Plerixafor Plus Granulocyte Colony-Stimulating Factor Improves the Mobilization of Hematopoietic Stem Cells in Patients with Non-Hodgkin Lymphoma and Low Circulating Peripheral Blood CD34$^+$ Cells

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Many institutions have adopted algorithms based on preapheresis circulating CD34+ cell counts to optimize the use of plerixafor. However, a circulating peripheral blood CD34+ cell threshold that predicts mobilization failure has not been defined. The superiority of plerixafor + granulocyte colony-stimulating factor (G-CSF) over placebo + G-CSF for hematopoietic stem cell mobilization and collection was shown for patients with non-Hodgkin lymphoma in a phase III, prospective, randomized, controlled study. The question remains as to which patients may benefit most from the use of plerixafor. In this post hoc retrospective analysis, mobilization outcomes were compared between the 2 treatment arms in patients stratified by peripheral blood CD34+ cell count (<5, 5 to 9, 10 to 14, 15 to 19, or ≥20 cells/μL) obtained before study treatment and apheresis. Compared with placebo plus G-CSF, plerixafor plus G-CSF significantly increased the peripheral blood CD34+ cells/μL over prior day levels in all 5 stratified groups. The probability of subsequent transplantation without a rescue mobilization was far greater in the plerixafor-treated patients for the lowest initial (day 4) peripheral blood CD34+ cells/μL groups (<5, 5 to 9, or 10 to 14). Engraftment and durability were the same for the 2 treatment groups for all strata, but the effect in the lower strata could be altered by the addition of cells from rescue mobilizations. These findings may provide insight into the optimal use of plerixafor in all patients undergoing stem cell mobilization.

INTRODUCTION

High-dose chemotherapy followed by autologous stem cell transplantation (ASCT) can elicit long-term remission in patients with chemotherapy-sensitive, relapsed, aggressive non-Hodgkin lymphoma (NHL) [1]. A key requirement for successful ASCT is the successful collection and cryopreservation of hematopoietic stem cells (HSCs) with a well-accepted minimum target number of 2×10^6 CD34+ cells/kg. Retrospective analyses have reported rates of mobilization failure in patients with NHL from approximately 20% to 30% with cytokines, either alone or in combination with chemotherapy [2-4]. Patients who are unable to collect this minimum number of HSCs often cannot proceed to ASCT [5].

One assay used to screen for poor mobilizers is flow cytometric peripheral blood CD34+ enumeration. The number of circulating CD34+ cells measured before apheresis has been shown by some to correlate positively with stem cell yields in patients with hematologic malignancies. In published clinical studies, patients with preapheresis CD34+ cell counts above a threshold level, ranging from 5 to 34 CD34+ cells/μL, had significantly greater stem cell yields than those patients with lower preapheresis cell counts [6-8]. To date, however, the optimal preapheresis CD34+ cell count to predict mobilization success has not been determined, and there is no consensus on the preapheresis CD34+ threshold level that should be used to identify patients at risk for failed collection [6-8].

Plerixafor is a first-in-class agent currently approved in the United States, in combination with granulocyte colony-stimulating factor (G-CSF), to mobilize HSCs in patients with NHL or multiple myeloma [9-11]. Plerixafor is an inhibitor of the CXCR4 chemokine receptor that blocks receptor binding of the stromal cell–derived factor-1α [12]. Disruption of the stromal cell–derived factor-1α–CXCR4 interaction contributes to the release and trafficking of stem cells from the bone marrow into the peripheral blood and results in elevated levels of circulating HSCs both in humans and in animal models [13,14].

The efficacy and safety of plerixafor + G-CSF in mobilizing stem cells in patients with NHL has been established in a phase III study (study 3101) [10]. Plerixafor + G-CSF was shown to significantly increase the proportion of patients

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achieving optimal ($\geq 5 \times 10^6$) CD34+ stem cell yields for ASCT in fewer apheresis days, compared with placebo + G-CSF [10]. Additionally, plerixafor + G-CSF in compassionate-use protocols was shown to effectively salvage patients with NHL who failed to mobilize peripheral blood stem cells after cytokines + chemotherapy [4,5,15,16]. Similarly, other published studies of plerixafor in combination with chemotherapy + G-CSF in patients with NHL or multiple myeloma have shown the tolerability and preliminary efficacy of such a regimen in augmenting peripheral blood CD34+ cell count and subsequent HSC collection [17-19].

Current guidelines acknowledge the potential impact of plerixafor on stem cell collection strategies, but debate over its optimal use remains, as outlined in a position paper on multiple myeloma [20]. The relatively large database from the plerixafor licensure study [10] provides information to assess any benefit for NHL patients with various levels of peripheral blood CD34+ cells/μL (<5, 5 to 9, 10 to 14, 15 to 19, or ≥20 cells/μL) after 4 days of G-CSF. The post hoc analyses presented here were conducted to assess the change in peripheral blood CD34+ cells/μL after addition of plerixafor or placebo on day 4 for apheresis start on day 5 and the subsequent effect on the total number of cells collected during apheresis and the ability of patients to proceed to transplantation. The potential limitation of data is that the study peripheral blood CD34+ cells/μL value was from a central laboratory, whereas the values used for decisions at the site were those of a local study site laboratory. Even so, these data may provide information about which patients benefit the most from plerixafor when G-CSF mobilization is used for NHL patients.

METHODS

Study Design

Post hoc analyses of patients enrolled in a phase III, randomized, double-blind, placebo-controlled study were performed to evaluate the safety and efficacy of plerixafor (.24 mg/kg s.c.) + G-CSF (10 μg/kg/day s.c.) versus placebo + G-CSF in mobilizing CD34+ cells in patients with NHL [10]. Patients were stratified by threshold levels of peripheral blood CD34+ cells: <5, 5 to 9, 10 to 14, 15 to 19, or ≥20 CD34+ cells/μL, as measured on the morning of day 4, before the first plerixafor/placebo dose. The increase in peripheral blood CD34+ cells on day 5, the apheresis yields, the number of patients proceeding to transplantation, time to engraftment, and graft durability were compared between the plerixafor and placebo groups for patients with different thresholds of peripheral blood CD34+ cells/μL.

Patient Eligibility

Patient eligibility followed guidelines of the previously published 3101 study [10]. Key inclusion criteria were as follows: first or second complete or partial response to prior therapy, last cycle of chemotherapy completed ≥4 weeks before enrollment, Eastern Cooperative Oncology Group performance score of 0 or 1, white blood cell count $>2.5 \times 10^9$ cells/L, absolute neutrophil count $>1.5 \times 10^9$ cells/L, platelet count $>100 \times 10^9$ cells/L, serum creatinine ≤2.2 mg/dL, and liver function tests <2.5 × upper limit of normal. Patients were not eligible if they had failed previous stem cell collection attempts, had prior stem cell transplantation, had received G-CSF within 14 days of the first dose of G-CSF on study, had >20% bone marrow involvement, or had received prior radioimmunotherapy. Patients who had their peripheral blood CD34+ cell counts measured on day 4, before apheresis, were included in these post hoc analyses [10].

Mobilization and Transplantation

Patients received G-CSF (10 μg/kg) s.c. daily for up to 8 days, given in the morning following the protocol-directed timing of administration. Starting on the evening of day 4 and continuing daily for up to 4 days, patients received either plerixafor (.24 mg/kg) or placebo s.c. Starting on day 5, patients began daily apheresis (3.0 blood volume ± 10%) for up to 4 days or until sufficient CD34+ cells were collected ($\geq 5 \times 10^6$ cells/kg). Within 5 weeks of last apheresis, patients received high-dose chemotherapy and underwent transplantation using collected CD34+ cells according to local practice guidelines. Patients who failed to collect either $\geq .8 \times 10^6$ CD34+ cells/kg after 2 days of apheresis or $\geq 2 \times 10^6$ CD34+ cells/kg after 4 days of apheresis were eligible to enter an open-label rescue protocol as described previously and are included in the analysis [10].

Determination of Hematologic Parameters for Endpoint Analysis

Peripheral blood CD34+ cell count was measured within 30 minutes before G-CSF administration on the morning of day 4 (before plerixafor/placebo treatment) and 10 to 11 hours after study drug treatment on the morning of day 5. Enumeration of CD34+ cells in peripheral blood and apheresis products was done by fluorescent activated cell sorter analysis at a local laboratory and a central laboratory (Esoterix, Inc., Austin, TX). The local laboratory values were used for all clinical decisions. Efficacy endpoints were calculated using the percentage of CD34+ cells determined by the central laboratory applied to the white blood cell count from the local laboratory. Neutrophil engraftment was defined as neutrophil count $\geq .5 \times 10^9$/L for 3 days or $\geq 1.0 \times 10^9$/L for 1 day. Platelet engraftment was defined as platelet count $\geq 20 \times 10^9$/L without a transfusion for the preceding 7 days.

Statistical Analysis

For continuous outcomes, *P* values were calculated using Wilcoxon rank sum test. For dichotomous outcomes, *P* values were calculated using chi-square test. $P < .05$ was considered statistically significant, and all analyses were performed using SAS version 8.2 or above (SAS Institute., Cary, NC).

RESULTS

Patients

A total of 298 patients were enrolled in the 3101 study and randomized to receive either plerixafor + G-CSF (n = 150) or placebo + G-CSF (n = 148) [10]. Day 4 peripheral blood CD34+ cell counts were available for 132 patients (88.0%) in the plerixafor group and for 124 patients (83.8%) in the placebo group. Patients were stratified by threshold levels of peripheral blood CD34+ cells: <5, 5 to 9, 10 to 14, 15 to 19, or ≥20 CD34+ cells/μL. Baseline characteristics and patient demographics, by threshold group, are presented in Table 1, including age, median time from diagnosis to progression, median time from most recent progression to randomization, and prior radiotherapy, and were not statistically different.

Efficacy

Peripheral blood CD34+ cells

Comparing plerixafor + G-CSF–treated patients with placebo + G-CSF–treated patients, the median absolute peripheral blood CD34+ cells/μL on day 4 were not significantly different between the 2 treatment arms for any of the 5 peripheral blood threshold groups (Table 2). On day 5, however, the median absolute number of circulating peripheral blood CD34+ cells/μL in the plerixafor-treated group were significantly greater compared with the placebo-treated patients for all threshold groups (<5 cells/μL group: 14.3 versus 3.6 cells/μL; 5 to 9 cells/μL group: 36.6 versus 11.2 cells/μL; 10 to 14 cells/μL group: 57.8 versus 18.5 cells/μL; 15 to 19 cells/μL group: 80.3 versus 23 cells/μL; ≥20 cells/μL group: 113.4 versus 42 cells/μL; $P < .001$ for all plerixafor versus placebo comparisons in all threshold groups) (Table 2).

CD34+ cell yields

During the first mobilization period, the peripheral blood stem cell collection yield was more than doubled for the plerixafor groups in all cases when the peripheral blood CD34+ cells/μL value was ≤15 (Table 2). The yield was higher for all 5 plerixafor groups. In the 3 combined groups with ≤15 peripheral blood CD34 cells/μL on day 4, only 12 of 93