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Increased Bacterial Infections after Transfusion of Leukoreduced Non-Irradiated Blood Products in Recipients of Allogeneic Stem Cell Transplants after Reduced-Intensity Conditioning

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A B S T R A C T

Blood components transfused to hematopoietic stem cell transplant (HSCT) recipients are irradiated to prevent transfusion-associated graft-versus-host disease (TA-GVHD). The effect of transfusing non-irradiated blood products in HSCT outcome, including incidence of transplant complications, bacterial infections, acute and chronic GVHD presentation, and characteristics, has not been documented. Clinical records as well as blood bank and electronic databases of HSCT patients grafted after reduced-intensity conditioning who received irradiated versus non-irradiated blood products, after blood irradiation became unavailable at our center, were scrutinized for transplant outcome, clinical evolution, engraftment characteristics including days to neutrophil and platelet recovery, acute and chronic GVHD, rate and type of infections, and additional transplant-related comorbidities. All transfused blood products were leukoreduced. A total of 156 HSCT recipients was studied, 73 received irradiated and 83 non-irradiated blood components. Bacterial infections were significantly more frequent in patients transfused with non-irradiated blood products, $P = .04$. Clinically relevant increased rates of fever and neutropenia and mucositis were also documented in these patients. No cases of TA-GVHD occurred. Classical GVHD developed in 37 patients (50.7%) who received irradiated blood products and 36 (43.9%) who received non-irradiated blood products, $P = .42$. Acute GVHD developed in 28 patients (38.4%) in the blood-irradiated and 33 patients (39.8%) in the non-irradiation group, $P = .87$. The 2-year GVHD-free survival rate was 40% in the irradiated versus 40.6% in the non-irradiation group, $P = .071$. Increased bacterial infections were found in HSCT recipients transfused with non-irradiated blood products, which ideally must always be irradiated.

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INTRODUCTION

A considerable body of clinical, basic science and animal model data have demonstrated that blood transfusions have significant effects on the immune system, including dysregulation of inflammation and innate immunity leading to susceptibility to microbial infection and down-regulation of cellular (T and natural killer cells) host defenses against tumors [1]. More recently, severe effects attributable to allogeneic blood transfusion by pro-inflammatory mechanisms, including multiple-organ failure and increased mortality, have been related to the transfusion-related immunomodulation (TRIM) effect [2]. Different mechanisms have been implicated in TRIM pathogenesis, including the presence of allogeneic mononuclear cells, WBC-derived soluble mediators, and soluble HLA peptides circulating in allogeneic plasma [3].

Although the immunomodulatory effects of allogeneic blood transfusion are not completely identified, there is sufficient evidence that both humoral and cellular immunity are altered [4]. In this respect, we previously showed that blood transfusion is associated to decreased overall survival in children with acute lymphoblastic leukemia, probably through the TRIM effect [5].

Transfusion-associated graft-versus-host disease (TA-GVHD) is a rare catastrophic complication seen in hematopoietic transplant recipients, resulting from the patient's

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incapacity to recognize and eliminate allogeneic T cells in the context of variable HLA similarity. Other susceptible patients include those who are immunosuppressed, including fetuses, very premature neonates, and patients who have an increased likelihood of possessing 1 HLA haplotype for which the blood component donor is homozygous [6]. Transfusion of irradiated blood components to prevent TA-GVHD is a time-honored standard of care in the support of bone marrow and hematoprogenitor transplant recipients [7]. Irradiation eliminates the proliferative capacity of T cells present in blood products [8]. T cell proliferation is halted by a 2500-cGy radiation dose, a standard recommended by the US Food and Drug Administration for all blood products [9]. Classical GVHD, on the other hand, is commonly observed after allogeneic hematopoietic stem cell transplant (allo-HSCT) but rarely after transfusion or solid organ transplantation [10]. GVHD is a major cause of morbidity and mortality, affecting 40% to 60% of recipients of an allo-HSCT, accounting for 15% of deaths after this intervention [11]. TA-GVHD differs from the classical form by its earlier presentation and involvement of the bone marrow, commonly leading to pancytopenia.

HSCT at our center has been performed for the past 20 years. Since the year 2000 we almost exclusively carry out hematopoietic grafting, using a reduced-intensity conditioning (RIC) regimen in an ambulatory setting developed at our and other centers [12,13]. RIC regimens cause less damage and less allo-GVHD [14] than total irradiation regimens. Because of budget restrictions at our public institution, no blood irradiator is available, leading us to make the decision to halt irradiation of blood products intended for HSCT patients after 2010. Before this year a linear accelerator at the oncology department, no longer available, was used for blood irradiation.

No studies documenting the effects of transfusing non-irradiated leukoreduced blood components to recipients of an allogeneic HSCT have been published. Mononuclear cells in non-irradiated blood products can modulate the immune status of the recipient through several mechanisms [3], with the potential to alter the dynamics of transplant recovery. We investigated differences in relevant aspects of transplant outcome, including days to neutrophil and platelet engraftment, infections, mucositis, and other complications as well as possible cases of TA-GVHD and rates of acute and chronic GVHD, between patients receiving irradiated versus non-irradiated leukoreduced blood components.

METHODS

A retrospective study was performed at the Hematology Department, Internal Medicine Division of the "Dr. José Eleuterio Gonzalez" University Hospital of the School of Medicine of the Autonomous University of Nuevo Leon, in Monterrey, México. The Ethics and Human Research Committees at the institution approved the study protocol.

We reviewed the clinical records of 156 hematology patients transplanted at our center who subsequently received transfusion of leukoreduced blood components from 2008 through 2013. Transfusion of products obtained from blood donated by relatives was avoided. Mobilized peripheral blood stem cells from HLA-identical sibling donors were used in all cases. For the purposes of the study, patients were divided in group 1 (n = 73), who received irradiated leukoreduced blood components, and group 2 (n = 83), those transfused with non-irradiated leukoreduced blood products after 2010.

Information regarding the source of the hematopoietic stem cells and time to recovery of the absolute neutrophil count $\geq .5 \times 10^9$/L and to a platelet count $\geq 20 \times 10^9$/L was obtained from the clinical records and electronic databases. The number, type, and frequency of blood products prepared and administered according to standard procedures were documented directly from the clinical files and the blood bank database. Leukoreduction was carried out by microfiltration at the bedside using Sepacell PLS-10A filters (Fenwall Inc., Lake Zurich, IL) following the instructions provided by the manufacturer. This leukoreduction method was used along the study for both groups. Standard bacterial cultures and serological tests were done for identifying etiological agents in all patients with suspected infection.

A RIC regimen, which causes less damage and less allo-GVHD [14] than total irradiation regimens, has been administered in an ambulatory basis at our center since the year 2000 [12]. Briefly, it consists of a scheme with dosage based on ideal weight, which includes busulfan 4 mg/kg p.o on days −6 and −5; cyclophosphamide 350 mg/m^2 once daily i.v. on days −4, −3, and −2; fludarabine 30 mg/m^2 i.v. once daily on days −4, −3, and −2; cyclosporine A (CyA) 5 mg/kg p.o. starting on day −1; and methotrexate 5 mg/m^2 i.v. on days +1, +3, +5, and +11. CyA is continued through to day 180, with adjustments to obtain serum CyA levels of 150 to 275 ng/mL, and then tapered over 30 to 60 days [12]. In patients with aplastic anemia, busulfan was not used and the cyclophosphamide dose was doubled from days −4 to −1. If GVHD developed, CyA was tapered over longer periods. Ondansetron 1 mg i.v. every hour over 4 hours after chemotherapy, an oral quinolone, and an azole were used in all patients until granulocytes were $>.5 \times 10^9$/L.

Donor lymphocyte infusions in allograft recipients were used if there was no evidence of GVHD 100 days after the transplant and if there was evidence of persisting or relapsed malignancy. Donors were stimulated with 10 μg/kg of granulocyte colony-stimulating factor s.c. for 5 days before CD34$^+$ cell automated collection [13]. CD34$^+$ cells at a dose $\geq 2.5 \times 10^6$/kg of body weight were infused on day 0. Afterward, patients were closely followed at the hematology transplant clinic to document time to neutrophil and platelet recovery to ≥500/μL and ≥20,000/μL, respectively.

Engraftment was also assessed by chimerism analysis by flow cytometry, and clinical follow-up was carried out on an outpatient basis. Transplants are performed as an outpatient procedure to make this modality of therapy financially viable and to reduce the risk of hospital-acquired post-transplant infections [12,13]. Diagnosis of acute and chronic GVHD was established based on previous guidelines [15,16].

Statistical Analysis

For data analysis, SPSS v.20.0 for MAC was used (IBM Corp., Armonk, NY). Descriptive analysis was performed, obtaining means and standard deviations or medians and ranges according to the variables distribution calculated with Kolmogorov-Smirnov. Fisher's test was used for 2 × 2 tables. Event-free survival was determined with the Kaplan-Meier method, calculating time, status, cumulative survival, and standard error with a 95% confidence interval (CI). Equality of data distribution was estimated with the log-rank test. A 2-sided $P = .05$ was considered statistically significant.

RESULTS

The general characteristics of the 156 patients as well as the type of blood product transfused, irradiated and non-irradiated, and number of blood products transfused are shown in Table 1. A secondary analysis regarding proportion of blood products transfused between groups was carried out, finding no statistical difference for either packed RBCs (.294) or platelet concentrates and single-donor platelet pheresis (.072) (Table 1).

Table 2 displays neutrophil and platelet recovery time (days). No case of TA-GVHD developed in the period of study in either group. Regarding differences in classical GVHD, it was found that 37 patients (50.7%) received irradiated blood components and 36 (43.9%) non-irradiated blood products, $P = .42$ (odds ratio [OR], 1.31; 95% CI, .68 to 2.47). Twenty-eight patients (38.4%) developed acute GVHD in the irradiated versus 33 (39.8%) in the non-irradiated blood components group, $P = .87$ (OR, .94; 95% CI, .49 to 1.79). Ten patients (13.7%) progressed from acute to chronic GVHD in the blood irradiation and 14 (16.9%) in the non-irradiation group, $P = .66$ (OR, .78; 95% CI, .32 to 1.88). Complete data are shown in Table 3.

Differences in morbidities between groups were assessed, and although no statistical differences were found, a higher clinical incidence in comorbidities was documented in the group of HSCT patients transfused with non-irradiated blood

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