 90% collecting for two APBPCTs (Fig. 2, Table 3). Even among poor mobilizers, the WBC-kit resulted in higher daily CD34/kg yields despite dismal peripheral CD34 counts and CD34/kg yields (Fig. 2D,E). These results agree with Morton and colleagues[37] who observed a higher success rate per collection with the WBC-kit over the Haemonetics MCS-3P, especially for target yields of greater than $5 \times 10^6$ CD34/kg. They also agree with Wilke and coworkers[39] who reported comparatively better CD34 yields with the WBC-kit at low CD34 concentrations (<10 CD34/μL, $p = 0.012$). Although some centers have been reluctant to use the WBC-kit due to concerns of procedure-related thrombocytopenia,[35,41,55,56] we did not encounter clinically significant thrombocytopenia in our patients in agreement with other investigators (Table 2).[34,43]

The WBC-kit also displayed a higher CD34 collection rate in certain populations, depending on underlying disease and mobilization regimen. Specifically, the CD34/kg collection rate per peripheral CD34/μL count was twofold higher with the WBC-kit in chemo + GF MM and Hodgkin's lymphoma patients (Fig. 3 and 5). When examined by peripheral %CD34, the CD34 collection was nonlinear, resulting in high CD34/kg yields even at relatively low CD34 concentrations. These results were not observed in NHL and GF-only–mobilized MM patients.

Finally, the WBC-kit appeared less sensitive than the AUTO-kit to high peripheral WBC counts. Although both kits exhibited a decrease in MNC-CE and CD34-CE with increasing peripheral WBC counts (Table 4), the impact was worse with the AUTO-kit. The AUTO-kit had a 50% decrease in CD34-CE at WBC counts greater than $20 \times 10^9$/L, accompanied by a twofold decrease in CD34 collection rate (Fig. 3, $p < 0.01$). The decrease in CD34 collection rate was not observed with the WBC-kit, or in lymphoma patients, suggesting that the phenomenon is unique for the AUTO-kit in MM.

A potential adverse effect by elevated peripheral WBC and MNC counts on CE has been reported by others.[26,30,31,38,51] In an early study, Benjamin and colleagues[27] noted an inverse relationship between the peripheral MNC count and MNC-CE, with the best CE observed at low WBC and MNC counts. Similar findings were reported by Heuft and colleagues[38] and Gidron and colleagues,[51] who noted a decrease in the calculated CD34-CE at higher WBC and CD34 counts. Gidron, in particular, reported a significant decrease in CD34-CE at peripheral WBCs greater than $20 \times 10^9$/L ($p < 0.0001$), prompting the authors to caution against GF-only mobilization regimens.[51] Finally, Burgstaler and colleagues[30] reported a significant decrease in CD34 yields (55%-77%), accompanied

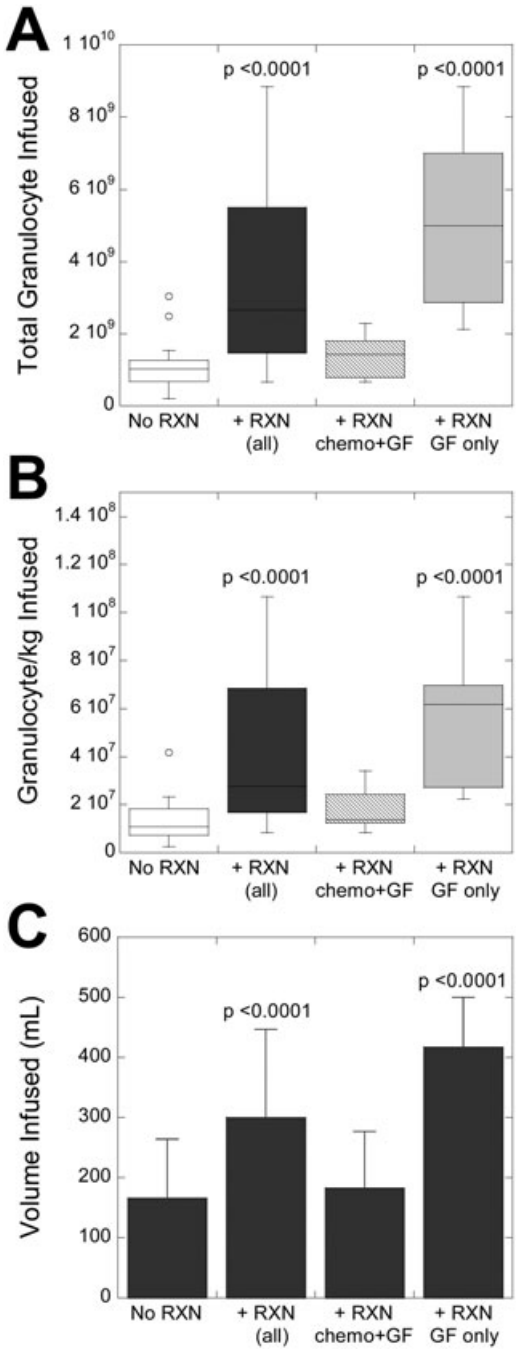


**Fig. 6. The influence of PBPC mobilization on infusion reactions (RXN). (A) Total granulocyte dose per transplant in patients with no reaction (□), granulocyte dose in all infusion reactions (■), infusion reactions in chemo + GF–mobilized (▧), and GF-only–mobilized patients (▩). Data displayed as a box plot, showing median, 25th and 75th quartile and data range (whiskers). (B) Granulocyte dose/kg body weight. (C) Mean volume infused (mL, mean ± SD) per APBPCT in patients with and without an infusion reaction. p Values determined by two-tailed t test.**

by a twofold increase in WBC contamination, in units collected at WBC counts of greater than $35 \times 10^9$/L and flow rates greater than 60 mL/min.

Benjamin and coworkers[26] hypothesized that *all* continuous flow centrifugation devices may be susceptible to a fall-off in CE with rising WBC and CD34 counts due to the fixed size of the collection aperture. These authors speculated that at low WBC counts, the MNC band is narrow relative to the collection channel, permitting an efficient collection of the entire MNC layer. CE decreases with increasing MNC and WBC counts as the MNC layer exceeds the fixed diameter of the collection channel and an increasing percentage of MNC escape collection. Our results suggest that the dual-stage design of the AUTO-kit may exacerbate the effect of elevated WBC on CD34 collection rate and efficiency in MM patients.

Several factors could synergistically depress CE with the AUTO-kit design in GF-only mobilized MM patients via effects on blood viscosity, laminar flow, and cell separation. Blood viscosity is sensitive to increases in Hct, WBCs, PLTs, fibrinogen, immunoglobulin, and other plasma proteins.[52] Hct and leukocrit, in particular, are major and synergistic contributors to whole blood viscosity, that are both increased with GF-only mobilization. The additional impact of paraprotein is variable; however, blood viscosity is elevated in more than 50% of MM patients when corrected for Hct.[52] G-CSF may further increase plasma and whole blood viscosity due to increases in fibrinogen, Factor VIII and von Willebrand factor, PLT count, and PLT activation.[64-66] In the Fenwal Amicus, high PLT counts and increased plasma viscosity are both theorized to interfere with cell collection, leading to decreased MNC-CE, lower CD34/kg yields, and missed collection cycles.[67] Although we were unable to demonstrate a direct association between CD34 collection and paraprotein levels, it is noteworthy that *only* MM patients demonstrated a drop in the CD34 collection rate at high WBC counts.

Finally, we compared infusion and engraftment data by kit and mobilization. All patients were transplanted with equivalent CD34/kg doses and had similar engraftment times. There was, however, a higher incidence of infusion reactions, accompanied by a higher granulocyte dose per APBPCT, with GF-only units. Zambelli and colleagues were the first to report an association between fever and granulocyte dose ($>10^9$/kg),[57,58] followed by Calmels and coworkers,[59] who reported a higher median granulocyte content ($3.3 \times 10^9$) in units associated with adverse reactions. Likewise, we observed a significantly higher total granulocyte content and granulocyte/kg dose with infusion reactions, particularly with GF-only units (Fig. 6).

Our study differs significantly from prior studies examining the AUTO-kit,[39-44] and other collection platforms, both in design and in postcollection analysis.

Although primary disease and mobilization regimen are known to be significant factors influencing CD34 mobilization,[16-20] most studies have examined device performance in a heterogenous pool of patients and normal donors, often using historical data for comparison purposes.[34-39,41-43] A few studies have performed 2-day randomized crossover studies to control for patient-related factors.[34-37,43] Although there are many advantages to a crossover design, our study allowed us to compare the collection kit performance over several consecutive days in individual patients. As a consequence, we were able to extend our analysis to the number of procedures/mobilization, the success rate per APBPCT, and infusion reaction rate. Our results highlight the need to consider the impact of patient diagnosis, mobilization regimen, and CD34 collection rates in the evaluation of new apheresis devices.

In summary, we have performed the first randomized, prospective study specifically comparing the AUTO- and WBC-kits for PBPC collection in MM. We demonstrate that the WBC-kit, combined with chemo + GF mobilization, improves CD34 yields in MM patients. GF-only mobilization was associated with more procedures and decreased CE, particularly with the AUTO-kit due to a fall-off in CD34 collection rates at higher WBC counts. We also showed an increase in infusion reaction rates and higher granulocyte doses with GF-only and AUTO-kit units. Because MM patients represent a significant proportion of our transplant population, we have discontinued the use of the AUTO-kit for all collections. In addition, there has been a significant shift toward chemo + GF mobilization for all patients unless medically contraindicated.

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#### CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest relevant to the submitted manuscript.

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