Trends in transfusion burden among long-term survivors of childhood hematological malignancies

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Abstract

The risk from cumulative erythrocyte transfusions is poorly understood in oncology populations. This analysis among long-term survivors explored variation in transfusional burden over progressive eras of treatment identifying those at risk for iron overload. Transfusion records of 982 survivors of hematological malignancies treated at St. Jude were reviewed. After exclusions, 881 (90%) were assessed for cumulative volume, weight-adjusted volume, and transfusion number. Treatment intensity was assigned using the ITR-3 scale. Hematopoietic stem cell transplant and acute myeloid leukemia survivors had greater transfusional burden than conventional therapy recipients and acute lymphoblastic leukemia survivors respectively. Survivors of 5-10 years were more likely than survivors of >10 years to receive 10 transfusions (OR=2.0, 95% CI 1.5-2.8). Those with higher ITR-3 scores and more recent decades of treatment had a higher transfusional burden. Comprehensive transfusion histories are useful in identifying those at highest risk for iron overload.

Keywords

Transfusion medicine; Iron Overload; Cancer survivors; Pediatric leukemia

INTRODUCTION

Important progress has been made in the treatment of childhood hematologic malignancies over the past several decades.[1] The 5-year survival rate for childhood acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) is now more than 85% and 60%, respectively.[2-6] Advancements in risk-directed therapeutics are largely responsible for these successes, but concurrent improvement in supportive care, such as availability of

broad-spectrum antibiotics, transfusions, hematopoietic growth factors, and nutritional support have also contributed substantially.

Packed red blood cell (PRBC) transfusions are an essential component of leukemia and hematopoietic stem cell transplant (HSCT) treatment regimens since the majority of chemotherapeutic agents will stunt the innate production of red cells. Most pediatric leukemia patients receive combination chemotherapy over many months or years, and it is rare for a patient to complete therapy without PRBC transfusions. Information regarding the risk of cumulative erythrocyte transfusions and tissue iron accumulation is well understood in non-malignant populations; however, very little is known about transfusion-related iron burden in oncology populations. In patients with compromised red cell production, such as thalassemia or bone marrow failure syndromes, and in those chronically transfused to abate complications of the underlying disease (e.g., sickle cell disease and other hemolytic disorders), laboratory and histological signs of transfusion-induced iron overload can be seen after approximately 10 to 20 transfusions.[7,8] Excess iron accumulates rapidly due to the lack of a physiologic mechanism for its excretion and deposits in tissues throughout the body, particularly the liver, myocardium, and endocrine organs, resulting in organ dysfunction.[9-14] Extrapolating from these populations, it is plausible that iron overload may be an undiagnosed condition among cancer survivors and that the transfusional burden may be a potentially important risk determinant.[7]

Iron overload in childhood cancer survivors has been demonstrated in small studies, but how one's transfusional burden correlates with accumulation of iron has not been sufficiently investigated. Although we did not evaluate for iron overload in this study, our retrospective review was conducted to evaluate transfusional burden among long-term survivors of hematologic malignancies treated with HSCT or conventional chemotherapy alone, with the aim of exploring variation in transfusion burden within progressive eras of treatment identifying those at highest risk for iron overload.

MATERIALS AND METHODS

Patient Population

Patients were included in the analysis if they were treated for a hematologic malignancy at St. Jude Children's Research Hospital (St. Jude) between 1962 and 2004, and were long-term (5 years) survivors. Subjects treated with conventional chemotherapy, with or without HSCT, were included in the analysis. Survivors undergoing routine survivorship care were included (those between 5 and 10 years post diagnosis regardless of age), as were survivors who were no longer in active follow-up care but eligible to return to the institution for participation in clinical research (those age 18 years or older and 10 years post diagnosis). Patients were excluded from the analysis if they received transfusions at other institutions because transfusion records were incomplete. Longstanding practice at St. Jude has been to initiate erythrocyte transfusion therapy when hemoglobin concentration falls below 8 g/dl, or if symptoms of anemia develop or worsen.

Data Ascertainment

Blood bank records were reviewed (MC) and the number of PRBC transfusions and transfusion volumes were recorded. A 10% random sample was re-abstracted to verify accuracy. Uniform medical record abstraction was performed to obtain cancer diagnosis, year of treatment, presence or absence of relapse, and mean body weight during therapy. Transfusional burden was defined as (1) number of transfusions, (2) total volume of PRBCs (ml), and (3) volume of PRBCs/mean kilogram of body weight during therapy (ml/kg). To account for variability in treatment intensity among different diagnoses and different disease

risk categories, a score of 1, 2, 3, or 4 was assigned using the Intensity of Treatment Rating Scale version 3.0 (ITR-3).[15] Decade at time of treatment was used to evaluate trends in treatment intensity and transfusional burden over time. This study was approved by the St. Jude Institutional Review Board with a waiver of consent from participants.

Statistical Analysis

Associations between categorical variables were evaluated with the Chi-Square test and differences in group medians were compared with the Wilcoxon Mann Whitney test. Transfusion data by decade and ITR-3 group are presented with boxplots. P-values less than 0.05 are considered statistically significant and all analyses were conducted in SAS Version 9.2 (Cary, NC).

RESULTS

Patients identified as eligible included 982 survivors treated from 1963 to 2004. Ninety-two survivors were excluded for incomplete blood bank records, resulting in 881 (90%) evaluable patients. Characteristics of the evaluable patients are shown in Table I. The median age at initiation of treatment was 5.64 years (range: 0.1-24.6) with slightly more males (55%) than females (45%) in the cohort, a 1.2:1 M:F ratio. HSCT survivors comprised 24% (n=215) of the patient population, with half (50%) of the study cohort being survivors of 5-10 years, and half >10 years. Of the survivors treated with conventional therapy alone, 14% (n=91) were survivors of 5 - 10 years and 86% (n=575) were > 10 years. AML was the most prevalent diagnosis among HSCT survivors (41%, n=89), and ALL was most prevalent among those treated with conventional therapy only (88%, n=584).

HSCT survivors were transfused more heavily than conventional therapy recipients with regard to median number of transfusions (20 vs. 7), median cumulative volume (3890 ml vs. 1250 ml), and median volume per kilogram of body weight (140 ml/kg vs. 61 ml/kg), all p-values <0.001. (Table II) Conventional therapy only recipients with AML had a significantly higher transfusional burden compared to those with ALL – i.e. median 21 vs. 6 transfusions, 3,793 ml vs. 1,134 ml, and 182 ml/kg vs. 57 ml/kg (all p-values <0.001), respectively. Recent survivors (5-10 years) were twice as likely (OR=2.0, 95% CI 1.5-2.8, p-value < 0.001) to have received 10 or more transfusions than were survivors of >10 years duration. (Table III)

An analysis of transfusion number and volume according to ITR-3 scores and treatment decade is shown in Figure I. Transfusion number and weight-adjusted volume (ml/kg) increased with increasing ITR-3 score and with more recent decade of treatment. Transfusional burden is highest among those treated in the 1990's and 2000's, particularly in those with an ITR-3 score of 4.

DISCUSSION

Our data illustrate that hematological malignancy survivors of 5-10 years received a higher number of transfusions and a higher volume of PRBCs than similar survivors treated >10 years ago. Survivors received greater amounts of blood in the setting of higher treatment intensity scores and more recent treatment decades. More liberal transfusion practices among clinicians could explain this finding, however the standard institutional transfusion threshold guidelines at St. Jude did not change throughout the time period under study. The evolution of more intensive chemotherapy regimens is another explanation as these treatments induce more severe or prolonged anemia necessitating greater transfusion support. Though we show that there are more survivors with greater treatment intensity scores, this may be impacted by survivor bias since patients from remote decades who had

more aggressive disease, more intensive treatment regimens, and potentially more PRBC transfusions, may have died in greater proportion than more recent patients before meeting the eligibility requirement of surviving at least 5 years from diagnosis to be part of this analysis.

The clinical implications of our data are that more modern survivors have received substantially more erythrocyte transfusions, placing them at risk for complications associated with repeated transfusions, namely iron overload. Our observation is that the risk for iron overload is higher for patients treated recently than that of survivors treated more than 10 years ago. Other important conclusions from our analysis are that, of the survivors treated with conventional chemotherapy alone, AML survivors have a significantly higher transfusional burden than survivors of ALL. In addition, the transfusional burden among survivors of HSCT is significantly greater than those treated with conventional chemotherapy alone.

Understanding transfusion patterns is an essential step toward characterizing those at risk for iron overload and any related organ dysfunction. Two previous studies have quantified PRBC transfusions in pediatric cancer populations. Eng and Fish reviewed 107 non-relapsed and non-transplanted pediatric ALL patients treated between 1995 and 2007 and concluded that those with high risk ALL received a greater volume of PRBC transfusions than did those with standard risk disease.[16] Ruccione et al. reported on 214 pediatric oncology patients that were treated between 2004 and 2009 for a variety of hematological and solid malignancies and found that higher treatment intensity scores, were associated with more transfusions.[17] Our analysis extends that beyond the previous studies cited, and is the first to delineate how survivor time, decade of treatment, primary diagnosis, and type of treatment (HSCT vs. conventional therapy only) may reflect transfusional burden and resultant risk of iron overload.

Importantly, as more pediatric patients become long-term cancer survivors, the relevance of comprehensive transfusion histories will be ever increasing. In 2009, there were an estimated 363,000 childhood cancer survivors living in the United States [18] and the prevalence of patients with a history of a large transfusional burden will continue to grow. It is well known that childhood leukemia survivors have a high risk of chronic health conditions as a result of their prior therapy.[19] In a study by investigators from the Childhood Cancer Survivor Study (CCSS), ALL survivors were nearly seven times more likely than their siblings to report the presence of a chronic cardiac condition.[20] The CCSS has also shown that survivors of leukemia are 1.5 times more likely to be hospitalized for cardiac causes and ALL survivors are 4.2 times more likely to die of cardiac-related illness compared to age-, calendar year–, and sex-specific rates in the United States population. [21,22] Endocrinopathies, in particular growth hormone deficiency and insulin resistance as a component of the metabolic syndrome, are also well established late effects in long-term ALL survivor populations.[23-25] These organ systems, while vulnerable to chemotherapy toxicity, are also the target of iron accumulation. Though it is not yet clear if iron overload is contributing to these chronic conditions, given that iron overload is a reversible condition with phlebotomy or chelating agents, further investigation is warranted.

Cancer survivors do not routinely undergo surveillance for iron overload, with the exception of HSCT survivors in whom an annual ferritin measurement is recommended by the Children's Oncology Group Long-term Follow-up Guidelines. Since ferritin is an acute phase reactant, it may be falsely elevated due to any systemic ongoing inflammatory process and thus may not be the most reliable measurement of body iron burden. Detailed transfusion histories may be a superior assessment of one's risk of iron overload; however,

research is lacking to confirm this assumption and transfusion data have not traditionally been collected by survivorship programs.

Direct quantification of tissue iron burden can be performed using invasive methods, such as liver biopsy, and non-invasive methods [e.g., superconducting quantum interference device (SQUID) susceptometer,[26-28] and R2 and R2* magnetic resonance imaging (MRI) techniques].[29-31] Liver iron content (LIC) is considered the reference method for body iron burden assessment, and R2 and R2* MRI modalities are increasingly being used for LIC assessment due to the non-invasive nature and growing availability of the technique. The value of these scans in routine survivorship care is yet unknown since its use as a tool to quantify LIC has been sparsely utilized. The high usage of blood in pediatric malignancy survivors justifies the utilization of precise techniques to define the breadth and depth of iron overload in this population.

In summary, our data show that modern survivors of hematological malignancies, particularly those who underwent high intensity therapy, have received a large transfusion burden leaving them at risk for iron overload. Higher survivor rates of pediatric hematological malignancies have paralleled the increased usage of blood. We suggest that comprehensive transfusion histories should become standard among survivors treated since 1980 to identify those at highest risk for iron overload. Further studies are needed to better delineate surveillance guidelines, the use of MRI, and, ultimately, when intervention is warranted.

Acknowledgments

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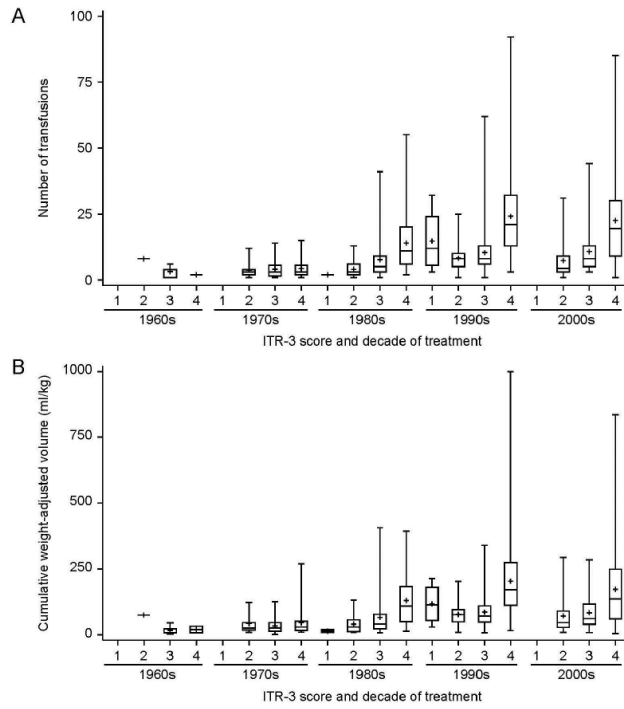
Figure 1. Transfusion burden as a function of decade of treatment and treatment intensity scores
(A) Total number of transfusions and (B) weight-adjusted volume is compared among different treatment intensity scores and decade of treatment. Boxplots are presented with the lower and upper fences at the minimum and maximum values. Group means are represented by the + symbol.

Table 1

Clinical characteristics of 881 survivors of childhood hematological malignancy treated at St. Jude Children's Research Hospital

Characteristic	N=881
Age at diagnosis (years)	
Median (range)	5.6(0.1-24.6)
Follow-up time (years)	
Median (range)	15.4 (5.3-48.1)
Gender	
Male	487 (55%)
Female	394 (45%)
Patient Type	
HSCT Survivors	215 (24%)
5-10 year duration	107 (50%)
>10 year survivors	108 (50%)
Non-HSCT Survivors	666 (76%)
5-10 year duration	91 (14%)
>10 year survivors	575 (86%)
Diagnosis	
HSCT Survivors	
Acute Lymphoblastic Leukemia	43 (20%)
Acute Myeloid Leukemia	89 (41%)
Chronic Myeloid Leukemia	30 (14%)
Hodgkin Lymphoma	21 (10%)
Non-Hodgkin Lymphoma	11 (5%)
Other	21 (10%)
Non-HSCT Survivors	
5-10 year duration	
Acute Lymphoblastic Leukemia	67 (74%)
Acute Myeloid Leukemia	23 (25%)
Other	1 (1%)
>10 year survivors	
Acute Lymphoblastic Leukemia	517 (90%)
Acute Myeloid Leukemia	49 (9%)
Other	9 (2%)
ITR-3 Score	
1 (lowest intensity)	6 (1%)
2	228 (26%)
3	304 (35%)
4 (highest intensity)	343 (39%)

Table II

Transfusion burden among survivors of hematological malignancies by primary treatment modality and diagnosis

	HSCT Recipients (N=215)	Recipients of Conventional Therapy only (N=666)	p-value
Median transfusion number (range)	20 (1-92)	7 (1-85)	p < 0.001
Median volume transfused (ml)	3,890 ml	1,250 ml	p < 0.001
Median volume/kg (ml/kg)	140 ml/kg	61 ml/kg	p < 0.001
Recipients of Conventional Therapy only			
	ALL (N=584)	AML (N=72)	p-value
Median transfusion number (range)	6 (1-62)	21 (1-85)	p < 0.001
Median volume transfused (ml)	1,134 ml	3,793 ml	p < 0.001
Median volume/kg (ml/kg)	57 ml/kg	182 ml/kg	p< 0.001

Table III

Comparison of survivor time versus number of transfusions

	SURVIVOR TIME		
	5-10 years	**>10 years**	**Total**
10 OR MORE TRANSFUSIONS	116	280	396 (45%)
l to 9 TRANSFUSIONS	82	403	485 (55%)
Total	198 (22.5%)	683 (77.5%)	881 (100%)

• Chi-Square p-value < 0.001

• Survivors of 5-10 years are twice as likely to have received 10 or more transfusions than survivors of >10 years. Unadjusted odds ratio: 2.0 (95% CI 1.5-2.8)