Estimation of iron overload with T2*MRI vs. serum ferritin in children treated for hematological malignancies

Vinay Munikoty[1], Kushaljit Sodhi[2], Anmol Bhatia[3], PRATEEK BHATIA[1], Savita Attri[3], ManojKumar Rohit[4], Amita Trehan[5], N Khandelwal[3], and Deepak Bansal[6]

[1]Post Graduate Institute of Medical Education and Research
[2]Post graduate Institute of Medical Education & Research
[3]Postgraduate Institute of Medical Education and Research
[4]Post Graduate Institute of Medical Education and Research, Chandigarh, India
[5]postgraduate Institute of Medical Education & Research
[6]Advanced Pediatric Center, Postgraduate Institute of Medical Education and Research

March 07, 2024

Abstract

Background. Iron overload may contribute to complications in childhood cancer survivors. Methodology. Patients treated for hematological malignancy, [?]6 months from the end of therapy, who had received [?]5 red-cell transfusions were enrolled in the cross-sectional study. Iron-overload was estimated by serum ferritin (SF) and T2*MRI. Results. Forty-five survivors were enrolled among 431 treated for hematological malignancies. The median age at diagnosis was 7-years. The median number of red-cell units transfused was 8 (IQR 7, 10). The median duration from the end of treatment was 15 months (IQR 8.75, 25). An elevated SF (>1000 ng/ml), elevated liver iron concentration (LIC) and myocardial iron concentration (MIC) were observed in 5 (11.1%), 20 (45.4%), and 2 (4.5%) patients, respectively. All survivors with SF >1000 ng/ml had elevated LIC. The LIC correlated with SF (p<0.001). MIC lacked correlation with SF or LIC. The number of red-cell units transfused and duration from last transfusion correlated with SF (p=0.001, 0.002) and LIC (p=0.012, 0.005). SF >500 ng/ml predicted elevated LIC with sensitivity/specificity of 80%/79%. A cut-off of 8 units of red-cells predicted elevated LIC with sensitivity/specificity of 95%/49.8%. Conclusions. Iron overload in survivors of hematological malignancies who had received [?]5 red-cell transfusions, estimated by SF, LIC, and MIC was 11.1%, 45.4%, and 4.5%. We suggest screening by SF for survivors who have received >8 transfusions. If SF is 500-1000 ng/ml, a T2*MRI is useful for estimating LIC. A T2*MRI can be avoided if SF exceeds 1000 ng/ml, as LIC will be expected to be elevated.

1 INTRODUCTION

Management of hematological malignancies with chemotherapy is accompanied by myelosuppression, often necessitating blood transfusions.[1] The burden of transfusion-related iron overload in childhood cancer survivors is less well researched.[2] There is overlap in organ toxicity due to iron overload and late effects of cancer chemotherapy which may contribute to poor quality of life in survivors. There are no established guidelines for monitoring iron overload in pediatric cancer survivors. In addition, there is a lack of information on the utility of T2* magnetic resonance imaging (T2*MRI) vs. serum ferritin to estimate iron overload in cancer survivors.

Serum ferritin is not a reliable predictor of tissue iron stores and organ dysfunction.[3] The estimation of liver iron concentration (LIC) by T2*MRI has a superior correlation with liver iron assessed with liver biopsy.[4,5] T2*MRI has emerged as a superior tool for estimating tissue iron overload in patients with hemoglobinopathies.

The objective of this study was two-fold, a) to measure the prevalence of iron overload in children treated for hematological malignancies, and b) define the indication(s) for requesting T2*MRI vis a vis serum ferritin for estimating iron overload in cancer survivors.

2 METHODS

A single-center, cross-sectional, observational study was conducted over 15 months (January 2016 to March 2017). Patients treated for hematological malignancy in the Pediatric Hematology-Oncology Unit, Postgraduate Institute of Medical Education and Research, Chandigarh, India, were screened. Children who were >6 months from completion of therapy and had received [?]5 red cell units during treatment or within 3 months before diagnosis were enrolled. Patients with relapsed disease, second-malignancy, or those who had received a hematopoietic stem cell transplant (HSCT) were excluded. Protocol adapted from UKALL 2003 trial was followed for risk stratification and treatment of patients with acute lymphoblastic leukemia (ALL).[8] Chemotherapy adopted from the AML15 trial was used to treat acute myeloid leukemia (AML).[9]

Serum ferritin and T2*MRI were performed for estimation of iron overload. The myocardial iron concentration (MIC) and LIC were measured by T2*MRI. C-reactive protein (CRP) was done as a surrogate marker of inflammation. A serum ferritin value was considered for assessment of iron status when the corresponding CRP level was within range. If CRP was elevated (>10 mg/L), serum ferritin and CRP were repeated 4 weeks later.

Iron overload was defined as serum ferritin exceeding 1000 ng/ml. LIC was graded as normal (<2 mg/g), mild (2-7 mg/g), moderate (7-15 mg/g) or severe (>15 mg/g) iron overload.[6] MIC was graded as normal (<1.16 mg/g), mild (1.16-1.65 mg/g), moderate (1.65-2.71 mg/g) or severe (>2.71 mg/g) iron overload.[7]Echocardiography was performed in children with cardiac iron overload (MIC >1.16 mg/g).

The study was approved by the ethics committee of the institution (INT/IEC/2016/1138). Informed consent was obtained from the participants/guardians.

2.1 Statistical Analysis

Chi-square and Fischer's exact test were utilized to compare categorical variables. The inter-group comparison was performed with the student's t-test for parametric and Mann–Whitney test for nonparametric data. Spearman's correlation was used to analyze the correlation between serum ferritin and LIC/MIC. Multiple linear regression was performed to predict the influence of independent parameters on serum ferritin and LIC. All tests were two-tailed, and a P-value <0.05 was considered significant. Analysis was performed using Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, version 23.0 for Windows).

3 RESULTS

The screening was performed in 431 patients treated for hematological malignancies. Forty-five patients who fulfilled the study criteria were enrolled and are discussed henceforth. The characteristics of the 45 patients are listed in Table 1. The median duration from the end of treatment was 15 months (IQR 8.75, 25). The median duration since the last transfusion was 33 months (IQR: 23.5, 47.5). The patients treated with more intensive chemotherapy (regimen B for ALL) had a greater (8.9 vs. 7.9 units) transfusion requirement as compared to those treated with standard (regimen A for ALL) chemotherapy, though it lacked significance (p=0.066).

3.1 Iron overload

Serum ferritin was available in all 45 patients. T2*MRI was performed in all except one patient due to the need for sedation. The mean serum ferritin was 581 ng/ml (range: 32-2115). Iron overload (serum ferritin >1000 ng/ml) was observed in 5 (11.1%) patients. CRP levels were <10 ng/ml in all. The mean LIC was 2.7 mg/g (range: 0.6-12.7). The LIC was elevated (>2 mg/g) in 20 (45.4%) patients; 18 (41%) had mild, and 2 (4.5%) patients had a moderate grade of hepatic iron overload. The mean MIC was 0.6 mg/g (range: 0-1.6). Merely 2 (4.5%) patients had an elevated MIC, both with a mild elevation. The two patients with the cardiac iron overload included a patient with high-risk ALL and another with AML. An echocardiogram was

performed in both patients with cardiac iron overload. The ALL survivor had grade 2 diastolic dysfunction, and the other had a normal function.

3.2 Correlation of serum ferritin with LIC and MIC

All patients with serum ferritin >1000 ng/ml had an elevated LIC. LIC had a linear correlation with serum ferritin (r=0.49, p<0.001) (Figure 1). MIC lacked correlation with serum ferritin (r=0.20, p=0.19) as well as LIC (r=0.04, p=0.81).

3.3 Variables influencing serum ferritin, LIC, and MIC

The patients receiving >10 red cell transfusions had higher mean serum ferritin (938 vs. 451 ng/ml, p=0.001) and a higher mean LIC (4.0 vs. 2.2, p=0.035) as compared to the group receiving <10 transfusions. The number of red cell units transfused correlated with serum ferritin and LIC. Children who were evaluated after 3 years from cessation of transfusions had lower serum ferritin (mean: 350 vs. 751 ng/ml) as well as a lower LIC (mean: 1.2 vs. 3.8 ng/ml) than those who were evaluated within 3 years from cessation of transfusions. The duration since the last transfusion inversely correlated with serum ferritin and LIC. The variables lacked a correlation with MIC (Table 2).

3.4 Predictive value of serum ferritin and number of red cell transfusions for abnormal LIC

A serum ferritin exceeding 500 ng/ml had a sensitivity of 80% and specificity of 79% to predict an elevated LIC. Serum ferritin exceeding 1000 ng/ml uniformly predicted elevated LIC in all the patients (specificity: 100%); however, the sensitivity dropped to 25%. A cut-off of 8 units of red cells predicted an elevated LIC with a sensitivity of 95% and specificity of 49.8%.

4 DISCUSSION

Blood transfusions are a vital component in the management of hematological malignancies. There is a cumulative increase in tissue iron burden with repeated blood transfusions. As an effective mechanism of excretion is lacking, the excess iron is sequestered as ferritin. Even with mild to moderate iron overload, the transferrin saturation exceeds 80%. It results in the production of non-transferrin bound iron. Subsequently, free cytosolic iron accumulates in the 'labile iron pool,' leading to lipid peroxidation, protein denaturation, and nucleic acid damage, ultimately resulting in tissue dysfunction.[10,11]

It is well known that severe iron overload results in cardiopulmonary, endocrine, liver, hematological, and other organ dysfunction.[12] Mild and moderate iron overload is not without adverse effects.[13] Iron overload hinders erythropoiesis by causing mitochondrial iron trapping and decreasing hemoglobin synthesis. It has been observed that the erythroid-specific colony-forming units reduce even with a mild increase in ferritin (>250 ng/ml).[14] Iron overload also results in immunological dysfunction. Iron induces oxidative damage in the immune system resulting in impaired defence mechanisms.[15] Iron metabolism in malignancies is altered. There is increased expression of transferrin binding proteins and the formation of low molecular weight siderophores. There is a decrease in the tumoricidal activity of lymphocytes and macrophages.[16] In addition, there is a substantial overlap of organ toxicities between cancer chemotherapy and iron overload. The risks of iron overload are exemplified further if there is a need for HSCT at relapse. Pre-transplant iron overload is associated with an increased risk of hepatic sinusoidal syndrome, graft versus host disease, infection, and mortality.[17] Hence mild to moderate iron overload merits monitoring in follow of cancer survivors.

About 15-20% of long-term survivors of adult leukemia develop iron overload.[18] The earlier studies on childhood cancer survivors report a variable (14-28%) range of iron overload. In a study from Finland, 3/22 (14%) children treated for ALL had iron overload (ferritin >1000 ng/ml) with median serum ferritin of 450 ng/ml.[19] Another study from Turkey reported iron overload in 20/53 (38%) children treated for ALL and AML.[20] In a study from India, 16/66 (24.2%) children treated for leukemia had iron overload (SF>1000 ng/ml).[21] A study conducted at Children Hospital Los Angeles evaluated 75 patients treated for pediatric cancers, both solid tumors and hematological malignancies. Serum ferritin was elevated in 21/74 (28.4%) at a median duration of 4.4 years after treatment completion and 4.9 years from cessation of transfusion.[22]

Prevalence of iron overload (ferritin >1000 ng/ml) was reported in 7/27 (25.9%) recipients of allogeneic HSCT in a study conducted at the University of Minnesota.[23] In our study, iron overload (ferritin > 1000 ng/ml) was observed in 5/45 (11.1%) patients. The plausible reasons for a lower burden of iron overload in our study are, a) patients with relapsed disease or those receiving HSCT were excluded, b) patients with high-risk ALL were treated with a less intensive regimen B and not regimen C (as per UKALL 2003 protocol) in accordance with the unit's policy, c) the threshold for transfusion was typically 8 g/dl as against 10 g/dl in a few earlier studies.

Several studies have attempted to correlate serum ferritin with LIC and MIC.[24-27] A study from St Jude Children's Research Hospital reported elevated serum ferritin (median 1337 ng/ml) and LIC (median 6.6 mg/g) in 8/63 (12.6%) childhood cancer survivors. A significant correlation was reported between serum ferritin and LIC (r=0.83, p=0.01).[23] Yet another study reported a significant correlation between serum ferritin and MRI-based signal intensity ratio of liver to the muscle (r=-0.76, p< 0.001, n=15).[25] In a study from California, 75 patients treated for childhood cancers were evaluated by T2*MRI. The LIC and pancreatic iron were elevated in 36/74 (49.3%) and 19/72 (26.4%) patients. None of the patients had an abnormal MIC. Both LIC and pancreatic iron stores correlated with serum ferritin (r=0.472, p<0.001).[22] Serum ferritin and T2*MRI-based iron estimation were performed in 48 adult recipients of HSCT who had received a median of 20 red cell transfusions. Iron overload (ferritin >1000 ng/ml) and liver iron overload (>5 mg/g) was reported in 33/48 (6%) and 41/45 (85%) patients, respectively. Serum ferritin and LIC had a significant correlation (r=0.75). Cardiac iron overload was reported in merely one patient, and there was no correlation with ferritin.[28] A study from Belgium evaluated 59 patients with pediatric cancers. The mean serum ferritin was 465 ng/ml. An elevated LIC and MIC were observed in 39/59 (69%) and 8/59 (14%) patients, respectively. Serum ferritin correlated with LIC (r=0.74), but not with MIC (r=-0.27).[29] In our study, similarly, serum ferritin correlated with LIC (r=0.49, p= <0.001) but not with MIC (r=0.20, p=0.19). In addition, the MIC did not correlate with LIC (r=0.04, p=0.81). Serum ferritin can thus be utilized as a surrogate indicator of liver iron overload. However, MIC cannot be predicted based on serum ferritin or LIC.

The proportion of patients with iron overload differs when assessment is performed by serum ferritin or . Armand et al., reported 33 (69%) patients with serum ferritin >1000 ng/ml and 41 (85%) with an abnormal (>1.8 mg/g) in 48 evaluated patients.[28] Kathleen et al., reported serum ferritin >1000 ng/ml in 21/74 (29%) and an elevated in 36/74 (49%) patients.[22] A recent study reported 27.3% patients with abnormal and 18.2% with abnormal MIC in patients with a serum ferritin below 1000 ng/ml.[26] In our study, the proportion of patients with an increased was 45.4%, considerably more than the proportion of patients with a raised ferritin (11.1%). All patients with a serum ferritin exceeding 1000 ng/ml had an increased (>2 mg/g). However, 6 (22.2%) patients with a serum ferritin below 1000 ng/ml had an abnormal as well. The MIC was abnormal in 2 patients; both had serum ferritin below 1000 ng/ml. Thus, although serum ferritin correlates well with , a cut-off >1000 ng/ml underestimates the proportion of patients with tissue iron overload.

The predictive factors that influence iron stores help establish risk factors for iron overload. In a prospective study of 59 patients, higher treatment intensity was the sole parameter predicting liver iron overload in multivariate analysis of risk factors (OR=19.54, β=2.97).[29] Similarly, another study from Lithuania evaluated 66 patients based on the intensity of treatment received. Serum ferritin was higher in the higher-intensity group (mean 1071 ng/ml vs. 402 ng/ml, p=0.008).[30] A recent study in children treated for acute leukemia (n=53) reported a higher treatment intensity to result in higher ferritin (mean 406 vs. 260 ng/ml, p<0.001).[20] In the above two listed studies, authors opined that the higher transfusion requirement in the group treated with the higher intensity treatment likely explained the increased iron load.[29,30] In our study as well, the patients treated with more intensive chemotherapy (regimen B for ALL) had a higher (8.9 vs. 7.9 units) transfusion requirement as compared to standard (regimen A for ALL) chemotherapy. However, the difference was not significant (p=0.066). In our study, the intensity of therapy was not a risk factor for higher serum ferritin or an elevated LIC (p=0.6, 0.73, respectively). The institutional policy of not utilizing regimen C for treating patients with ALL likely contributed to a lack of correlation of treatment intensity with iron overload.

Childhood cancer survivors receiving multiple transfusions are expected to have greater serum ferritin than non-transfused patients.[31] A study from Turkey evaluated 22 children treated for ALL with T2*MRI. LIC and MIC were elevated in 11 (50%) and 6 (27%) patients. None of the patients receiving less than 10 transfusions had liver or cardiac iron overload. Abnormal LIC (27.3%) and MIC (18.3%) were observed in patients receiving more than 10 transfusions, although the SF was <1000 ng/ml. The number of blood transfusions was a more reliable parameter than serum ferritin (p=0.021 vs. 0.324) in predicting cardiac iron overload.[26] In another study from Turkey, 7 (23.3%) had mild and 1 (3.3%) had moderate liver iron deposition among 30 children treated for ALL. LIC correlated with the serum ferritin, the number of red cell units transfused, and the volume of red cell transfused.[32] In a study of 36 patients from New Jersey, iron overload and serum ferritin were significantly elevated in the group receiving >10 transfusions (mean ferritin: 3939 vs. 372 ng/ml, p= 0.05) as compared to the group receiving <10 transfusions. All patients with iron overload (ferritin >1500 ng/ml) had received >10 transfusions.[33] Two other similar studies reported a correlation between liver iron overload and the volume of blood transfused (r=0.67, 0.78).[25,29] Two recent studies have suggested serum ferritin and transfusion history as the best parameters for predicting an elevated LIC.[19,28] Number of blood transfusions was a significant predictor for iron overload in our study as well. A positive correlation was observed with both serum ferritin (r=0.6, p=0.001) and LIC (r=0.375, p=0.012). In our study, patients receiving >10 red cell transfusions had higher mean serum ferritin (938 vs. 451 ng/ml, p=0.001) and a higher mean LIC (4.0 vs. 2.2, p=0.035) as compared to the group receiving <10 transfusions. Indeed, a restrictive transfusion strategy would minimize the burden of iron overload.

In childhood cancer therapy, the need for red cell transfusions is often limited. The iron loading halts following the cessation of transfusions. However, there is no mechanism of excretion of the residual iron load. The cumulative iron stores may persist in the human system for a long duration and result in organ dysfunction. Halonen et al. evaluated serum iron parameters in children treated for ALL at the end of treatment (n=30) and again 1-3 years (n=22) after completion of therapy. All iron parameters improved, and iron profile normalized in most.[19] Similarly, serial measurements of serum ferritin demonstrated a reduction from 28% (8/28) to 14% (4/28) at 1 and 2 years of follow-up in 66 children evaluated for transfusion-related iron overload.[30] In our study, children were evaluated at a median duration of 33 months from the last transfusion. Our study was cross-sectional, and iron parameters were not serially evaluated. However, serum ferritin and LIC levels negatively correlated with 'duration since the last transfusion' (r=-0.45, -0.41, respectively). Children who were evaluated after 3 years from cessation of transfusions had lower serum ferritin (mean: 350 vs. 751 ng/ml) as well as a lower LIC (mean: 1.2 vs. 3.8 ng/ml) than those who were evaluated within 3 years from cessation of transfusions. It indicates that iron overload tends to reduce with time.

There are no established guidelines for the treatment of iron overload in cancer survivors. The need for chelation has not been systematically studied. Several groups have initiated chelation at a ferritin level exceeding 1000 ng/ml. Few studies report a decrease in iron overload with iron chelation for a brief period.[20,34,35] A short-term chelation therapy may thus halt the adverse effects that would ensue in mild to moderate iron overload for several years. We were not inclined to administer iron chelation to our patients with iron overload. The factors influencing the decision included a) likelihood of drop-in body iron stores in growing children and with menstruation in females, b) predominant vegetarian diet in the community, and c) a lack of robust evidence of harm with mild iron overload.

Earlier studies have reported an incidence of 14-18% cardiac dysfunction in long-term survivors of childhood cancers.[36,37] In a study by Cheung et al. (n=58), adult survivors of pediatric leukemia were evaluated for evidence of myocardial iron overload on MRI. None of the patients had an abnormal MIC. Subnormal left ventricular ejection fraction (<55%) was documented in 5/58 (9%).[38] Lutz et al. reported three pediatric leukemia cases with high cumulative red cell transfusions (45-114 units). MIC was mildly elevated in two. None of the patients had cardiac function abnormality as evaluated by Echocardiography.[39] In our study, of the two patients who had elevated MIC, one patient had diastolic dysfunction.

Our study has addressed a focused aspect of survivorship.The study population was homogenous. Patients

with hematologicmalignancies treated with chemotherapy and in complete remission were enrolled. It is one of the largest studies to perform MRI-based tissue iron estimation in children treated for childhood cancer. The results aided in calculating the cut-off value of serum ferritin and the number of red cell transfusions received to predict an abnormal LIC. It would help formulate chelation therapy guidelines in cancer survivors with iron overload.

The study has limitations. The volume of blood transfused (ml/kg) was not recorded. Hence the critical volume of blood and transfused iron at which iron overload ensues was not estimated. The study was a cross-sectional, observational study. Serial measurements of ferritin and T2*MRI were not done. It would have provided additional information on ironutilization during the follow-up. In addition, the study was not intended to answer the question of indication or requirement for iron chelation in children treated for cancers.

In conclusion, the occurrence of elevated LIC and MIC in children treated for hematological malignancies who had received >5 red cell transfusions were 45.4% and 4.4%, respectively. No patient had a severe degree of elevation of LIC or MIC. Screening for iron overload by serum ferritin is suggested for patients who have received more than 8 transfusions. If the serum ferritin is between 500-1000 ng/ml, a T2*MRI may be considered for estimating liver iron overload. The LIC was uniformly elevated in patients with serum ferritin exceeding 1000 ng/ml. Therefore, a T2*MRI may be avoided in patients with serum ferritin >1000 ng/ml for optimal resource utilization. A prospective study with serial evaluation of iron load will aid in understanding the dynamics of iron overload with time. The indications and necessity for treating mild or moderate iron overload in children treated for cancer needs to be ascertained.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

REFERENCES

1. Watkins T, Surowiecka MK, McCullough J. Transfusion indications for patients with cancer. Cancer Control. 2015;22:38-46.
2. Nottage K, Gurney JG, Smeltzer M, Castellanos M, Hudson MM, Hankins JS. Trends in transfusion burden among long-term survivors of childhood hematological malignancies. Leuk lymphoma. 2013;54:1719-1723.
3. Telfer PT, Prestcott E, Holden S, Walker M, Hoffbrand AV, Wonke B. Hepatic iron concentration combined with long-term monitoring of serum ferritin to predict complications of iron overload in thalassaemia major. Br J Haematol. 2000;110:971-977.
4. Wood JC. Magnetic resonance imaging measurement of iron overload. Curr Opi Hematol. 2007;14:183-190.
5. Kirk P, He T, Anderson LJ, et al. International reproducibility of single breathhold T2* MR for cardiac and liver iron assessment among five thalassemia centers. J Magn Reson Imaging. 2010;32:315-319.
6. Hankins JS, McCarville MB, Loeffler RB, et al. R2* magnetic resonance imaging of the liver in patients with iron overload. Blood. 2009;113:4853-4855.
7. Carpenter JP, He T, Kirk P, et al. On T2* magnetic resonance and cardiac iron. Circulation. 2011;123:1519-1528.
8. Vora A, Goulden N, Wade R, et al. Treatment reduction for children and young adults with low-risk acute lymphoblastic leukaemia defined by minimal residual disease (UKALL 2003): a randomised controlled trial. Lancet Oncol. 2013;14:199-209.
9. Burnett AK, Russell NH, Hills RK, et al. Optimization of chemotherapy for younger patients with acute myeloid leukemia: results of the medical research council AML15 trial. J Clin Oncol. 2013;31:3360-

3368.
10. Shenoy N, Vallumsetla N, Rachmilewitz E, Verma A, Ginzburg Y. Impact of iron overload and potential benefit from iron chelation in low-risk myelodysplastic syndrome. Blood. 2014;124:873-881.
11. Papanikolaou G, Pantopoulos K. Iron metabolism and toxicity. Toxicol Appl Pharmacol. 2005;202:199-211.
12. Cappellini MD, Cohen A, Porter J, Taher A, Viprakasit V. Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT). 3rd edition. Nicosia, Cyprus. 2014.
13. Weinberg ED. The hazards of iron loading. Met Integr Biometal Sci. 2010;2:732-740.
14. Hartmann J, Braulke F, Sinzig U, et al. Iron overload impairs proliferation of erythroid progenitors cells (BFU-E) from patients with myelodysplastic syndromes. Leuk Res. 2013;37(3):327–332.
15. Weinberg ED. Iron withholding: a defense against viral infections. Biometals Int J Role Met Ions Biol Biochem Med. 1996;9(4):393–399.
16. Weinberg ED. Iron in neoplastic disease. Nutr Cancer. 1983;4:223–233
17. Koreth J, Antin JH. Iron overload in hematologic malignancies and outcome of allogeneic hematopoietic stem cell transplantation. Haematologica. 2010;95:364-366.
18. Barton JC, Bertoli LF. Transfusion iron overload in adults with acute leukemia: manifestations and therapy. Am J Med Sci. 2000;319:73-78.
19. Halonen P, Mattila J, Suominen P, Ruuska T, Salo MK, Mäkipernaa A. Iron overload in children who are treated for acute lymphoblastic leukemia estimated by liver siderosis and serum iron parameters. Pediatrics. 2003;111:91-96.
20. Olcay L, Hazirolan T, Yildirmak Y, et al. Biochemical, radiologic, ultrastructural, and genetic evaluation of iron overload in acute leukemia and iron-chelation therapy. J Pediatr Hematol Oncol. 2014;36:281-292.
21. Nair M, Kuttath V, Nair AR, et al. Iron Overload in Children with Leukemia Receiving Multiple Blood Transfusions. Indian Pediatr. 2018;55:962-965.
22. Ruccione KS, Wood JC, Sposto R, Malvar J, Chen C, Freyer DR. Characterization of transfusion-derived iron deposition in childhood cancer survivors. Cancer Epidemiol Biomark. 2014;23:1913–1919.
23. Schempp A, Lee J, Kearney S, Mulrooney DA, Smith AR. Iron Overload in Survivors of Childhood Cancer. J Pediatr Hematol Oncol. 2016;38:27–31.
24. Au WY, Lam WM, Chu WC, et al. A magnetic resonance imaging study of iron overload in hemopoietic stem cell transplant recipients with increased ferritin levels. Transplant Proc. 2007;39:3369-3374.
25. Vag T, Kentouche K, Krumbein I, et al. Noninvasive measurement of liver iron concentration at MRI in children with acute leukemia: initial results. Pediatr Radiol. 2011;41:980-984.
26. Unal S, Cetin M, Hazirolan T, et al. Number of erythrocyte transfusions is more predictive than serum ferritin in estimation of cardiac iron loading in pediatric patients with acute lymphoblastic leukemia. Leuk Res. 2014;38:882-885.
27. Chirico V, Rigoli L, Lacquaniti A, et al. Endocrinopathies, metabolic disorders, and iron overload in major and intermedia thalassemia: serum ferritin as diagnostic and predictive marker associated with liver and cardiac T2* MRI assessment. Eur J Haematol. 2015;94:404-412.
28. Armand P, Kim HT, Rhodes J, et al. Iron overload in patients with acute leukemia or MDS undergoing myeloablative stem cell transplantation. Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant. 2011;17:852-860.
29. de Ville de Goyet M, Moniotte S, Robert A, et al. Iron overload in children undergoing cancer treatments. Pediatr Blood Cancer. 2013;60:1982-1987.
30. Rascon J, Rageliene L, Stankeviciene S, et al. An assessment of iron overload in children treated for cancer and nonmalignant hematologic disorders. Eur J Pediatr. 2014;173:1137-1146.
31. Gurram MK, Newman W, Kobrinsky N. Prevalence of iron overload in pediatric oncology patients after blood transfusion. Clin Adv Hematol Oncol HO. 2012;10:363-365.
32. Acar S, Gözmen S, Bayraktaroğlu S, et al. Evaluation of Liver Iron Content by Magnetic Resonance Imaging in Children with Acute Lymphoblastic Leukemia after Cessation of Treatment. Turk J Haematol. 2020;37:263-270.

33. Sait S, Zaghloul N, Patel A, et al. Transfusion related iron overload in pediatric oncology patients treated at a tertiary care centre and treatment with chelation therapy. Pediatr Blood Cancer. 2014;61:2319-2320.
34. Sirvent A, Auquier P, Oudin C, et al. Prevalence and risk factors of iron overload after hematopoietic stem cell transplantation for childhood acute leukemia: a LEA study. Bone Marrow Transplant. 2017;52:80-87.
35. Ktena YP, Athanasiadou A, Lambrou G, Adamaki M, Moschovi M. Iron chelation with deferasirox for the treatment of secondary hemosiderosis in pediatric oncology patients: a single-center experience. J Pediatr Hematol Oncol. 2013;35:447-450.
36. Armstrong GT, Plana JC, Zhang N, et al. Screening adult survivors of childhood cancer for cardiomyopathy: comparison of echocardiography and cardiac magnetic resonance imaging. J Clin Oncol Off J Am Soc Clin Oncol. 2012;30:2876-2884.
37. Ylänen K, Poutanen T, Savikurki-Heikkilä P, Rinta-Kiikka I, Eerola A, Vettenranta K. Cardiac magnetic resonance imaging in the evaluation of the late effects of anthracyclines among long-term survivors of childhood cancer. J Am Coll Cardiol. 2013;61:1539-1547.
38. Cheung Y-F, Lam WW-M, Ip JJ-K, et al. Myocardial iron load and fibrosis in long term survivors of childhood leukemia. Pediatr Blood Cancer. 2015;62:698-703.
39. Lutz K, von Komorowski G, Dürken M, Engelhardt R, Dinter DJ. Myocardial iron overload in transfusion-dependent pediatric patients with acute leukemia. Pediatr Blood Cancer. 2008;51:691-693.

LEGENDS

FIGURE 1 Scatter plot depicting the correlation between liver iron concentration and serum ferritin. The parameters had a linear correlation (r=0.49). As the serum ferritin increased, the LIC increased as well ($p<0.001$).

Hosted file

`TABLE 1.docx` available at https://authorea.com/users/741197/articles/713606-estimation-of-iron-overload-with-t2-mri-vs-serum-ferritin-in-children-treated-for-hematological-malignancies

Hosted file

`TABLE 2.docx` available at https://authorea.com/users/741197/articles/713606-estimation-of-iron-overload-with-t2-mri-vs-serum-ferritin-in-children-treated-for-hematological-malignancies