Prevalence of Iron Overload in Pediatric Oncology Patients After Blood Transfusion

Murali Krishna Gurram, MD, William Newman, MD, and Nathan Kobrinsky, MD

Dr. Gurram is an Internal Medicine Resident, Dr. Newman is Chairman of the Department of Internal Medicine, and Dr. Kobrinsky is Professor of Pediatrics at the School of Medicine and Health Sciences, University of North Dakota, in Fargo, North Dakota. Dr. Kobrinsky is also Director of the Hemophilia Program and Head of the Pediatric Oncology/Hematology Department, at Sanford Health Roger Maris Cancer Center, in Fargo, North Dakota.

Address correspondence to:
Murali Krishna Gurram, MD
360 Spring Street, Apt #338
Saint Paul, MN 55102
Phone: 701-540-1729
Fax: 651-326-3706
E-mail: gmk_doctor@yahoo.co.uk

Abstract: *Background*: Studies evaluating the prevalence of iron overload and its relationship to blood transfusion in pediatric oncology patients are limited. *Methods*: Medical records of all pediatric oncology patients treated at Roger Maris Cancer Center (Fargo, North Dakota) were screened. Subjects with measurements of serum ferritin levels after completion of therapy (N=52) were further evaluated. *Results*: Of the total study population, 37 patients (71.2%) underwent red blood cell (RBC) transfusion and 15 patients (28.8%) did not. Among the transfused patients, 20 patients (54%) had elevated serum ferritin values greater than 250 ng/mL. Among the patients who did not undergo blood transfusion, only 1 patient (6.6%) had an elevated serum ferritin value ($P<.01$; Fischer exact test). None of the nontransfused patients had ferritin levels greater than 501 ng/mL. *Conclusion*: This study demonstrated that ferritin levels were more likely to be elevated in transfused patients than nontransfused patients. The number of subjects in this study was limited, and further prospective studies are needed.

Keywords
Iron overload, blood transfusion, serum ferritin, pediatric oncology

Iron overload can lead to end organ damage of the heart, liver, and pancreas in patients with hemochromatosis.[1] Pediatric hematology and oncology patients often require multiple red blood cell (RBC) transfusions and are therefore at high risk of iron overload. Iron overload, as measured by serum ferritin, has deleterious effects on survival.

Methods

Institutional review board approval was obtained for this retrospective study. Medical records of all subjects younger than 30 years who were treated for malignancy at the Roger Maris Cancer Center (RMCC) in Fargo, North Dakota from January 1, 1998 to January 31, 2009 were reviewed. Patients with measurements of serum ferritin taken after the completion of therapy were included in this study. We gathered data for age at diagnosis; date of start and completion of therapy; date of post-therapy ferritin determination; therapeutic modalities,

Table 1. Demographics of the Study Population

Category	Number of Subjects With Available Data	Mean or Median	Standard Deviation or IQR*
Ferritin Level Post-Treatment	52	153.5 ng/mL	(21.5–506.8 ng/mL)
Erythrocyte Sedimentation Rate	43	8 mm/hr	(5.5–11 mm/hr)
C-Reactive Protein	41	0.1 mg/L	(0–0.21 mg/L)
Number of Transfusions	0=15 ≥1=37		
RBC Transfusions	37	8	(5–16)
Platelet Transfusions	26	4.5	(2.3–7.8)

IQR=interquartile range; RBC=red blood cell.

*Data displayed as mean +/- standard deviation with normal distribution median (IQR) if non-normally distributed.

such as surgery, radiation therapy, chemotherapy, or a combination; and the numbers of RBC and platelet units transfused. Patients ranged in age from 2–30 years. Thirty-five were male and 17 were female.

Serum ferritin levels were used as a surrogate marker for iron overload. Patients were stratified according to their ferritin levels as normal (<250 ng/mL), mildly elevated (250–1,000 ng/mL), and markedly elevated (>1,000 ng/mL). These categories represent standard demarcations used in the cancer literature to define iron overload risk due to blood transfusion.[2,3] We reviewed measurements of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) to exclude inflammatory conditions as a cause of elevated ferritin levels. Subjects were also stratified according to whether or not they received RBC transfusions during the cancer treatment period.

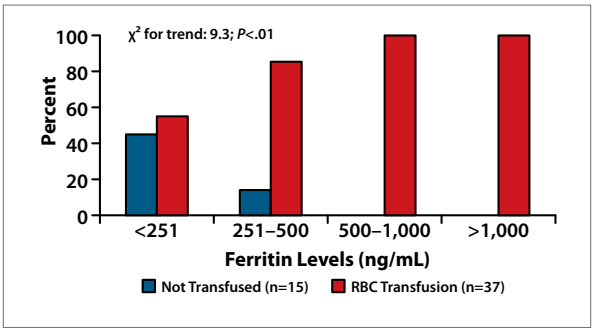

Figure 1. The difference in ferritin levels between transfused and nontransfused patients. None of the nontransfused patients had ferritin levels greater than 501. Among patients with ferritin levels of 500–1,000 and greater than 1,000, all were transfused patients. RBC=red blood cell.

Results

Data are displayed as the mean plus or minus the standard deviation for normally distributed variables and as the median (interquartile range [IQR]) for abnormally distributed variables (Table 1). Because of the remarkable right-skewed distribution of the ferritin data, ferritin levels were log transformed. Regression analysis was undertaken using log ferritin as the dependent variable, with the RBC transfusion number, platelet transfusion number, and CPR/ESR as potential independent variables. Only the RBC transfusion number contributed significantly to the model. Therefore, the selected model used only the RBC transfusion number as the independent (predictor) variable. The program R version 2.6.2 was used for all graphics generation and statistical analysis.

Of the total study population, 37 patients (71.2%) had received RBC transfusions and 15 (28.8%) had not. Among the transfused patients, 20 (54%) had elevated serum ferritin values (>250 ng/mL; Figure 1). In contrast, only 1 (6.6%) nontransfused subject had elevated serum ferritin values (P<.01; Fischer exact test). Among the 21 patients with elevated serum ferritin values, 17 (80.95%) had values between 250–1,000 ng/mL and 4 (19.05%) had values greater than 1,000 ng/mL. Serum ferritin levels correlated with the number of RBC transfusions administered (P<.001; multiple R^2=0.48). The CRP and/or ESR values were evaluated concurrently with ferritin in 42 patients and were normal in 41 patients.

Discussion

Iron toxicity is dose related. A study of myelodysplastic syndrome (MDS) showed improved survival in patients with ferritin levels less than 1,000 ng/mL.[4] In a study of pediatric oncology patients who underwent bone marrow transplantation, Lee and colleagues[5] found an increased survival rate in patients with pretransplant ferritin levels of less than 1,000 ng/mL. Another study of MDS revealed that patients treated with iron chelation therapy had improved survival compared with patients who did not receive treatment.[6]

In a study of patients who underwent allogeneic hematopoietic cell transplantation, elevated pretransplant serum ferritin levels (>1,000 ng/mL) were associated with decreased overall survival and increased incidence of graft-versus-host disease and bloodstream infections.[7] Pediatric patients with Hodgkin disease demonstrated poor progression-free survival with high ferritin levels.[8] Iron overload can occur in patients who receive blood transfusions, particularly patients with thalassemia and sickle cell anemia. Blood transfusions in children with sickle cell anemia demonstrated a positive correlation between hepatic iron overload and transfusion volume.[9]

Reducing the iron burden has been shown to improve outcomes in a number of settings. Bomford and coworkers observed an increase in 5- and 10-year survival rates in patients with idiopathic hemochromatosis who were treated with venesection.[10] Similarly, another study of patients with hereditary hemochromatosis demonstrated improved survival in patients treated with phlebotomy.[1] Since phlebotomy may have an important role in preventing complications from iron overload in a number of disease states, our study aimed to determine the prevalence of iron overload and the relationship between serum ferritin and the number of RBC transfusions in pediatric hematology and oncology patients. Our study demonstrated a strong association between iron overload and RBC transfusion. Platelet transfusion had no effect on iron overload. The inflammatory contribution to the elevated ferritin level was minimal or absent, as all of the patients with elevated ferritin levels had normal ESR and CRP. Limitations of this retrospective study include the small number of subjects, as well as differences in the time at which ferritin levels were determined. The effect of this time variance on serum ferritin is unclear.

Despite these limitations, we believe that this study provides a strong indication for evaluation of iron burden in pediatric oncology patients and the need for appropriate treatment. Given the high prevalence (40.4%) of iron overload in pediatric oncology patients and its strong relation to blood transfusions, further prospective studies will be required to examine the correlation of ferritin level with end organ damage and the optimal time to intervene with phlebotomy to reduce the iron burden.

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