Research Article

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Iron overload during the treatment of acute leukemia: pretransplant transfusion experience

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Background: Recent studies have shown the increased risk of mortality in cases with acute leukemia and iron overload. We aimed to determine the status of iron overload in patients with acute leukemia. **Materials & Methods:** Patients diagnosed with acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) between January 2015 and December 2019 were included in the study. **Results:** At 6 months, there were statistically more patients with serum ferritin >1000 in the AML group compared to the ALL group (p = 0,011). **Conclusion:** Iron overload occurs earlier in patients with AML; the difference disappears after 6 months of treatment. It is the correct point to emphasize that iron overload is an important factor of pretransplant morbidity, especially in AML cases.

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Keywords: acute lymphoblastic leukemia (ALL) • acute myeloid leukemia (AML) • iron overload • prognosis • transplantation

Introduction

Acute myeloid leukemia (AML) is a clonal malignant disease in adults, characterised by the abnormal proliferation of myeloid precursor cells, resulting in haematopoietic failure [1]. Acute lymphoblastic leukemia (ALL) is a hematological malignancy originating from lymphoid progenitor cells and is more common in children [2]. Cases achieving remission following chemotherapy are referred to bone marrow transplantation in accordance with risk stratification [3]. Methods and strategies aimed at reducing non-relapse early/late complications have been investigated recently [4].

Iron is an essential mineral involved in basic metabolic reactions. Excess iron is stored in tissues as ferritin. On the other hand, excess iron exerts toxic effects on cells through free oxygen radicals [5]. Owing to the lack of an active excretion system from the body, it contributes to the production of reactive oxygen species and therefore to cell damage [5].

Iron overload disorders are examined in two ways: primary (hereditary) and secondary (acquired) [6,7]. Increased iron levels, which are associated specifically with transfusions, may accumulate in organs such as heart and liver and cause toxic effects. Recent studies have shown the increased risk of transplantation-related mortality, posttransplant fungal infection, and the increase in additional morbidity in cases with acute leukemia and iron overload [6,7].

As plasma ferritin level correlates with iron overload, serum ferritin level is very important in the diagnosis of iron metabolism diseases [8]. When iron overload is suspected, plasma ferritin and transferrin saturation are measured as part of a screening test [9]. While phlebotomy is preferred in nonanemic patients, chelation therapy is preferred in anemic patients [10].

As a result of the damage caused by the iron storage in parenchymal cells, liver diseases such as cirrhosis and diabetes mellitus may occur [11–13]. Reducing iron burden with the treatment of patients with iron overload in pretransplant period is a current area of discussion. It is possible to observe these effects, especially in myelodysplastic

syndrome (MDS) patients. Iron overload begins to develop in MDS patients before they become transfusion dependent, and ineffective erythropoiesis suppresses hepcidin production in the liver, thus leading to increased iron absorption from intestinal mucosa. However, the most important cause of iron overload in MDS is chronic transfusions. Iron accumulation has a negative effect on overall survival and also causes endothelial and cardiac dysfunction. The most important effect is the exacerbation of bone marrow failure with iron overload. Therefore, chelation therapies are of great importance in the follow up of MDS [14]. Also in cases of leukemias, the negative effect of iron overload on transplant-related mortality and overall survival has been demonstrated; therefore, pretransplant chelation therapies are seen as part of transplant conditioning [15].

Therefore, we aimed to determine the status of iron overload, the need for iron reduction therapy and the number of transfusion units that caused iron overload in patients with acute leukemia during therapy.

Materials & methods

Patients diagnosed with ALL and AML between January 2015 and December 2019 at the Department of Hematology, Istanbul Training and Research Hospital were included in the study. In addition to the basal ferritin levels of the patients, the ferritin levels at 3, 6 and 12 months were also recorded. The number of erythrocyte suspension transfusions received by the patients during the treatment was also recorded. The relationship between different ferritin levels and iron overload with the number and frequency of transfusions was investigated. The ferritin limit, which is significant for iron overload, was accepted as 1000 μg/l.

Exclusion Criteria

All patients were in the pretransplant period. Patients who had undergone bone marrow transplantation during the 12-month follow up were excluded from the study. Patients with congenital or acquired bone marrow failure syndromes, chronic liver disease, or nephrotic syndrome, which could directly or indirectly affect serum iron parameters, were excluded from the study. Patients with a C-reactive protein (CRP) value of >10 mg/l as an indicator of acute infections likely to affect ferritin levels or who were taking drugs likely to affect iron parameters were excluded from the study. CRP was measured in all patients.

Statistical Analysis

The data obtained from the study were summarized by using descriptive statistics and were tabulated as mean ± standard deviation and median, minimum and maximum, depending on the distribution for continuous (numerical) variables. Categorical variables were summarized as numbers and percentages. Normality of numeric variables was checked with Shapiro–Wilk test. For the comparison of two independent groups, Mann–Whitney U test was used in the cases where numerical variables did not show normal distribution. Friedman test was used to examine the changes between two or more measurements taken from the same individuals, when the numerical variables did not show normal distribution. Fisher's exact test was used in 2 × 2 tables for comparing differences between categorical variables. Statistical analysis and some figures obtained were done by "Jamovi project" (2020), Jamovi program (Version 1.2.22 [Retrieved from https://www.jamovi.org]) and some graphics were done in Microsoft Excel. The significance level was considered as $p \leq 0.05$ in the analyzes.

Results

Of the 142 patients included in the study, 62 of them who had undergone bone marrow transplantation during the 12-month follow up, 4 patients with congenital or acquired bone marrow failure syndromes, chronic liver disease, or nephrotic syndrome and 26 patients with a CRP value of >10 mg/l as an indicator of acute infections were excluded from the study (Figure 1). A total of 50 patients were included in our study. Twenty-nine (58%) of these patients were males, and 21 (42%) were females. The mean age of the patients was 57 ± 20,4 years. Thirty-two (64%) patients were diagnosed with AML, and 18 patients (36%) were diagnosed with ALL. The mean of overall survival (OS) of the patients was 436,7 ± 395,3 days. While 39 patients (78%) died during the study, 11 patients were alive. In Table 1, age and gender distribution, diagnosis and survival status of patients are shown.

It was found that the mean age of AML patients was significantly older than ALL patients (AML patients 67,8 ± 12,1 years; ALL patients 37,8 ± 18,1 years; $p < 0,001$). Gender distribution was similar in AML and ALL groups. Twenty-eight (87,5%) of AML patients and 11 (61,1%) of ALL patients exited during the study. The mortality rate in the AML group was statistically significantly higher than the ALL group ($p = 0,041$). Median OS was 278 days in AML and 373 days in ALL patients ($p = 0,130$). Table 2 shows the age, gender distribution and

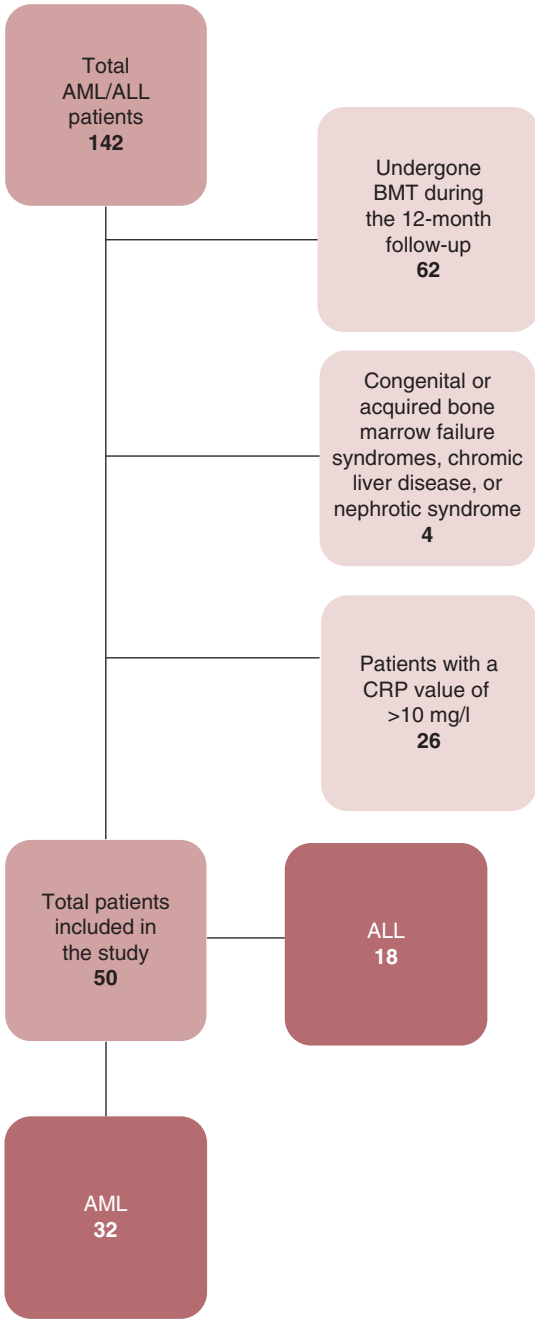

Figure 1. Flow chart of patients selection.
ALL: Acute lymphoblastic leukemia; AML: Acute myeloid leukemia; CRP: C-reactive protein.

Table 1. Age, gender and diagnosis distribution and survival status of patients.

Mean age at initial diagnosis, years ± SD		57 ± 20,4
Gender	Male	29 (58%)
	Female	21 (42%)
Diagnosis	AML	32 (64%)
	ALL	18 (36%)
Survival status	Alive	11 (22%)
	Exitus	39 (78%)
Mean overall survival, days ± SD Median (range)		436,7 ± 395,3 353 (29–2182)

ALL: Acute lymphoblastic leukemia; AML: Acute myeloid leukemia; SD: Standard deviation.

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Table 2. Comparison of AML and ALL patients in terms of demographic data and survival.

	AML (n = 32)	ALL (n = 18)	p-value
Mean age at initial diagnosis, years ± SD	67,8 ± 12,1	37,8 ± 18,1	**<0,001**
Gender			
Male	17 (53,1%)	12 (66,7%)	0,352
Female	15 (46,9%)	6 (33,3%)	
Survival status			
Alive	4 (12,5%)	7 (38,9%)	0,041
Exitus	28 (87,5%)	11 (61,1%)	
Mean overall survival, days ± SD Median (range)	424,6 ± 450,6 278 (29–2182)	467,6 ± 210,4 373 (260–954)	0,130

Boldface values indicate statistical significance.
ALL: Acute lymphoblastic leukemia; AML: Acute myeloid leukemia; SD: Standard deviation.

Table 3. Comparison of serum ferritin levels in patient subgroups: 1st, 3rd, 6th and 12th month of treatment.

	AML (n = 32)		ALL (n = 18)		p-value
Ferritin level (μg/l)					
Basal	334,4 ± 316,1	247 (4–1130)	413,4 ± 500,2	237 (13–1500)	0,936
1st month	929,6 ± 456,7	870 (110–1574)	1083 ± 484,8	1295 (550–1500)	0,648
3rd month	1102,3 ± 384,8	1181 (352–1500)	886,2 ± 611,6	870 (122–1500)	0,511
6th month	1304,4 ± 296,2	1500 (578–1500)	746,6 ± 545,1	621 (237–1500)	0,018
12th month	1280,6 ± 364,7	1500 (479–1500)	1415 ± 135,3	1472 (1216–1500)	0,938
p-value	0,095		N/A		

ALL: Acute lymphoblastic leukemia; AML: Acute myeloid leukemia.

Table 4. Comparison of patients with serum ferritin levels >1000 μg/l at basal and other measurement time points according to patients subgroups.

	AML (n = 32)	ALL (n = 18)	p-value
Ferritin level >1000 (μg/l)			
Basal	2 (6,3%)	3 (16,7%)	0,336
1st month	6 (37,5%)	3 (60%)	0,611
3rd month	10 (66,7%)	2 (40%)	0,347
6th month	14 (87,5%)	2 (28,6%)	0,011
12th month	8 (80%)	4 (100%)	0,999

ALL: Acute lymphoblastic leukemia; AML: Acute myeloid leukemia.

survival status of AML and ALL patients.

There was no statistically significant difference between AML and ALL patient groups in terms of basal serum ferritin levels measured at the beginning of the treatment (p = 0,936). Ferritin levels at 6 months was found to be significantly higher in AML patients (p = 0,018). Table 3 shows serum ferritin levels measured at baseline and other time points in AML and ALL patient groups.

In the first evaluation, serum ferritin levels of 2 patients in the AML and 3 patients in the ALL group were >1000 μg/l. It was observed that the number of patients with ferritin level >1000 in the AML group increased to 14 patients (87,5%) at 6 months of treatment. In ALL patient group, it was observed that these values remained constant in the measurements performed at the same time point, and only 2 patients had serum ferritin values >1000 at 6 months. At 6 months measurements, there were statistically more patients with serum ferritin >1000 in the AML group compared to the ALL group (p = 0,011) (Table 4).

There were 23 patients alive at 6 months of treatment. During this period, the number of patients with serum ferritin value >1000 μg/l was 14 (87.5%) in the AML group and only 2 (12,5%) in the ALL group. There was a statistically significant difference between the AML and ALL groups in terms of the number of patients with

Table 5. Comparison of patients with serum ferritin >1000 μg/l and <1000 μg/l (at 6 months of treatment) in terms of disease distribution, total number of transfusions and survival.

		Ferritin level (3–6 months)		p-value
		>1000 (n = 16)	<1000 (n = 7)	
Diagnosis	AML	14 (87,5%)	2 (28,6%)	0,011
	ALL	2 (12,5%)	5 (71,4%)	
Total number of transfusions		42,5 (21–67%)	23 (10–38%)	0,003
Last status	Alive	2 (12,5%)	2 (28,6%)	0,557

ALL: Acute lymphoblastic leukemia; AML: Acute myeloid leukemia.

Table 6. Comparison of the number of erythrocyte transfusions received by patient subgroups and at time intervals up to the 1st, 3rd, 6th and 12th month of treatment.

	AML (n = 32)	ALL (n = 18)	p-value
Erythrocyte Transfusions (Unit)			
Up to 1st month	8 (4–13)	7 (4–12)	0,182
1–3. months	2 (0–6)	2,5 (0–6)	0,633
3–6 months	2 (0–12)	0,5 (0–6)	0,501
6–12 months	0 (0–4)	0 (0–16)	0,685
p-value	**<0,001**	**<0,001**	

Boldface values indicate statistical significance.
ALL: Acute lymphoblastic leukemia; AML: Acute myeloid leukemia.

iron overload (p = 0,011). During this period, patients with iron overload received a median total of 42,5 units of erythrocyte transfusion, while patients without iron overload received 23 units of erythrocyte transfusion. Patients with iron overload received higher number of erythrocyte transfusions compared to patients without iron overload (p = 0,003). Of the 16 patients with iron overload, 14 (87,5%) were exitus, while only 5 (71%) patients were exitus without iron overload. There was no statistically significant difference between the patients who were alive and exitus in terms of the frequency of iron overload (p = 0,557) (Table 5).

In both AML and ALL patient groups, it was observed that the most transfused period was the first month of treatment. During this period, the median number of erythrocyte transfusions was 8 units in the AML and 7 units in the ALL group. There was no statistically significant difference in the number of erythrocyte transfusions between the two groups during this period. It was observed that the number of erythrocyte transfusions decreased significantly as the treatment progressed in both AML and ALL groups (p < 0,001). When AML and ALL groups were compared in terms of the median number of transfusions at the study measurement time points, no statistically significant difference was found in any period (Table 6).

Discussion

With the increasing cure rate in hematological malignancies, more focus has been put on supportive treatment of these diseases and prevention of their complications. In acute leukemias, iron overload secondary to multiple transfusions during intensive chemotherapy is one of the major complications that develop in patients with treatment [16].

Ferritin concentration remains the most practical and economical method for measuring total body iron [17]. In diseases such as acute leukemias and MDS, the main reason for iron overload is multiple blood transfusions, although cytotoxic chemotherapy and ineffective erythropoiesis also contribute to this process [18]. It is known that as a result of approximately 20 units of erythrocyte transfusion, body depot iron will increase to a level above the severely toxic limit of 1000 μg/l [4].

In a study, the requirements for erythrocyte transfusion during induction and consolidation chemotherapy were evaluated in 206 newly diagnosed AML patients from 5 different hospitals, and it was found that a patient received a mean of 18 erythrocyte suspensions over a 4-month period [19]. In another study, the amount of transfusion during the chemotherapy process of 19 newly diagnosed AML patients was examined. It was found that a patient received a mean of 14 erythrocyte suspensions, and the need for transfusion during induction chemotherapy was greater than during consolidation therapy [20].

In our study, it was observed that the most transfused period in both AML and ALL patients was the first month of treatment, which is the period when remission induction treatment was given. During this period, the median number of red cell transfusions was 8 units in AML group and 7 units in ALL group. There was no statistically significant difference in the number of erythrocyte transfusions between the two groups during this period. In both AML and ALL groups, it was observed that the number of erythrocyte transfusions decreased statistically significantly as the treatment progressed, i.e. during the consolidation treatment periods ($p < 0,001$). When AML and ALL groups were compared in terms of the median number of transfusions at the study measurement time points, there was no statistically significant difference found in any period. Ferritin was found to be >1000 µg/l in 14 of 23 patients living at 6 months of treatment. During this period, patients with iron overload received a median total of 42,5 units of erythrocyte suspension transfusion, while patients without iron overload received 23 units of erythrocyte transfusion. When compared with patients without iron overload, it was found that they received higher number of erythrocyte transfusions ($p = 0,003$). A mean of 14 (5–21) transfusions were performed in an AML patient in our study, while a mean of 12 (5–16) transfusions were performed in an ALL patient. It has been observed that these results are consistent with previous studies. To avoid the negative effects of iron overload, it can be assumed that early iron reduction therapies may come into question in patients with acute leukemias. As iron overload is found more in the AML patient group, this group requires more care. In a study conducted by James C. Barton *et al.*, in a total of 5 patients who had successfully undergone chemotherapy with a diagnosis of acute leukemia and had a mean ferritin value of 1531 ng/ml, it was reported that iron overload was brought under control when these patients underwent weekly phlebotomy [16].

In different studies, it was observed that high ferritin levels in patients with acute leukemia increase the risk of developing fungal infections after bone marrow transplantation and have a negative effect on mortality. In many of these studies, the threshold ferritin value for iron accumulation was accepted as 1000 µg/l [21]. In a study conducted by Albert-Altes *et al.*, in a total of 81 patients, it was observed that high ferritin levels and transferrin saturations at the pretransplant stage affected posttransplant mucositis, bacteremia, and febrile days [22].

In a study conducted by Lebon *et al.*, it was revealed that hyperferritinemia in AML is a negative factor on relapse [23]. In a study performed by Potaznik *et al.*, in 136 patients with ALL, the group with high ferritin and transferrin saturations showed a significant decrease in OS [24]. In another study performed by Tunçcan *et al.*, in 255 hematological malignancies, it was observed that high ferritin and CRP levels during the pretransplant period of patients with hematological malignancies and undergoing stem cell therapy were associated with hepatosplenic candidiasis developing after transplantation [25].

It is important to prevent iron overload for oncogenesis, transplantation process, transplant-related mortality or OS. Recent studies indicate that iron overload leads to p53 inactivation and induction of oncogenesis and chelation therapies cause an increase in p53 expression [26]. Deferoxamine showed anti-tumour effect in patients with advanced hepatocellular carcinoma [27,28]. In addition, iron chelator triapine showed positive results for patients with cervical cancer [29]. New studies are needed to prove the anti-tumour efficacy in hematological malignancies.

The most important limitation of our study was our limited number of patients. The most important reason for keeping the number of patients limited was that all patients included in the study were in pretransplantation period, which is an important process that will affect iron accumulation. Posttransplantation cases were excluded during the 12-month follow-up period. Among the patients were cases with different cytogenetic results, there were also Bcr/Abl positive ALL cases. However, there was no statistically significant correlation between cytogenetic results and our hypothesis. No statistical correlation was detected between the cytogenetic distribution and our study results. These results could also be attributed to the limited patient population.

Conclusion

Acute leukemia patients mostly need transfusion during the first months of induction chemotherapy. Iron overload occurs earlier in patients with AML than in patients with ALL; the difference between these two groups disappears after the 6 months of treatment. Patients with a critical ferritin level of >1000 µg/l received statistically significant more transfusions. No difference was found between AML and ALL cases in terms of transfusion numbers. It is necessary to emphasize that iron overload is an important factor of pretransplant morbidity, especially in AML cases.

Future perspective

The most important point of the study for the future is its striking result, especially in terms of pretransplant mortality and morbidity. Following adequate awareness of iron overload, it is thought that in the near future, pretransplant target ferritin levels will be determined for pretransplant and posttransplant follow up, and it will be an important key point in leukemia cases.

Summary points

- Leukemia cases achieving remission following chemotherapy are referred to bone marrow transplantation in accordance with risk stratification.
- Methods and strategies aimed at reducing nonrelapse early/late complications have been investigated recently.
- Iron levels associated with transfusion may accumulate in organs such as heart and liver and cause toxic effects.
- The objective of this study was to determine the status of iron overload, and the need for iron reduction therapy and the number of transfusion units after severe iron overload develops in patients with acute leukemia due to frequent erythrocyte transfusions during pretransplant therapy.
- A total of 50 patients were included in this study. Thirty-two (64%) patients were diagnosed with AML, and 18 patients (36%) were diagnosed with ALL.
- Ferritin levels at 6-months was found to be significantly higher in AML patients ($p = 0,018$).
- At 6-month measurements, there were statistically more patients with serum ferritin >1000 in the AML group compared to the ALL group ($p = 0,011$).
- Patients with iron overload received a median total of 42,5 units of erythrocyte transfusion, while patients without iron overload received 23 units of erythrocyte transfusion.
- It is necessary to emphasize that iron overload is an important factor of pretransplant morbidity, especially in AML cases.

Author contributions

All authors contributed to the editing of the manuscript. I Serin wrote the manuscript and made the accompanying figure and tables.

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

This study was approved by the ethics committee of our hospital (Approval date: 22.11.2019; no.: 2055). An informed consent was obtained from all of our patients to participate.

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