1. ABSTRACT

Title

Incidence of Hematologic and Non-Hematologic Malignancies, Thrombotic Events, and Autoimmune Disorders in Unrelated Normal Donors Undergoing Bone Marrow Harvest Versus Peripheral Blood Stem Cell Mobilization with Recombinant Human Granulocyte Colony-Stimulating Factor (rHuG-CSF).

Keywords

Peripheral Blood Stem cells, filgrastim, transplant, unrelated donors, bone marrow

Rationale and Background

Hematopoietic stem cells are typically collected from unrelated donors in two ways: via unstimulated bone marrow (BM) harvest or by filgrastim-mobilized peripheral blood stem cell (PBSC) collection. Since the recognition that filgrastim (Neupogen®, Amgen, Thousand Oaks, CA) is a highly effective PBSC mobilizing agent, the proportion of filgrastim-mobilized PBSC collections in normal donors has continually increased (Lipton 2003). Data collected to date, however, have been primarily focused on short-term outcomes, for both unstimulated BM and filgrastim-mobilized PBSC donors and long-term adverse effects for the donor remain poorly characterized.

There is some evidence to suggest that granulocyte colony stimulating factor (G-CSF) may cause epigenetic changes in lymphocytes (Nagler et al. 2004; Hernandez et al. 2005), and if similar changes were to occur in myeloid hematopoietic progenitors, there could be an increased risk of hematological malignancies such as acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) or of alterations in immune tumor surveillance.

A causal association between filgrastim and the exacerbation of underlying autoimmune disease has not been confirmed, however, there have been literature reports of exacerbated underlying autoimmune disease following filgrastim administration for mobilization of PBSCs prior to autologous hematopoietic cell transplantation (HCT) and for treatment of neutropenia in patients with multiple sclerosis (MS) (Burt et al. 2001; Openshaw et al. 2000), systemic lupus erythematosus (SLE) (Euler et al. 1997; Vasiliu et al. 2006), rheumatoid arthritis (RA) (Snowden et al. 1998), and other immune-mediated vasculidities (Farhey et al. 1995; Iking-Konert et al. 2004).

Additionally, while an association between thrombosis and filgrastim has not been demonstrated, it has been reported with red blood cell growth factors (Filgrastim PBRER #36 dated 26 November 2015).

Research Question and Objectives

The hypothesis of this study was that the incidence of malignant, thrombotic, and autoimmune disorders after unrelated hematopoietic stem cell donation is similar between unstimulated BM and filgrastim-mobilized PBSC donors.

Primary objective was to describe the long-term incidence of malignant myeloid hematologic disorders (AML, MDS, CML, chronic myeloproliferic disorders) in donors who received and in those who did not receive filgrastim.

Secondary objectives were to:

- Describe the long-term incidence of malignant non-myeloid hematologic disorders (ALL, CLL, Hodgkin lymphoma, Non-Hodgkin lymphoma) in donors who received and in those who did not receive filgrastim.

- Describe the long-term incidence of non-hematologic malignant disorders in donors who received and in those who did not receive filgrastim.
- Describe the long-term incidence of thrombotic events in donors who received and in those who did not receive filgrastim.
- Describe the long-term incidence of autoimmune diseases in donors who received and in those who did not receive filgrastim.
- Assess the drop-out rate (lost to follow-up, withdrawal of consent) of long-term donor follow-up over time.

Study Design

This was an observational study of unstimulated BM and filgrastim-mobilized PBSC donors. The primary goal was to evaluate the hypothesis that the incidence of targeted malignant, thrombotic, and autoimmune disorders after unrelated hematopoietic stem cell donation are similar between unstimulated BM and filgrastim-mobilized PBSC donors. Donors underwent biennial surveys over approximately 10 years until study completion. Cases of targeted disorders were reviewed by the medical monitors to confirm the veracity of the report.

The study population was comprised of unrelated donors from the United States whose unstimulated BM or filgrastim-mobilized PBSC donation was facilitated by the National Marrow Donor Program (NMDP) between 01 July 1999 and approximately 5 years post study activation (this also included those donors who receive at least one injection of filgrastim during this timeframe but do not actually proceed to collection). It was anticipated that the study would enroll up to 10 000 unstimulated BM donors and 20 000 filgrastim-mobilized PBSC donors.

Setting

The first follow-up assessment for donors who donated prior to this study occurred either in the first or second year of the study near the anniversary date of their donation and biennially thereafter for approximately 10 years post study activation. Donors who donated after the study was implemented underwent their first assessment near the first anniversary of their donation and biennially thereafter until approximately 10 years.

All donor follow-up assessments were administered by trained staff members of the Center for International Blood and Marrow Transplant Research (CIBMTR) Survey Research Group (SRG) and Donor Center staff using a standardized telephone interview script Language Line services were utilized for non-English speaking donors who were eligible for the study. Donors were asked if they have developed any of the targeted malignant, thrombotic, or autoimmune disorders since the last follow-up assessment.

Subjects and Study Size, Including Dropouts

A total of 32 634 donors were contacted and of those, 21 833 were enrolled in the study. Of the subjects enrolled, 21 794 were eligible for analysis. Subsequently, subjects with missing or incomplete data were removed leaving 21 653 donors who were included in the final analyses.

Variables and Data Sources

Baseline patient demographics and clinical characteristics (i.e. age, sex, time to follow-up, etc.) were described. Age and year of first G-CSF exposure was defined. Time to myeloid follow-ups and myeloid outcomes were described. The full description of variables is provided in Section 9.4.

Donors reported diagnosis with a Malignancy, Autoimmune, or Thrombotic (MAT) event through follow-up calls with their donor center or the SRG. Donor reported MAT events were recorded by the donor center or the SRG on forms in the FormsNet3 system. The full description of variables is provided in Section 9.5.

Results

There were 14 530 donors that were exposed to filgrastim (PBSC donors) and 7123 donors that were not exposed to filgrastim (BM donors). Incidence rate of malignant myeloid hematologic disorders (AML, MDS, CML, chronic myeloproliferative disorders) in normal unrelated donors who underwent PBSC mobilization with filgrastim was 2.53 and in those who underwent BM harvest without filgrastim was 4.13 per 100 000 person years, resulting in an incidence rate ratio of 0.61 (95% CI: 0.12, 3.03; p-value: 0.55). Incidence rate of malignant non-myeloid hematologic disorders (ALL, CLL, Hodgkin lymphoma, Non-Hodgkin lymphoma) in normal unrelated donors who underwent PBSC mobilization with filgrastim was 14.33 and in those who underwent BM harvest without filgrastim was 13.78 per 100 000 person years, resulting in an incidence rate ratio of 1.04 (0.48, 2.27; p-value: 0.92). Incidence rate of non-hematologic malignancies, in normal unrelated donors who underwent PBSC mobilization with filgrastim was 460.36 and in those who underwent BM harvest without filgrastim was 521.59 per 100 000 person years resulting in an incidence rate ratio of 0.88 (0.77, 1.00; p-value: 0.05). Incidence rate of thrombotic events (venous and arterial) in normal unrelated donors who underwent PBSC mobilization with filgrastim was 132.23 and in those who underwent BM harvest without filgrastim was 131.63 per 100 000 person years resulting in an incidence rate ratio of 1.01 (0.78 , 1.30; p-value: 0.95). Incidence rate of autoimmune diseases (RA, psoriatic arthritis, SLE, scleroderma, vasculidities, MS and Immune thrombocytopenic purpura) in normal unrelated donors who underwent PBSC mobilization with filgrastim was 385.19 and in those who underwent BM harvest without filgrastim was 367.62 per 100 000 person years resulting in an incidence rate ratio of 1.03 (0.89, 1.21; p-value: 0.66). Overall, the incidence and incidence rate ratio of malignant, thrombotic, and autoimmune disorders in filgrastim-mobilized PBSC donors were not significantly different than in unstimulated BM donors.

Discussion

Allogeneic hematopoietic cell transplantation (alloHCT) is a life-saving procedure for the treatment of a variety of devastating diseases. The NMDP was founded in 1987 to facilitate alloHCT from anonymous unrelated donors. Hematopoietic stem cells are typically collected from unrelated donors in two ways: via unstimulated BM harvest or by filgrastim-mobilized PBSC collection. For donors, the data collected to date has been primarily focused on short-term outcomes related to filgrastim. The goal of this study was to evaluate long-term outcomes in relation to malignancies, thrombotic events, and autoimmune disorders to understand if filgrastim causes an increase in these events. This was the first study that analyzed long-term effects of filgrastim on donors over a 10-year period, specifically at outcomes related to malignancy, thrombosis, and autoimmune disorders which had all been theoretical risks. The incidences rate ratios of malignant, thrombotic, and autoimmune disorders after unrelated hematopoietic stem cell donation were not significantly different between unstimulated BM donors and filgrastim-mobilized PBSC donors. Amgen believes that the current benefit/risk profile continues to support the use of filgrastim in the approved indications.

Marketing Authorization Holder

Amgen Europe B.V.

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