Adverse Events During Hematopoietic Stem Cell Infusion: Analysis of the Infusion Product

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Abstract

Stem cell transplantation is a treatment option for patients with various malignancies. However, a risk of adverse events might exist in the peritransplant period associated with the infusion itself. We studied the adverse events in 460 patients undergoing transplantation at the Northwestern University Robert H. Lurie Comprehensive Cancer Center. Of the 460 patients, 56.7% experienced adverse events, which were generally cardiopulmonary in nature.

Background: Stem cell transplantation is a treatment option for patients with cancer. However, a risk of adverse events might be associated with the infusion itself. An understanding of the types and grades of adverse events occurring during infusion and the patient and infusion characteristics that might be associated with these events could allow for interventions to minimize these complications. The risk factors associated with transplant-related adverse events are not well understood. **Materials and Methods:** We retrospectively analyzed the adverse events occurring within 1 hour after infusion in 460 patients with cancer undergoing stem cell transplantation at the Northwestern University Robert H. Lurie Comprehensive Cancer Center from January 1, 2008 and May 1, 2011. Of the 460 patients, 382 received autologous transplants and 78 allogeneic transplants. The incidence, types, and National Cancer Institute Common Terminology Criteria grade of toxicity for adverse events were noted (primary objective). Univariate analyses were performed to study which patient and infusion characteristics might be associated with the occurrence of adverse events (secondary objectives). **Results:** Of the 460 patients, 261 (56.7%) experienced adverse events (66.7% during allogeneic infusion and 54.7% during autologous infusion). Most events were cardiopulmonary. Univariate analysis of the infusion and patient characteristics revealed that a second transplant ($P = .005$) was associated with more adverse events for autologous transplant patients. For allogeneic transplant patients, a higher infusion red blood cell volume ($P = .01$) was associated with more adverse events. **Conclusion:** Adverse events are common during stem cell infusion and are generally cardiopulmonary.

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Introduction

Stem cell transplantation has emerged as a viable treatment option for patients with a variety of malignancies. However, adverse events can occur in the peritransplant period, associated with the infusion itself. The exact incidence of these types of events is not clear; however, recent studies have suggested that both cardiovascular and noncardiovascular events can occur in transplant recipients.[1-3] The cause of the adverse events occurring during stem

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cell infusion is also not known. In the past, these events were attributed solely to the cryoprotectant used in cell preparation, often dimethyl sulfoxide (DMSO).[4] Although the cryoprotectant used might contribute to the development of these events, the persistence of these events in the setting of DMSO depletion[5,6] suggests the involvement of other factors. These other factors could include infusion characteristics such as cell contamination and infusion time.[2-9] The factors that might contribute to the development of adverse events during infusion and the types and incidence of adverse events occurring during stem cell infusion are not well understood.

At the Northwestern University Robert H. Lurie Comprehensive Cancer Center, we have noted adverse events occurring in patients receiving stem cell infusions. Five of these events were formally reported to our Stem Cell Quality Assurance Facility. However, we questioned whether more than this number of events could have occurred, because some investigators have suggested that adverse events might occur frequently.[3,10] Our transplant population provided a large sample size (n = 460) to study adverse events in both an autologous and an allogeneic transplanted population. We questioned which patient and infusion characteristics might be associated with these events to identify potentially modifiable factors to prevent adverse events. Previous studies have not well discerned the risk factors that might be associated with transplant-related adverse events.

Materials and Methods

Study Design and Patient Selection

We performed a retrospective analysis of 460 patients with cancer who had undergone stem cell transplantation at the Northwestern University Robert H. Lurie Comprehensive Cancer Center from January 1, 2008 to May 1, 2011. The Northwestern University institutional review board approved the study. We included patients receiving allogeneic and patients receiving autologous peripheral blood stem cell transplants. Patients who had undergone transplantation more than once were also included in our study. Detailed patient characteristics were collected from the medical records at Northwestern Memorial Hospital, including patient age, gender, ethnicity, body weight, type of malignancy, number of previous therapies, number of transplants, and transplant type (allogeneic or autologous). Detailed stem cell infusion characteristics were collected from the medical records at the Northwestern University Stem Cell Processing Facility, including the total volume infused, DMSO volume, red blood cell volume, and granulocyte volume. The infusion time (in minutes) was also collected from the Northwestern medical records. The infusion time was defined as the actual time of infusing the stem cells and did not include the time between the bags of stem cells. The rate of infusion (mL/min) was then determined as the total volume infused over the infusion time. The primary objectives were the type, number, and National Cancer Institute Common Terminology Criteria (NCI CTC) grade of adverse events occurring during stem cell infusion (from the start of the infusion to 1 hour after infusion).

Stem Cell Infusion Preparation

The stem cells were mobilized using granulocyte colony-stimulating factor, in conjunction with chemotherapy for autologous transplants, and collected using apheresis. After cell quantification, the cells were preserved in 10% DMSO using a controlled rate freezer and stored in a liquid nitrogen freezer at −150°C to −196°C. Before infusion, the stem cells were thawed in a 37°C water bath and then infused cold, after premedicating all the patients with prednisone and diphenhydramine.

Adverse Event Determination

The patient medical records at transplantation were retrospectively evaluated to identify any adverse events. An adverse event was defined as any reaction occurring in a patient during stem cell infusion to ≤ 1 hour after transplant that had been documented prospectively at the time of the infusion in the medical record as a narrative note. Patient vital signs during the infusion and ≤ 1 hour after transplantation were evaluated retrospectively to identify the adverse changes, including hypotension (systolic pressure < 90 mm Hg if previously normotensive or a decrease in systolic pressure of 20 mm Hg), hypertension ($> 150/100$ mm Hg if previously normotensive or an increase > 20 mm Hg in diastolic blood pressure), bradycardia (heart rate < 60 bpm), tachycardia (heart rate > 100 bpm), arrhythmia, hypoxia (oxygen saturation $< 95\%$), tachypnea (respiratory rate > 20), fever (temperature $> 38°C$), and hypothermia (temperature $< 35°C$) defined according to the NCI CTC criteria. These vital signs were prospectively collected at the time of infusion at 15-minute intervals and documented in the medical record. All adverse reactions were graded according to the NCI CTC criteria.

Statistical Analysis

Univariate analyses using Fisher's exact test for categorical variables and the Wilcoxon rank sum test for continuous variables were performed to determine the differences between the grades and types of adverse events between the allogeneic and autologous groups and to study whether any of the patient and stem cell infusion characteristics were associated with adverse events (secondary objectives). For all statistical analyses, $P < .05$ was considered statistically significant.

Results

We studied 460 patients who had received stem cell transplants (peripheral blood) at the Northwestern University Robert H. Lurie Comprehensive Cancer Center from January 1, 2008 to May 1, 2011. Of these patients, 78 (17.0%) received allogeneic transplants and 382 (83.0%) autologous transplants. The baseline characteristics of the patients included in the present study stratified by transplant type are listed in Table 1. For the patients who received allogeneic transplants, the median age was 55 years (range, 51-62 years), and 64.1% were men. Of the patients receiving allogeneic transplants, 55.1% had leukemia (acute myelogenous leukemia, acute lymphocytic leukemia, chronic myelogenous leukemia, or myelodysplastic syndrome), 26.9% had lymphoma (non-Hodgkin's lymphoma, Hodgkin's lymphoma, or chronic lymphocytic leukemia), and 17.9% had a plasma cell dyscrasia (multiple myeloma or amyloid).

For the patients who received autologous transplants, the median age was 56 years (range, 29-76 years), and 66.2% were men. Of the patients receiving autologous transplants, 75.9% had a plasma cell dyscrasia (multiple myeloma or amyloid) and 22.3% had lymphoma