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

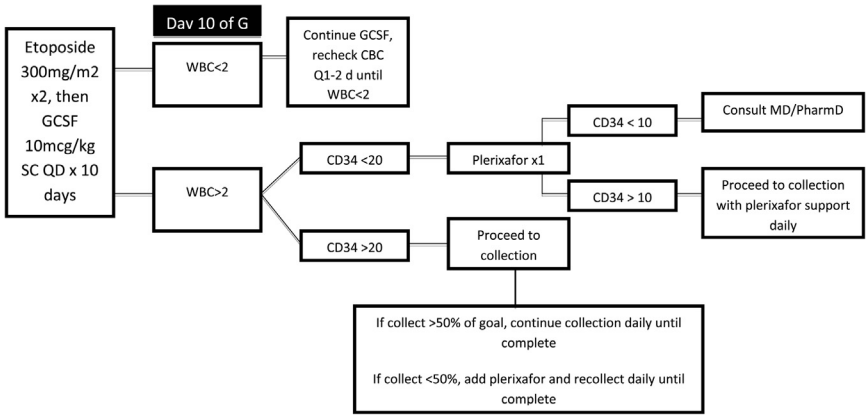

Figure 1. Chemomobilization algorithm.