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Effect of Pre-Transplant Red-cell Transfusion Events on Transplant Related Mortality and Overall Survival in Children with Leukemia Undergoing Hematopoietic Stem Cell Transplant

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Abstract

Background: Recent studies have shown that an elevated ferritin level prior to hematopoietic stem cell transplant (HSCT), serving as a surrogate marker of body iron load, is independently associated with transplant related mortality (TRM) and inferior overall survival (OS) in adult oncology patients.

Study Design and Methods: We performed a retrospective cohort study of 112 children with leukemia treated at our institution over a 10 year period, and compared TRM and OS after HSCT in those children with and without high red-blood cell (RBC) transfusions. Both groups were similar in regards to age, diagnoses, donor type (matched related, matched unrelated, mismatched related, mismatched unrelated), stem cell source (peripheral blood, umbilical cord, bone marrow), baseline liver, cardiac and renal function, and median follow-up time. However, more children in the low RBC transfusion event cohort had high Karnofsky/Lansky performance scores (83.5% vs 54.5%, p=0.001) and fewer had recurrent leukemia or other forms of advanced disease compared with the children more heavily transfused (41.8% vs 87.9%, p<0.0001).

Results: No association was observed between high RBC transfusion exposure and TRM. High RBC transfusion events were associated with lower OS at 5 years in univariate analysis (38% versus 61%, p=0.04); in multivariate analysis, this association was not significant (hazard ratio=1.3, 95% confidence interval 0.7-2.5).

Conclusion: Further studies in children are needed to investigate iron overload and HSCT outcomes.

Keywords: Transfusion; Leukemia, Stem cell transplantation

Abbreviations

RBC: Red Blood Cell; AML: Acute Myeloid Leukemia, ALL: Acute Lymphoblastic Leukemia; CML: Chronic Myelogenous Leukemia; CMML: Chronic Myelomonocytic Leukemia; JMML: Juvenile Myelomonocytic Leukemia; CMV: Cytomegalovirus

Introduction

The generation of hydroxyl radicals catalyzed by non-transferrin bound iron (NTBI) and subsequent tissue damage is responsible for the toxicity of iron overload [1]. In adults with hematologic malignancies, pre-transplantation transfusional iron overload, as measured by serum ferritin, is independently associated with transplant related mortality (TRM) and inferior overall survival (OS) following hematopoietic stem cell transplantation (HSCT) [2-6].

The only published study in pediatrics concluded that elevated ferritin (>1000 nanogram/milliliter [ng/mL]) due to pre-HSCT red-blood cell (RBC) transfusion events is independently predictive of TRM and inferior OS in Korean children with hematologic malignancies [7]. We aim to investigate the association between iron load, as measured by a surrogate marker, number of pre-transplantation RBC transfusions, and TRM and OS following HSCT in a heterogeneous group of pediatric patients with hematologic malignancies in the US.

Materials and Methods

We retrospectively reviewed the charts of 112 consecutive patients with leukemia who were treated with HSCT at a large tertiary pediatric center in Atlanta, GA between 1 January 2000 and 1 January 2010 for whom pre-transplantation RBC transfusions were known. Institutional Review Board approval was granted prior to data collection by Emory University and Children's Healthcare of Atlanta.

Definitions

TRM was defined as death resulting from any cause other than relapse by 180 days post HSCT. For OS, death from any cause was considered an event. The day of first HSCT was considered day 0, and only RBC transfusions given prior to day 0 were tabulated.

Early disease was defined as acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML) in first complete remission (CR), chronic myelogenous leukemia (CML) in first chronic phase (CP) or chronic myelomonocytic leukemia (CMML). Advanced disease was defined as ALL or AML in second or greater CR, CML in accelerated phase or blast phase or second or greater CP, primary induction failure of ALL or AML, biphenotypic leukemia and juvenile myelomonocytic leukemia (JMML).

RBC transfusion events were used as a surrogate marker of iron load because of their significant correlation with liver iron concentration (LIC), the gold standard measurement of iron load, as well as convenience of measurement [8-10]. High (>12 RBC events) and low (≤ 12 RBC events) transfusion groups were separated based on historical data in thalassemia patients showing an association between adverse clinical outcomes and serial transfusions of approximately 100 mL of RBCs/kilogram (kg) of body weight (the equivalent of 7–10 RBC transfusions in children) [11] Packed RBC transfusions given on the same day were considered one event.

Statistical analysis

The clinical characteristics and baseline organ function of patients in the high and low transfusion groups were compared using the student's t-test for continuous variables and $\chi 2$ or Fisher's exact test as appropriate for categorical variables. TRM for both groups was estimated using cumulative incidence curves taking into account the competing risk of relapse, and compared with the Gray's test [12]. OS for each group was estimated from day 0 of HSCT using Kaplan-Meier curves, and compared with the log-rank statistic. Multivariate analysis was performed using Cox proportional hazards models for both OS and TRM taking into account competing risk. Analyses were performed using SAS software, version 9.2 (SAS Institute, Inc., Cary, NC, USA) and R software, version 2.12.0, 'cmprsk' package. A cutoff level of $p \leq 0.05$ (two-sided) was used for assessing statistical significance.

Results

Patient, disease and transplant characteristics

Median RBC events for all patients were 9 (interquartile range 6 -15). Patients exposed to high RBC transfusion events comprised 29% of the sample. Table 1 provides detailed clinical characteristics of the patients in each cohort.

High and low RBC transfusion event groups were well matched in regards to age, gender and race. The most common diagnosis in each group was AML (57.6% in the high RBC exposure group and 41.8% in the low RBC exposure group), with no significant differences in diagnoses between the two groups. There were no significant differences in donor type or hematopoietic stem cell source. Over 95% of children had full intensity conditioning chemotherapy treatment prior to HSCT.

Characteristic	Patients with high RBC transfusion (n=33)	Patients with low RBC transfusion (n=79)	P-value
Median age (years) (range)	10.1 (1.4, 18.1)	10.2 (0.3, 18.9)	0.9
Gender (male %)	17 (51.5)	43 (54.4)	0.8
Race (%) Caucasian African American Hispanic Asian Other	19 (57.6) 9 (27.3) 4 (12.1) 1 (3.0) 0 (0)	39 (49.3) 26 (32.9) 9 (11.4) 2 (2.5) 3 (3.8)	1.0
Disease (%) AML ALL Biphenotypic CML CMML JMML	19 (57.6) 12 (36.4) 1 (3) 0 (0) 0 (0) 1 (3)	33 (41.8) 28 (35.4) 7 (8.9) 7 (8.9) 1 (1.3) 3 (3.8)	0.3
Donor type (%) Auto Matched related Mismatched related Matched unrelated Mismatched unrelated	1 (3) 8 (24.2) 5 (15.2) 6 (18.2) 13 (39.4)	1 (1.3) 37 (46.8) 8 (10.1) 14 (17.7) 19 (24.1)	0.1
Stem cell source (%) Peripheral blood Bone marrow Cord Double cord	2 (6.1) 19 (57.5) 10 (30.3) 2 (6.1)	3 (3.8) 57 (72.2) 15 (19) 4 (5)	0.4
Performance score (%) <90 ≥90	15 (45.5) 18 (54.5)	13 (16.5) 66 (83.5)	0.001
Disease status (%) Early Advanced	4 (12.1) 29 (87.9)	46 (58.2) 33 (41.8)	<0.0001
CMV status Recipient +/Donor– Recipient +/Donor+ Recipient -/Donor + Recipient -/Donor -	11 (33.4) 14 (42.4) 4 (12.1) 4 (12.1)	32 (40.5) 25 (31.7) 8 (10.1) 14 (17.7)	0.7
Median follow-up of survivors (months) (range)	44.3 (13.7, 100.8)	28.1 (4.7, 83.4)	0.1

Table 1: Baseline characteristics of study population.

In addition, liver function (measured by albumin, alanine aminotransferase, aspartate aminotransferase and bilirubin), cardiac function (measured by ejection and shortening fractions) and renal function (measured by glomerular filtration rate) were normal in over 95% of patients (data not shown). However, more children in the low

RBC transfusion event cohort had Karnofsky/Lansky performance status scores ≥ 90 (83.5% in low versus [vs] 54.5% in high RBC group, p=0.001) and fewer had recurrent leukemia or other forms of advanced disease compared with the children more heavily transfused (41.8% vs 87.9% respectively, p<0.0001).

Impact of High RBC transfusion on TRM

The cumulative incidence of TRM for children with high RBC event was 21% and for children with low RBC event was 15% (p=0.5) (Figure 1A).

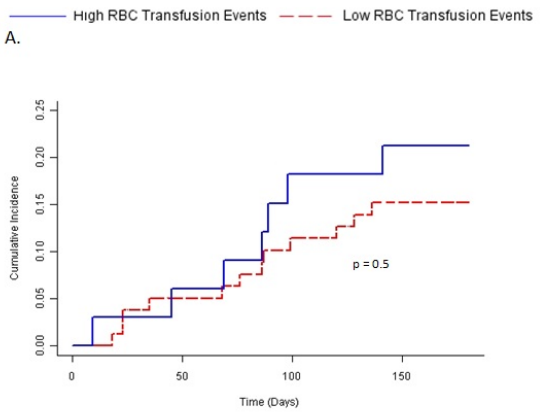

Figure 1A: Outcome of patients stratified by pre-transplantation red-blood cell (RBC) events (Transplant related mortality)

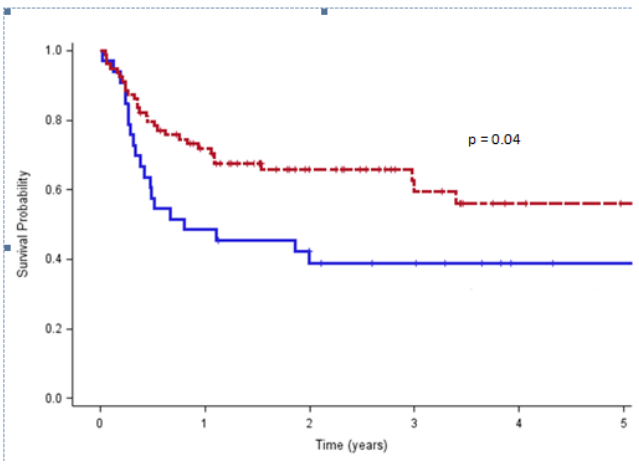

Figure 1B: Outcome of patients stratified by pre-transplantation red-blood cell (RBC) events. (Overall survival)

In multivariate analysis controlling for age, stage of disease, transfusion events, type of donor and Karnofksy/Lansky performance score status, only the use of alternative donor was associated with TRM (hazard ratio [HR]=5.7, 95% confidence interval [CI] 1.3-25.6, p=0.02).

Impact of High RBC transfusion on OS

The 112 patients were followed for a median of 1.4 years (range 9 days – 8.3 years). The estimated 5-year OS rate for the high and low transfusion groups was 38% and 61%, respectively (p=0.04) (Figure 1B).

In multivariate analysis, high transfusion exposure was not associated with mortality after adjusting for age, stage of disease, transfusion events, type of donor, and Karnofsky/Lansky performance score (HR=1.3, 95% CI 0.7-2.5). Only high Karnofsky/Lansky performance score decreased 5-year mortality risk (HR=0.5, 95% CI 0.3-0.9, p=0.02).

Discussion

Pre-transplantation transfusional iron overload, as indirectly assessed by serum ferritin, has been found to be independently associated with TRM and inferior OS following HSCT in adults and children with hematologic malignancies [2-7]. However, in this study, iron overload as surrogately measured by high RBC transfusion events prior to transplantation was not associated with TRM at 180 days post-HSCT or inferior 5-year OS in children with leukemia treated at our institution. This study is, to date, the only investigation in a heterogeneous cohort of children with leukemia treated with HSCT in the US examining this potential association.

RBCs contain elemental iron, and any excess transfused iron is either stored as ferritin or causes damage as NTBI since the body has no passive excretory mechanism for any abundance [13]. However, in children excess iron may be used in growth and this may, in part, explain our results [8].

Additionally, ferritin acts as an acute phase reactant and may not be an accurate measure of body iron status, and this could account for misclassification bias in other studies. RBC transfusion number may represent a more accurate measure of total body iron. Recent research in pediatric ALL patients has shown that children who receive as little as 101 mL/kg of RBCs (the equivalent of 7 – 10 RBC transfusions) have evidence of iron overload as measured by hepatic MRI LIC (Spearman correlation coefficient 0.8), a more sensitive and direct measure of tissue iron deposition [14].

The magnitude of iron overload and rate of iron accumulation that correlates with iron toxicity in children is not known [15]. Transfusional hemosiderosis may occur in children with leukemia, but the degree of iron overload may be inadequate to cause sufficient organ damage to affect HSCT outcome. In addition, the majority of children in this study had normal organ function studies prior to HSCT, contrary to many adult patients who undergo HSCT with multiple co-morbidities. Conceivably, adults with pre-existing organ dysfunction may be more susceptible to iron loading and subsequent damage thus producing worse HSCT outcomes.

In addition, our results may differ from those published by Lee et al. because our cohort of patients is likely more heterogeneous and was only evaluated after first HSCT. Lee et al. included children who underwent multiple HSCTs with the inherent increased risk of TRM. Lee et al. also did not include data on baseline organ function in their patients prior to HSCT, and their cohort may have pre-existing organ dysfunction and thus be more susceptible to iron loading, organ dysfunction and worse HSCT outcomes [7].

No studies to date have examined the association between direct iron deposition in the organs and HSCT outcomes in a prospective design in children. A better understanding of iron deposition following RBC transfusions in pediatric oncology patients is necessary so that clinicians can intervene if appropriate to improve HSCT outcomes.

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