Effectiveness of an Algorithm-Based Approach to the Utilization of Plerixafor in Patients Undergoing Chemotherapy-Based Stem Cell Mobilization

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A B S T R A C T

Autologous stem cell transplantation remains a mainstay of therapy for diseases such as multiple myeloma and relapsed lymphoma. The use of plerixafor has been shown to augment the ability to collect adequate stem cells, but the optimal use of this agent when used with chemotherapy is not yet clear. We utilized an algorithm-based approach with the addition of plerixafor to 54 patients undergoing chemomobilization with reduced-dose etoposide who had a less than optimal preapheresis $CD34^+$ cell count. We used a $CD34^+$ precount of 20 cells/μL as a threshold to initiate stem cell apheresis. Ninety-four percent of patients were successfully collected and proceeded to transplantation. Fourteen of 51 (28%) patients who successfully collected required plerixafor to augment stem cell yield. Of the patients who successfully collected, 94% (89% of the entire population) were able to collect in 2 or fewer days. Compared with previous data from our institution, the rate of patients collecting $> 4 \times 10^6$ $CD34^+$ cells/kg in a single collection was increased from 39% to 69%. The safety profile of this approach was acceptable. The use of this algorithm-based method to determine when and whether to add plerixafor to chemomobilization was shown to be a successful and cost-effective approach to stem cell collection.

INTRODUCTION

High-dose chemotherapy followed by autologous stem cell transplant (ASCT) remains an essential treatment modality in efforts to achieve a durable complete remission for patients with non-Hodgkin's lymphoma (NHL), Hodgkin's disease, and multiple myeloma (MM) [1,2]. The mobilization and adequate collection of hematopoietic stem cells (HSCs) by apheresis is necessary for allowing patients to undergo this procedure. Strategies for HSC mobilization include the administration of granulocyte colony–stimulating factors (GCSF), with or without chemotherapy, to stimulate the production of these cells. Unfortunately, factors such as age > 65 years, advanced disease with bone marrow involvement, and exposure to radiation and/or HSC-toxic agents can lead to poor mobilization or mobilization failure. Published data has reported a range for mobilization failure between 5% and 30% of patients [3,4]. As a result, current research regarding HSC mobilization has continued to focus on optimizing the efficiency of apheresis collection in an effort to reduce cost and minimize the number of procedures required to collect sufficient cells [5].

For single transplantations, the collection of at least 2×10^6 $CD34^+$ cells/kg is accepted as the minimal yield to proceed with transplantation, although for patients with MM, consensus guidelines have recommended a collection yield of at least 4×10^6 $CD34^+$ cells/kg in preparation for potential tandem transplantation [6]. Plerixafor is a novel agent that interferes with the interaction between stromal derived factor-1 and the CXCR4 receptor. Disruption of this interaction causes a rapid release of HSCs from the bone marrow into peripheral circulation [7]. For patients with MM and lymphoma who have difficulty achieving the required minimum yields for transplantation, plerixafor combined with GCSF has been shown to significantly increase $CD34^+$ collection yields [8-12]. Given the cost of plerixafor, limited apheresis availability, and cost of HSC product storage, recent studies have focused on determining the appropriate use of plerixafor in combination with GCSF to optimize mobilization and collection.

Abhyankar et al. described a risk-based algorithm that used peripheral $CD34^+$ screening to help guide the administration of plerixafor in addition to filgrastim in an effort to optimize collection and decrease resource utilization. Using this risk-based approach, their patients were able to collect an adequate number of cells within 2 apheresis sessions and plerixafor was only needed in 34.5% of patients, with a 2% failure rate [13].

Chemotherapy-based mobilization is a mobilization strategy that uses chemotherapy to stimulate the production of HSCs in the bone marrow and their subsequent release into the peripheral blood. When combined with GCSF,

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Table 1
Patient Characteristics

Characteristic	Value
N	54
Male, %	63%
Age, average (range), yr	53.9 (20-74)
Disease	
NHL	31
MM	21
Other (APL, germ cell)	2
Characteristics of patients requiring plerixafor	
n	15
Disease	
NHL	11
MM	4
First pre-CD34$^+$ count	
$<$10 cells/μL	9
$\geq$10 but $<$ 20 cells/μL	6
Post-plerixafor CD34$^+$ count	
$<$10 cells/μL	3
$\geq$10 cells/μL	12

APL indicates acute promyelocytic leukemia; NHL, non-Hodgkin's lymphoma; MM, multiple myeloma.
Data presented are n, unless otherwise indicated.

peripheral blood stem cell (PBSC) yields with chemomobilization have been shown to be significantly higher than with GCSF alone [14,15]. Additionally, mobilization with chemotherapy and GCSF has been shown to overcome known factors that predict difficult mobilization in MM and NHL such as advanced age, prior thalidomide/lenalidomide, radiation exposure, or heavy pretreatment [6,16].

Despite the improvement in HSC yield seen with chemotherapy-based mobilization, there remain a number of patients who either fail to mobilize, have lower HSC yields, or require multiple days and large collection volumes of apheresis collections to obtain adequate HSC yields. Previous data from our institution has demonstrated that mobilization with etoposide and GCSF results in an overall successful collection rate of 100% in MM patients and 94% in lymphoma patients. Ninety-nine percent of MM patients and 57% of lymphoma patients were classified as "good mobilizers," defined as those who collected $> 5 \times 10^6$ CD34$^+$ cells/kg in 2 or fewer apheresis sessions [5,16]. This CD34 dose is meaningful because it has been shown that infusion of $> 5 \times 10^6$ CD34 cells/kg is associated with significantly faster neutrophil and platelet recovery in ASCT patients compared to doses of 2 to 5×10^6 cells/kg [17-21]. Although good mobilizers collected $> 5 \times 10^6$ cells/kg in $\leq$ 2 days, patients who did not meet this definition, ie, "poor mobilizers," required double the number of apheresis sessions (ie, 4), with 27% not achieving the goal of 5×10^6 cells/kg.

The optimal use of plerixafor combined with chemotherapy and GCSF has not been well described in the literature. Recent studies involving plerixafor combined with chemotherapy and GCSF have shown significant increases in HSC yields and reductions in apheresis utilization [22-24]. However, questions remain on whether every patient undergoing chemomobilization requires plerixafor or if there are strategies that can be employed to selectively administer plerixafor to patients at high-risk of failing chemomobilization.

The use of peripheral WBC and CD34$^+$ cell counts to predict successful GCSF mobilization and apheresis collection has been demonstrated at other institutions [13,25]. We used these 2 factors to develop an algorithm that incorporates chemotherapy with predetermined decision points to help guide the administration of plerixafor and when to proceed with HSC collection. The purpose of this analysis was to evaluate the safety and efficacy of this etoposide-based chemomobilization algorithm with predetermined decision points for plerixafor administration to selectively use plerixafor for high-risk patients, augment HSC collection yields, and reduce apheresis utilization.

MATERIALS AND METHODS

Study Patients

Institutional review board approval from the University of North Carolina at Chapel Hill was obtained for the purpose of this analysis. Between May 2012 and May 2013, patients with lymphoma and MM who were likely to be difficult mobilizers received etoposide and GCSF with or without plerixafor according to institutional guidelines. Difficult mobilizers were defined as any patient with lymphoma, MM patients who had received greater than 6 cycles of a lenalidomide-containing regimen, patients undergoing predetermined tandem transplantations, or patients who had previously failed GCSF mobilization. Overall patient characteristics are illustrated in Table 1.

Mobilization and PBSC Collection Regimen

A chemomobilization algorithm was developed combining circulating WBCs and peripheral CD34$^+$ cell counts after at least 10 days of GCSF to guide decisions on CD34$^+$ cell collection and the administration of plerixafor (Figure 1). HSCs were mobilized with etoposide at a dose of 300 mg/m^2 diluted to a concentration of .4 mg/mL and infused over 4 hours for 2 consecutive days. Patients received ondansetron, 24 mg daily, and dexamethasone, 20 mg orally, before each etoposide infusion, as well as prochlorperazine, 10 mg every 4 hours as needed, for nausea or emesis. Antimicrobial prophylaxis was given concurrently using levofloxacin 500 mg orally once daily to all patients beginning on day 5. GCSF was administered at a dose of 10 μg/kg/day beginning on day 3 and continued

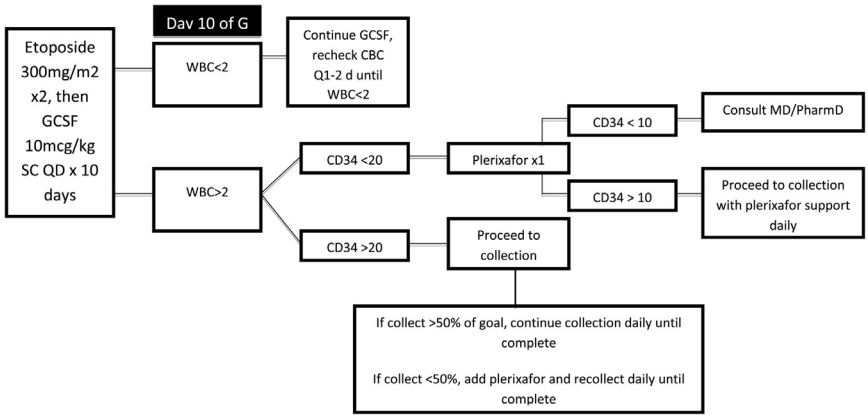

Figure 1. Chemomobilization algorithm.

until a minimum 2×10^6 $CD34^+$ cells/kg or a goal of 4×10^6 $CD34^+$ cells/kg had been collected.

Beginning on day 12 after chemotherapy administration, evaluation of each patient's WBC and $CD34^+$ cell count determined whether they would proceed to apheresis collection, continue filgrastim, or receive plerixafor in addition to filgrastim. A $CD34^+$ count of ≥ 20 $CD34^+$ cells/μL was used as the initial determinant for proceeding to apheresis collection. Patients whose initial $CD34^+$ count was ≤ 20 cells/μL received plerixafor, and if their subsequent $CD34^+$ count was > 10 $CD34^+$ cells/μL, apheresis collection with daily plerixafor support was attempted to maximize the potential for obtaining a transplantable dose of HSCs. Target volumes of collection were calculated based on an algorithm that includes the patient's weight in kilograms, the peripheral precollection $CD34^+$ count, and the requested HSC dose. The algorithm predicts the number of liters of patient's blood that must be processed. If the algorithm predicts a collection volume that exceeds 6 times the patient's total blood volume, the collection is ended after 6 hours and, if the dose is not achieved, a second day of collection occurs. Patients unable to collect the minimum 2×10^6 $CD34^+$ cells/kg yield in 3 days of collection or those who fail to adequately respond (peripheral blood count < 10 $CD34^+$ cells/μL) after 1 dose of plerixafor were considered mobilization failures. All collections were performed using the COBE Spectra Apheresis System (TerumoBCT, Lakewood, CO). The complete decision tree is shown in Figure 1.

Study Objectives

The goals of this analysis were to (1) establish the safety and efficacy of chemomobilization with a reduced dose of etoposide with regards to mobilization yield, apheresis time, and incidence of adverse effects, and (2) assess the effectiveness of an algorithm-based approach to the use of plerixafor to augment stem cell collection yields in patients who are at high risk of failed mobilization while optimizing resource utilization.

Safety

Safety endpoints with regards to rate of febrile neutropenia and hospitalizations of any kind were assessed for all available patients. Data for safety was obtained retrospectively from electronic medical records.

Statistical Analysis

Descriptive statistics were used in this analysis.

RESULTS

Efficacy

Between May 2012 and May 2013, a total of 54 patients attempted PBSC mobilization with etoposide in preparation for ASCT at the University of North Carolina Hospitals and Clinics. Of the 54 patients, 51 (94%) were collected successfully with an HSC yield greater than 2×10^6 $CD34^+$ cells/kg. Forty-eight of these 51 patients (94%) collected in 2 or fewer apheresis sessions. In our NHL population, all of the patients ($n = 19$) who did not require plerixafor and 7 of the 10 patients who did require plerixafor were able to collect the minimum yield of 2×10^6 $CD34^+$ cells/kg in 2 apheresis sessions or fewer. Plerixafor was required in 15 (28%) patients, whereas 37 (69%) were able to collect adequate HSCs without plerixafor support. Comparing those requiring plerixafor with those who did not, patients not requiring plerixafor collected a higher median $CD34^+$ cell yield (5.99×10^6 cells/kg versus 4.30×10^6 cells/kg); did not require plerixafor support during collection, indicating that all patients were able to collect $> 50\%$ of goal after the first apheresis session; and required fewer median apheresis sessions (1 session versus 2 sessions). The majority of plerixafor patients were still able to successfully collect within 2 apheresis sessions, with only 11 requiring 1 to 2 plerixafor doses. Patients requiring plerixafor were more likely to carry an underlying diagnosis of lymphoma and were older than patients who collected successfully without plerixafor. All patients who successfully collected have proceeded to transplantation.

Three of the 54 patients failed to collect adequate HSCs. Two of the 3 were heavily pretreated NHL patients, one of whom received 2 doses of plerixafor and still failed to mobilize because of persistently low $CD34^+$ cell counts (<10 cells/μL) after each plerixafor administration. After consultation between the providers and the pharmacist, the patient proceeded with a bone marrow harvest in lieu of remobilization. The other patient with mobilization failure had an undetectable preapheresis $CD34^+$ cell count at day 14 after chemotherapy, so plerixafor was not administered and the patient proceeded to bone marrow harvest, as well. The last individual who failed mobilization was a MM patient who was hospitalized and expired before a preapheresis $CD34^+$ count was checked. Thus, 14 of 15 patients who received plerixafor had successful stem cell collections and were able to proceed to ASCT. Full results are available in Table 2.

Safety

Of the 54 patients who received etoposide mobilization, 8 patients (15%) were hospitalized for neutropenic fever. One of these 8 patients was a 69-year old heavily pretreated MM patient who was hospitalized for febrile neutropenia, subsequently suffered a myocardial infarction during hospitalization, and expired before a peripheral $CD34^+$ assessment was performed. This patient had underlying cardiovascular comorbidities, which likely increased his/her risk for cardiovascular events.

DISCUSSION

For patients who have risk factors for difficult mobilization of PBSC, chemotherapy combined with GCSF and plerixafor is effective in successfully mobilizing HSCs in preparation for ASCT. Previous data from our institution using etoposide mobilization at a dose of 375 mg/m^2 for 2 consecutive days in our heavily pretreated MM and lymphoma patients demonstrated that 99% of MM and 57% of lymphoma patients were good mobilizers, defined as the ability to collect at least 5×10^6 cells/kg in 1 to 2 days [5,16]. In our current experience, we show that in a mixed population of heavily pretreated MM and NHL/Hodgkin disease patients, we were able to use a reduced dose of etoposide

Table 2
Results of Successful Collections

Overall N = 51	Plerixafor	No Plerixafor
n	14*	37
Age, mean (range), yr	59 (37-66)	51 (20-74)
Disease		
NHL	9	19
MM	5	16
Other	0	2
$CD34^+$ cell collection, median, $\times 10^6$ cells/kg	4.30	5.99
No. of collections, median (range)	2 (1-4)	1 (1-2)
No. of plerixafor doses, median (range)	2 (1-4)	-
Days of collection required (%)		
1	6 (43)	29 (78)
2	5 (36)	8 (22)
3	2 (14)	-
4	1 (7)	-
Good mobilizers, n (%)†	9 (64)	31 (84)
Patients hospitalized, n (%)	4 (29)	4 (11)

NHL indicates non-Hodgkin's lymphoma; MM, multiple myeloma.

* Mobilization was aborted for 1 patient after having persistently low $CD34^+$ counts (<10 cells/μL) after 2 doses of plerixafor; thus, this patient was not included in the analysis above.

† Defined as collecting $> 4 \times 10^6$ cells/kg within 2 apheresis sessions.

and an algorithm-based approach to plerixafor utilization to maintain both the overall rate of successful mobilizations along with a high rate of good mobilization. The efficiency of collection with this approach was better than with etoposide alone at a higher dose, as 48 of 51 successful collectors collected in 2 or fewer apheresis sessions, compared with a median of 4 apheresis sessions in poor mobilizers with our previous experience [5,16]. Of note, the approach resulted in 69% of patients being able to collect $> 4 \times 10^6$ cells/kg in a single collection day. This is a marked improvement from our prior experience, where without the use of this algorithm, only 39% of patients collected $> 4 \times 10^6$ cells/kg in a single collection.

When we analyzed resource utilization in patients requiring plerixafor, our current experience demonstrated that the majority of patients were still able to successfully collect within 2 apheresis sessions, albeit with lower collection yields. Only 2 of the 15 patients requiring plerixafor met the criteria for good mobilization, as defined in our previous publication as the ability to collect $\geq 5 \times 10^6$ cells/kg within 2 apheresis sessions. However, it is important to note that current standard practice at our institution is to collect a goal of 4×10^6 cells/kg. With the modification of our definition of good mobilization to reflect this new collection goal, 9 of the 15 patients (60%) who were given plerixafor now met criteria for good mobilization. In our approach, we used a preapheresis $CD34^+$ cell count of 20 $CD34^+$ cells/μL as a threshold for initiating apheresis collection. The success rate and the efficiency of apheresis reported here affirms that this threshold adequately predicts successful collection, while limiting the use of plerixafor to only those who require it, as well as reduces the number of apheresis procedures required for adequate collection, compared with our previous experience. Although a formal cost analysis was not done, we previously performed a break-even analysis that compared the cost of mobilization with the reference cohort with the estimated cost of mobilization when a median of 2 doses of plerixafor was administered to predicted poor mobilizers. In that break-even analysis, the authors concluded that 49% of predicted poor mobilizers who received a median of 2 doses of plerixafor would have to convert from poor to good mobilization to achieve cost neutrality. In our present analysis, we were able to demonstrate that of the 15 patients who required a median of 2 doses of plerixafor and would have been classified as poor mobilizers, 60% were able meet criteria for good mobilization, exceeding the 49% required for cost neutrality [5].

The results of our study are consistent with similar studies utilizing preapheresis collection $CD34^+$ screening for GCSF mobilization combined with plerixafor support. At the University of Kansas, the implementation of their risk-based algorithm for GSCF mobilization resulted in only 35% of their patients receiving plerixafor along with a significant reduction in patients who required remobilization [13]. In our study using chemomobilization, we were also able to demonstrate selective use of plerixafor in patients undergoing chemomobilization with etoposide with a high rate of success and limited its use to 28% of our high-risk population. With regards to safety, our use of etoposide at a dose of 300 mg/m^2 over 2 consecutive days resulted in 8 patients (15%) requiring hospitalizations, with the most frequent diagnosis being neutropenic fever, despite all patients receiving antimicrobial prophylaxis during the mobilization process. This rate did not differ significantly from our previous experience in a mixed population of 311 patients, which resulted in 32 patients (10%) requiring hospitalization for neutropenic fever, with an additional 4 patients receiving outpatient intravenous antibiotics. In studies using cyclophosphamide at doses ranging from 1.2 g/m^2 to 7 g/m^2, the incidence of neutropenic fever ranged from 15% to 72% [14,15,21]. Although our rate of hospitalization and incidence of neutropenic fever compares favorably with historical data utilizing chemotherapy-based mobilization, it also highlights the inherent risk associated with this modality of mobilization.

In summary, we were able to demonstrate a high rate of successful HSC collection with low resource utilization and adequate safety through the application of a chemomobilization algorithm that included reduced-dose etoposide and GCSF combined with predetermined decision points for plerixafor support and collection.

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Role of Acute Graft-Versus-Host Disease in the Risk of Bacteremia and Invasive Fungal Disease after Allogeneic Hemopoietic Stem Cell Transplantation in Children. Results from a Single-Center Observational Study

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Data on epidemiology of severe infectious complications, ie, bacteremia or invasive fungal disease (IFD), in children with acute graft-versus-host disease (aGVHD) after allogeneic hemopoietic stem cell transplantation (HSCT) are scarce. In a retrospective, single-center study, we analyzed the risk (hazard ratio [HR]) and the rate (episodes/1000 patients days at risk) of bacteremias and IFD in children receiving allogeneic HSCT, according to the type of donor (matched related [MRD] or alternative [AD]) and presence and grade of aGVHD. From 2000 to 2009, 198 children receiving 217 allogeneic HSCT developed 134 severe infectious episodes (103 bacteremias and 31 IFD). The type of donor (AD versus MRD) was the most important risk factor for the severe infections ($P = .0052$). In separate multivariable analysis for bacteremia and IFD, children receiving an AD HSCT had increased HR and rate of bacteremia compared with those receiving a MRD transplantation ($P = .0171$ and $P = .0001$, respectively), whereas the HR and the rate of IFD were significantly influenced by the grade of aGVHD ($P = .0002$ and $P < .0001$, respectively). Finally, infectious episodes occurred late after HSCT, especially in presence of severe aGVHD, and bacteremias were 3 to 6 times more frequent than IFD. These data may be important to design management strategies of infections in pediatric allogeneic HSCT.

INTRODUCTION

Bacteremia and invasive fungal diseases (IFD) represent severe complications for patients receiving allogeneic hemopoietic stem cell transplantation (HSCT) [1-4]. These infections are more frequent in subjects receiving HSCT from an alternative donor (AD) than from a matched related donor (MRD) [1]. During a prospective survey of adverse events occurring in patients with steroid-resistant acute graft-versus-host disease (aGVHD), we observed that the

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