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A Randomized Controlled Trial to Compare Once- versus Twice-Daily Filgrastim for Mobilization of Peripheral Blood Stem Cells from Healthy Donors

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ABSTRACT

Although the mobilization of peripheral blood stem cells from normal donors using granulocyte colony-stimulating factor is widely used, the ideal method for the administration of filgrastim has not been determined. Therefore, we compared the efficacy of peripheral blood stem cell mobilization on day 4 of filgrastim between once-daily (group O) and twice-daily (group T) administration of filgrastim at 400 μg/m^2/d. In all, 38 and 34 donors were randomly assigned to groups O and T, respectively. The number of CD34$^+$ cells collected on day 4 was not significantly different (1.74 × 10^6 cells/kg in group O and 2.08 × 10^6 cells/kg in group T, $P = .37$). The incidence and severity of adverse events were similar in the two groups. The baseline white blood cell count was the strongest predictor of poor mobilization. Donor age, sex, and serum concentrations of several cytokines did not significantly affect the CD34$^+$ cell yield. In conclusion, once-daily administration of filgrastim at 400 μg/m^2/d appeared to be appropriate for the mobilization of CD34$^+$ cells in normal donors when apheresis is planned on day 4 of filgrastim. Selection of a donor with a steady-state white blood cell count of 5.0 × 10^9/L or more may lead to a lower incidence of poor mobilization.

KEY WORDS

Peripheral blood stem cell transplantation • Mobilization • Granulocyte colony-stimulating factor • Filgrastim • Randomized controlled trial

INTRODUCTION

Peripheral blood stem cell (PBSC) graft is widely used for both autologous and allogeneic transplantation and produces faster neutrophil recovery than bone marrow (BM) cells [1]. A recent meta-analysis showed that allogeneic PBSC transplantation is associated with a decreased relapse rate and better survival in patients with late-stage hematologic malignancies compared with allogeneic BM transplantation, although it is also associated with a higher incidence of extensive chronic graft-versus-host disease [2]. As for donors, PBSC and BM donors experienced similar levels of discomfort, but the symptoms were resolved sooner in PBSC donors [3].

Granulocyte colony-stimulating factor (G-CSF) is the most widely used cytokine for PBSC mobilization.

However, the ideal method for PBSC mobilization has not been determined. A dose-response relationship between G-CSF and the number of collected $CD34^+$ cells has been shown in healthy donors and patients with cancer [4-7]. The European Group for Blood and Marrow Transplantation recommended the administration of G-CSF at 10 μg/kg/d for healthy PBSC donors [8]. Although most centers administer G-CSF once daily, others recommended the administration of G-CSF in two divided doses at a 12-hour interval [9,10]. In a retrospective study by Kröger et al. [10], more $CD34^+$ cells were collected with twice-daily (2×5 μg/kg/d) filgrastim than with once-daily (1×10 μg/kg/d) filgrastim. On the other hand, Anderlini et al. [11] showed that there was no difference in the efficacy of PBSC mobilization between the two methods. The only prospective randomized controlled trial showed that twice-daily administration was superior to once-daily administration in mobilizing $CD34^+$ cells on day 5 of G-CSF administration [12]. However, it is a common practice to start apheresis on day 4 to reduce the cost of G-CSF. Therefore, in this multicenter, open-labeled, randomized controlled trial, we intended to compare the efficacy of PBSC mobilization on day 4 of filgrastim, the frequency and severity of adverse events, and medical costs between once-daily and twice-daily administration of filgrastim. In addition, we prospectively evaluated the impact of potential confounding factors on $CD34^+$ cell yield, including serum levels of several cytokines.

DONORS AND METHOD

Donor Selection

Healthy PBSC donors aged 16 to 65 years were enrolled in this study. Donors with any organ dysfunction were excluded. This protocol was approved by each institutional review board and written informed consent was obtained from each donor.

Assignment, Mobilization, and Apheresis

Donors were randomly assigned to receive filgrastim either at 400 μg/m^2 once daily (group O) or at 200 μg/m^2 twice daily (group T). Assignment was stratified by the institute. Donors were hospitalized before filgrastim administration. Subcutaneous injection of filgrastim was started in the evening for group O, and in the morning for group T, to make the interval from the last filgrastim administration to the beginning of apheresis similar in both groups. The first apheresis was performed on the morning of day 4. When the number of collected $CD34^+$ cells per recipient body weight did not reach the target for each recipient, filgrastim was administered in the evening and apheresis was repeated on the next day. Apheresis was performed using a continuous-flow cell separator (COBE Spectra, Gambro BCT, Lakewood, USA). A total blood volume of 150 to 200 mL/kg was processed per apheresis at a flow rate of 60 to 80 mL/min.

Monitoring of Adverse Events

Physical examination, and subjective and objective findings were recorded at entry, every day from the start to the end of filgrastim administration, and at a follow-up a few weeks later. The severity of pain was recorded twice daily by the donors using the visual analog scale during filgrastim administration [13]. The severity of adverse events was recorded according to the National Cancer Institute-Common Toxicity Criteria version 2.0. For the treatment of bone pain caused by filgrastim, oral acetaminophen at 400 mg, with at least a 4-hour interval, was prescribed.

Statistical Analysis

The primary end point was the number of $CD34^+$ cells per donor body weight collected on day 4. Secondary end points included bone pain, the dose of acetaminophen, platelet counts immediately after the first apheresis, and medical costs. Poor mobilizers were defined as those with a collection of less than 2.0×10^6 $CD34^+$ cells per donor body weight on day 4. We planned to include 40 donors, 20 in each group, because 37 and 17 donors in each group were required to detect a difference in the number of $CD34^+$ cells of 1×10^6/kg and 1.5×10^6/kg, respectively, with a 2-tailed alpha error of 5% and a beta error of 20%. The target number of included patients was increased to 72 patients at an interim analysis. Continuous variables were analyzed with Student *t* test or the Mann-Whitney *U* test and dichotomous variables were analyzed with Fisher exact test.

RESULTS

Donors and Assignments

Between April 2001 and May 2002, a total of 72 healthy donors from 4 institutes were enrolled into this study. In all, 38 and 34 donors were assigned to the groups O and T, respectively. Filgrastim was not administered in one donor of group O because of the recipient's condition, and this donor was excluded from the analysis. The two groups were equivalent with regard to sex ($P = .64$), age ($P = .12$), body weight ($P = .70$), and white blood cell (WBC) ($P = .35$) and platelet ($P = .44$) counts. Group O included 22 male and 15 female members with a median age of 43 years (range 17-62). Group T included 18 men and 16 women with a median age of 51 years (range 19-65). The mean body weight of the donors was 60.1 kg (SD 10.7) in group O and 59.2 kg (SD 8.7) in group T, respectively. The mean WBC and platelet counts were $6.2 \times$