Serum Iron as an independent predictor of Survival in Childhood Acute Leukemia

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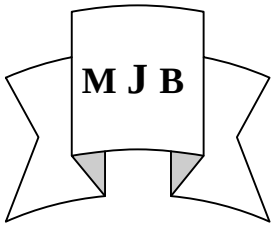

Abstract

The present investigation was motivated from the consideration that a host environment rich in iron, might offer favorable growth conditions for leukemic cells in addition to infection, thus affecting survival. Hypothesizing that any effect of an increased serum iron on the risk of bacterial infection would be particularly important in immunosuppressed patients during chemotherapy.

Serum iron measurments were obtained on fifty – eight (58) pediatric patients with acute Lymphocytic Leukemia (ALL) before and after chemotherapy and after achieving clinical remission. The relationship between serum iron and survival was observed when patients were stratified according to length of time from diagnosis, risk group and French – American – British (FAB) classification.

A significant difference ($P< 0.001$) was found between the survival of patients according to whether their first measured serum iron was greater than 165 µg/dL or less than 165 µg/dL, with no deaths in the group with serum iron less than 65µg/dL.

It is suggested that infectious complications (pneumonia , sepsis, etc..), FAB classification should be taken into consideration in evaluating serum iron levels as prognostic variable in survival of acute lymphocytic leukemia; however, these findings suggest the need for a prospective study.

الخلاصة

شملت هذه الدراسة قياس مستوى الحديد في مصل ٥٨ طفلاً مصاب بأبيضاض الدم اللمفاوي الحاد، كذلك في ٢٥ طفلاً سوياً اخذوا كنموذج ضابط بنفس معدل العمر (١-١٢ سنة)تم تقسيم المرضى الى مجموعتين اعتماداً على مستوى انزيم alanine aminotransferase عند التشخيص، وتم اخذ النماذج عند التشخيص، خلال اخذ العلاج وبعد الوصول الى فترة المهادنة السريرية.

لوحظ وجود دلالة بينية ($P<0.001$) بين مستويات الحديد وزمن البقاء على قيد الحياة في المرضى المصابين باللوكيميا، وان قياس مستوى الحديد في مرض اللوكيميا دليل مفيد لمراقبة حالة المريض.

Introduction

Infection is the leading cause of death in patients with acute Leukemia [1]. This susceptibility to infection is accounted for only partly by immunosuppression or a decrease in granulocyte count [2]. Normal human serum inhibits the growth of many microorganisms [3]. The mechanism for this inhibition appears to be multifactorial, but key inhibitory factors are iron and transferrin.

Iron is an essential nutritional growth factor for bacteria, and many experiments suggested that hyperferre-mia increase bacterial growth in serum [4]. Most microorganism require an exogenous source of iron for DNA synthesis and other vital functions [5].

The iron binding function of transferrin can be decisive factor in determining survival from bacterial infection [6].

Circumstantial evidence showed that most patients with (ALL) have hyperferremia, which results in an increased percentage saturation of transferrin with iron [7].

However, the clinical importance of hyperferremia in increasing the risk of infection has not been clearly demonstrated.Because of the potential importance of hyperferremia as a parallel risk factor for infection in severly immunosuppressed patients, the present work was an observational study planned to extend earlier results and to explore further the possible association between serum iron and survival in pediatric patients with (ALL).

Patients and Methods

Measurements of serum iron were obtained on 23 female and 35 male pediatric ALL patients (aged 1-12 years), seen at Al-Mansour Teaching Hospotial and Central Hospital for Children between Octobre 2000 and October 2001. All the patients entered this study at the time of their diagnosis of ALL, and all baseline information was available for the study.

Table 1 summarizes the patients according to conventional clinical and laboratory parameters at diagnosis.All the patients were at disease remission following intensive chemotherapy within two months [8,9]. A group of (25) healthy children of age and sex method were studied as controls.

Upon their admission and prior to any therapeutic intervention, blood samples were drawn, and again within 4 days of receiving chemotherapy, and after termination of treatment while achieving clinical remission.

Serum iron levels were determined by Atomic Absorption Specrophotometer [10].

Serum alanine aminotransferase (ALT) levels were measured. [11-13].

By protocol design, treatement was continued without modification in the presence of ALT elevations if there was no other evidence of liver dysfunction [14]. Additional liver function tests (alkaline phosphatase, bilirubin, and prothrombin time) were not routinely performed.

Statistical analyses were performed using student –t- test. The significance level was set at 0.05.

Survival Data

The survival of each patient was calculated as the number of months from the date of the first serum iron measurment taken for the purpose of this study (until October 2001).

For the analysis of survival, patients were grouped according to the first serum ALT measurement.

This method of grouping was a retrospective classification of patients, the cut off points were chosen prior to analysis of the survival data; the serum iron and ALT cut off values are the middle of the normal range.

Results

A summary of pateints examined by grouping measurments according to stage of treatment (i.e at diagnosis, on therapy and after clinical remission) is given in Table 2. Serum ALT values were retrospectively examined in the patients as a marker of hepatocellular damage [12,13].

At the time of diagnosis of ALL only 20 of 58 patients (34%) had greater than a two fold elevation of ALT. Normal ALT values in our laboratory are 6-12 U/L. These patients are designated as group 1. The remaining 38 patients are designated as group 2. The children in group 2 had occasional mild ALT elevations that did not usually exceed the upper limit of normal.

At diagnosis, 10 of the patient in group 1 (50%) had hyperferremia, while only 7 patients in group 2 (18%) had elevated serum iron levels. None of the controls had an elevated value (120 ±33 µg/dL, range = 65-165 µg/dL).

A marked elevation in serum iron concentration was observed within 4 days of receiving chemotherapetic agents. Thirty-nine (67%) of the original patients with ALL had elevated serum iron (> 165 µg/dL)

Elevated ALT values did not correlate significantly with treatment regimen. They did, however correlate

significantly with older age at diagnosis.

For the remission groups, serum iron reverted to normal when clinical and hematologic remission was achieved. Only 15 patients (24%) of the original patients (9 in group 1and 6 in group 2) had elevated serum iron levels (>than cutoff value = mean + 2 SD).

When disease and treatment stage, FAB classification, presence of fever or sepsis and serum ALT and serum iron were examined jointly, serum iron remained significantly associated with survival analysis revealed an almost "dose - related" relationship between first iron measurment and survival (p=0.005).

The observed survival of patient with serum iron level at diagnosis 65 µg/dL was longer than the survival of those patients with serum iron > 165 µg/dL.

The FAB classification, serum ALT and serum iron at entry into this study was most strongly predictive of survival in these patients. During the end of the observation period, four patients from group 1 (2L1 , 2L3) with first iron 165 µg/dL died (20%), and four patients from group 2 (4 L2), with first iron > 165 µg/dL died (10%), while 2 patients from group 1 (1L2 , 1L3) died in first iron between (65-165 µg/dL) (10%), none died from group 2 circulation [21].

Like other investigators, I found that transfusions administered during the induction chemotherapy significantly increased serum iron in these patients, however, serum iron continued to increase in 24 / 58 patients during the follow-up, although none of them received further transfusions after chemotherapy completion. In fact, I did not find a significant correlation between the follow-up serum iron and total amount of iron transfused.

Abnormal iron status at diagnosis and during treatment can be easily explained by the evidence of inflammation and the transfusions carried out. A possible cause for this phenomenon could be increased intestinal iron absorption caused by chemotherapy- induced mucosal damage [22].

Halonent et al 2003 , observed a long-term iron overload was detected in at least 14% of children after therapy for ALL [23]. Nevertheless, when immunocompromised patients have elevated serum iron concentration, it may pose a clinically

important parallel risk factor for survival in ALL.

The results of the present analysis are compatible with the earlier suggestions. This data confirm that there is not a clear-cut association between iron overload and survival in ALL patients. However, as a significant percentage of surviving ALL patients develop iron overload, the follow-up of these patients should include iron status measurement in order to intervene to prevent the development of complication. To clarify further the implications of the associations observed, however prospective large group studies are indispensable.

Table 1 Summary of patients according to conventional clinical and laboratory parameters at diagnosis

	No. of patients
Sex	
Male	35
Female	23
FAB* classification	
L1	36
L2	14
L3	8
Age (yr)	
1 - 2.9	15
3 - 6.9	33
7 - 12	10
Risk groups**	
Low	38
High	20

* FAB, French –American – British
**Risk groups were formed according to the levels of ALT at diagnosis.

Table 2 Serum iron studies in patients before, undergoing chemotherapy and after achieving clinical remission.

Patients

No. of patients	Before treatment	During chemotherapy	After achieving remission	P value
	58	58	58	
Iron (µg/dL) Group 1 no=20 Mean ±SD Range	 141 ± 20 70 - 188	 302 ± 38 198 - 390	 116 ± 33 66 - 148	 <0.009* <0.005**
Group 2 no=38 Mean ±SD Range	 127 ± 11 98 - 160	 261 ± 25 172 - 290	 108 ± 22 60 - 121	 <0.001* <0.005**

Normal value for controls = 120 ± 33 µg/dL, range = 65 - 165 µg/dL
* for comparison between Leukemic patients before treatment and during chemotherapy.
** for comparison between Leukemic patients before treatment and after achieving clinical remission.

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