Original article

C- Reactive protein and iron status in Iraqi patients with acute myeloid leukemia before and after treatment

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ABSTRACT

Background: Acute Myeloid Leukemia (AML) is a clonal hematopoietic disorder, leading to a premature arrest of the normal differentiation of stem cells. C - reactive protein (CRP) is a marker of inflammation. Serum level of C-reactive protein may be increase in patients with AML. This association between CRP levels and acute myeloid leukemia influenced by multiple factors. Acute myeloid leukemia commonly associated with iron overload. Many factors are participating to the hyperferritinemia associated with AML, inflammation chemotherapy, blood transfusion and ferritin hepatic clearance disorders

Objectives: To assess serum C-reactive protein (CRP) and iron status (serum Iron, Total iron binding capacity, serum ferritin levels) in patients with acute myeloid leukemia (AML) before and after chemotherapy

Materials and Methods: A prospective cohort study included 58 patients (30 male and 28 female) with acute myeloid leukemia with age range (15-65 years). Patients divided into two groups: Group (1) Patients with AML before starting chemotherapy. Group (2) the patients after 4 weeks of chemotherapy In addition to 43 healthy subjects (24 male and 19 female) were included. They were age and sex matched to patients group and considered as controls as (Group 3). This study conducted at the National Center of Hematology and Baghdad Teaching Hospital in the Medical City from February 2014 to June 2014. All patients were subjected to complete history and physical examination. Diagnosis as AML patients was established by complete blood count and blood film, bone morrow aspiration and biopsy. C-reactive proteins. iron, s.total iron binding capacity and s. ferritin were estimated for all .

Results: Serum CRP levels increased in AML patients before and after treatment , while there were a significant increase in mean serum ferritin levels observed in (Group 2) compared to newly diagnosis patients (Group 1)(P<0.002) and the levels were significantly higher in newly diagnosis group compared to healthy controls (P<0.015). Patients with (AML) during remission show significant decrease in iron levels compared to newly diagnosis group (P<0.0001), while levels in healthy controls recorded higher values than both (Group 2) and (Group 1) (P<0.0001). Serum total iron binding capacity (TIBC) levels showed a significant decrease in (Group 2) after treatment compared to (Group 1) before treatment(P<0.0001) but the levels were significantly higher in healthy controls compared to (Group 1) and (Group 2) (P<0.0001)

Conclusion: CRP does not predict response to chemotherapy while it may be of benefit in predicting infection or inflammation in patient with AML post chemotherapy. Regarding Iron status: s.ferritin increase significantly post chemotherapy while s.iron and TIBC decrease.

Keywords: CRP, iron status, AML

Introduction:

Acute Myeloid Leukemia (AML) is a clonal hematopoietic disorder arising from the acquisition of genetic and epigenetic alterations, leading to a premature arrest of the normal differentiation of stem cells and to the accumulation of immature neoplastic cells in the blood and bone marrow [(1).] Changes in white blood cells lead to impaired ability to fight infection and decrease the ability of the bone marrow to form red blood cells and platelets [(2)]. Rate of (AML) incidence raises in male than in female and with progressive of age [(3)]. The development associated with myelodysplastic syndromes (MDS), genetic disorders, acquired diseases, exposures to ionizing radiation and alkylating agents and exposure to anti-cancer chemotherapy [(4)]

Main induction therapy consists of cytarabine (Ara-C) and anthracycline based regimen. It has been found that the complete remission (CR) rate is approximately 60% to 80% in newly diagnosed younger adult patients with AML treated with 3+7" [(5)]. The remission induction therapy in leukemia produces normal bone marrow function, thereby complete remission is defined when the patients have full recovery of normal peripheral blood counts with recovery of normal bone marrow cellularity, and less than 5% blast cells are present in the bone

marrow" [6] Post remission therapy "consolidation therapy" is needed to damage remaining Leukemic cells and prevent relapse [7, 8]

C-reactive protein (CRP), a plasma protein of the pentraxin family and an acute phase reactant, which displays high sensitivity as a general inflammation marker [9]. It is produced and secreted mainly by liver in response to cytokines such as interleukin-6 [10], released from leukocyte within tumor microenvironment such as (location, age, gender). Blast cells growth could cause inflammatory response, thereby increasing CRP levels. Alternatively, chronic inflammation could lead to the development of cancer. CRP is a marker of inflammation, has a direct role in carcinogenesis [11].Serum level of C-reactive protein has a plasma half-life of 19 hours. [12] The association between CRP levels and acute myeloid leukemia risk influenced by multiple factors

During immune activation, ferritin is known as an acute phase reactant because of its intracellular iron storage abilities [13]. By hepatocytes, and also by other cell types, including macrophages and cancer cells it is produced and secreted [14]. Serum ferritin levels may be elevated in infection, systemic inflammation, and malignancies [15]. Evidences were suggested that, there was association between high body iron stores and the risk of developing cancer [16]. So, increased in serum ferritin might indicate the exists of malignant disease spatially in acute and chronic leukemia [17] Acute myeloid leukemia commonly associated with iron overload [18] Many factors are participating to the hyperferritinemia associated with AML , inflammation chemotherapy, blood transfusion and ferritin hepatic clearance disorders [19]. In other study on malignant cells predicted that malignant cells need a high requirement of iron due to the rapid division of the cells. Tumor cells were changed routes of the uptake of iron. These routes may be important in achieving raised iron levels under this condition [20].

Recent study predicted that iron is a risk factor for different types of cancers mainly due to its prooxidant activity. Non–protein-bound iron ("free" or catalytic iron) is a prooxidant, as its participation in the redox cycling which is associated with the generation of reactive oxygen species (ROS) such as the hydroxyl radicals. ROS are highly reactive molecules capable of oxidative damage to DNA [21]. Increased cellular iron may cause tumorigenesis. Neoplastic cells were higher iron requirements than normal cells; therefore decreasing iron level was developed as efficient strategies in chemotherapy and from malignant cells themselves [18]

Total iron binding capacity (TIBC) determines the maximum amount of iron that serum proteins can bind. TIBC assay measure the total number of transferrin binding sites per unit volume of plasma or serum. Normally, almost all the binding capacity is due to transferrin. One third of plasma TIBC is saturated with iron [22] Plasma TIBC rises in iron deficiency, but often tends to be low in patients with iron overload and in protein losing states such as infections, neoplasms, anemia of chronic disease and after trauma [23]. Elevated TIBC, were associated with increased risk for developing various types of cancer such as acute myeloid leukemia [21].

Materials and methods

The prospective cohort study conducted at the National Center of Hematology in Al-Mustansiriyah University and Baghdad Teaching Hospital in the Medical City from February 2014 to June 2014. This study was approved by scientific committee of Mustansiriyah Medical College. Questioner history and consent was obtained from all patients prior to study, fifty-eight (58) patients (30 male, and 28 patients female) aged between (15-65 years)

Inclusion criteria included patients with newly diagnosis of AML, age between (15-65 years), and no history of illness, while the exclusion criteria included patients of AML with subtype M3, age of patients was under 15 years and above 65 years, patients with relapse and refectory of AML and Frail patients not suitable for chemotherapy.

Fifteen patients (15) out of fifty-eight (58) were excluded from the study because preventing to take chemotherapy, went to another center outside Baghdad, loss of follow up or early death during period of study. After exclusion of fifteen patients, forty three patients (43) contained the study, (24 male and 19 female). Patients divided into two groups: Group (1): Patients with AML before starting chemotherapy. Group (2): Patients after 4 weeks of chemotherapy. Group (3): Forty-three (43) healthy subjects (24 male and 19 female) were included in the study mainly from medical staff and their families. They were age and sex matched to patients group and considered as controls.

All Patients were subjected to complete history and physical examination. The diagnosis was established by complete blood count and blood film, bone morrow aspirated and biopsy, liver function tests, and renal function tests. Other parameters were done in this study such as ferritin, CRP, S. iron, and total iron binding capacity.

Patient's treatment was done according to international protocol which is called (3+7)

when Daunorubicin was given in the first day to third day and Cytarabine (Ara-C) was given from the first day to seventh day then evaluation is done on twenty eighth day to evaluate response of patients. Five milliliters (5 ml) of venous blood were taken from each patients and controls. Blood samples were put in plain polyethylene tube and allowed to clot at room temperature for thirty minutes, then samples were centrifuged at (3000 rpm) for (10 min). The obtained serum were frozen at -20 C to be analyzed later, hemolyzed samples were discarded. Latex Agglutination Slide Test was used for the Qualitative and Semi-quantitative Determination of serum C - reactive protein (CRP) in Non-diluted (manufactured by Human-Germany). This measurement depends on the immunological reaction between C-reactive protein (CRP) of a patient specimen serum and the corresponding anti-human CRP antibodies bound to latex particles. In the test cell of the slide, the positive reaction is reflected by a visible agglutination of the latex fractions [24]

Estimation of serum ferritin levels was done by immunoenzymometric assay required essential reagents such as antibodies with affinity and specificity (enzyme and immobilization) using kit (manufactured by Monobind- UAS) [25]. Serum iron concentration was determined by iron Colorimetric test. Estimation of Serum Total Iron Binding Capacity (TIBC) was measured using kit manufactured by (Human-Germany) [27]. TIBC in serum is saturated with a further concentration of Fe+3 ions. Unbound iron (increase) is absorbed by aluminium oxide and precipitated

Statistical analysis: Data were analyzed using the available statistical package of SPSS-22 (Statistical Packages for Social Sciences- version 22), and presented in simple measures of frequency, percentage, mean, standard deviation, and range (minimum-maximum values)

The significance of difference of different means (quantitative data) were tested using Students-t-test for difference between two independent means or Paired-t-test for difference of paired observations (or two dependent means), or ANOVA test for difference among more than two independent means. The significance of difference of different percentages (qualitative data) was tested using Pearson Chi-square test with application of Yate's correction or Fisher Exact test whenever applicable. Pearson correlation was calculated for the correlation between two quantitative variables with its t-test for testing the significance of correlation.

Results:

Regarding distribution of age and gender for AML patients and controls were shown in Table (1). Results of this study demonstrated that the screening test for C-reactive protein (CRP) levels in the most patients showed positive test while all controls showed negative test therefore the comparison is done between two groups of AML patients. CRP levels showed significant differences in two groups of AML : before starting treatment and after treatment in all titers of CRP in(mg/L) (≤6 x >6, ≤12 x >12, ≤24 x >24) with P-Value of 0.014, 0.045, 0.013 respectively as shown in Table(2)

Regarding serum ferritin levels changes in AML patients show a significant increase in patients during remission compared to newly diagnosis , values were statistically significant (849.1±777.6 ; 624.0±197.68 ng/ml , respectively [P<0.002] and the mean values were significantly higher in newly diagnosis patients compared to controls (624.0±197.68; 132.4±138.7 ng/ml ,respectively [P<0.015]) and significantly increase in the patients during remission compared to controls (849.1±777.6; 132.4±138.7 ng/ml , respectively [P<0.0001]) as shown in the Table (3).

In addition, results of iron study showed that the mean serum iron levels in acute myeloid leukemia patients during remission were significantly lower compared to newly diagnosis patients (12.57±1.98; 15.11±2.32 mmol/L), respectively [P<0.0001] .In the same time these mean iron values were significant lower in both newly diagnosis and during remission patients compared to controls (15.11±2.32;12.57±1.98; and 23.19±2.66 mmol/L, respectively [P<0.0001]) as shown in the Table (4) ,

Estimation of total iron binding capacity (TIBC) observed that there were a significant decrease in mean serum TIBC levels in acute myeloid leukemia patients during remission compared to newly diagnosis patients , values were statistically significant (37.63±7.63; 51.32±4.78 mmol/L, respectively [P<0.0001]) , and the mean significantly decrease in the newly diagnosis compared to controls (51.32±4.78; 58.24±5.27 mmol/L, respectively [P<0.0001]) and significantly decrease in the patients during remission compared to control (37.63±7.63;58.24±5.27mmol/L

Discussion:

the prevalence of age in AML group was(40-59) years and (≥ 65 years) (30.2%) were higher than other age groups. Our result results predicting that

AML is more common in elderly. So, AML is generally a disease of old age [28]. These findings consisted with previous report [29, 30]. The results of this study showed that there were a significant increase in serum C- reactive protein CRP) levels in patients with acute myeloid leukemia before treatment because of the response to tumor necrosis, local tissue damage, or associated inflammation. These results were agreed with other studies results [31,32], after treatment, infections in the immunocompromised host as a result of chemotherapy, were associated with elevation occurrence of neutropenic complication, which influences to response to chemotherapeutic, and cause morbidity and mortality. Additionally, malignant process itself causes increasing in CRP levels in spite of the presence of systemic bacterial infections [33]. These findings were in agreement with study done by Endo et al. [34]

Serum ferritin concentrations were estimated in this study for AML groups and it was found that there was an increase in values of serum ferritin in newly diagnosed patients and post chemotherapy when compared to healthy controls. These results were agreed with [35] results, who found that serum ferritin levels among patients newly diagnosed or on remission stage were significantly increased which may indicate that leukemia cell could affect iron metabolism leading to iron overload .Other study showed that the highest levels of ferritin were found in AML patients under chemotherapy course treatment [36].

There was a growing in evidences which predicted that iron overload is common in patients with hematologic malignancies [37], and the excessive iron body stores are known to interfere with natural body defenses and the increase in body stores of iron lead to increase growth rate of cancer cells [38]. Previous study suggested factors that may contribute to the increase in serum ferritin levels in acute myeloid leukemia including as followings:

1. All patients of acute myeloid leukemia are anemic and have an elevation in the amounts of iron storage which are presented by further serum ferritin levels. In large mass of leukemic cells elevated the production of ferritin, this leads to raise in serum ferritin levels.

2. Treatment by chemotherapy leads to damage most of the cells in the body, which lead to release of abnormal amounts of ferritin. There was no correlation between the elevation in the circulating of ferritin during chemotherapy with the amount of blood transfused or the degree of liver damage.

3. The elevation in ferritin levels is a marker of acute phase response, and this acute phase usually founds in the acute myeloid leukemia due to increase in the concentrations of ferritin in the body [39]

Regarding to serum iron levels investigation in this study, the results showed a significant decrease in serum iron levels in pre and post chemotherapy treatment comparing to healthy subjects. The evaluation of deregulations of iron metabolism is very important in serum iron studies, especially iron deficiency and iron excess. Physiological function of iron is importance to produce red blood cells and to use as antimicrobial defense [40] several previous studies also indicated that reducing in serum iron levels in AML patients may due to iron deficiency anemia and acute and chronic infections. These results are in agreement with previous results reported [41].

Other study agreed with these results was by sheikh et al [42], who observed that iron was thought to be a risk factor for cancer development in epidemiological studies in humans. The reducing in serum iron level leads to interfere with the vital functions and increased mortality risk. Before and after chemotherapy treatment, serum iron is effected by several factors including iron absorption from diets; infection, inflammation, and diurnal variation. Patients with AML have inflammation which caused reducing in the iron availability to cells [43]

Other related study showed that two biological effectors change the plasma iron concentration: infection and inflammation .Serum iron concentrations were affected by inflammatory factors that released from cells of immune system during the inflammatory process. Inflammation stimulate the movement of iron from the plasma pool into storage sites in macrophages, this explain the reduction in iron concentrations with the releasing of the inflammatory factors and lead to reduce in the hormone erythropoietin production, reduce response to erythropoietin, and interference with iron metabolism. Finally, anemia of inflammation caused reducing in serum iron levels [44]

In this study, the total iron binding capacity of acute myeloid leukemia patients before and during chemotherapy was lower than in the controls. These findings consisted with previous report which suggested that the production of iron binding proteins is became weak pre, during, and post chemotherapy and decrease the ability of the liver to absorb from the circulation non transferrin bound iron [45] Total iron-binding capacity (TIBC) presents the availability of iron-binding sites, which is influenced by factors: iron status, malnutrition, inflammation, chronic

infection, and cancer. Patients with hematologic disorder including AML cannot mobilized and utilize iron, which is stored in excess in reticuloendothelial system leading to decrease in serum (TIBC) [44]

Conclusion

CRP does not predict response to chemotherapy while it may be of benefit in predicting infection or inflammation in patient with AML post chemotherapy. Regarding Iron status: s.ferritin increase significantly post chemotherapy while s.iron and TIBC decrease

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Table (1): Age gender distribution of studied groups

Characterization		AML		Control	
		No.	%	No.	%
Age(years)	<20	7	16.3	8	18.6
	20-39	10	23.3	10	23.3
	40-59	13	30.2	12	27.9
	≥65	13	30.2	13	30.2
	Mean ±SD(Range)	43.0 ±18.6	(15-65)	43.0 ±18.6	(15-65)
Gender	Male	24	55.8	24	55.8
	Female	19	44.2	19	44.2
*Significant difference between proportions using Pearson Chi-square test at 0.05 level					

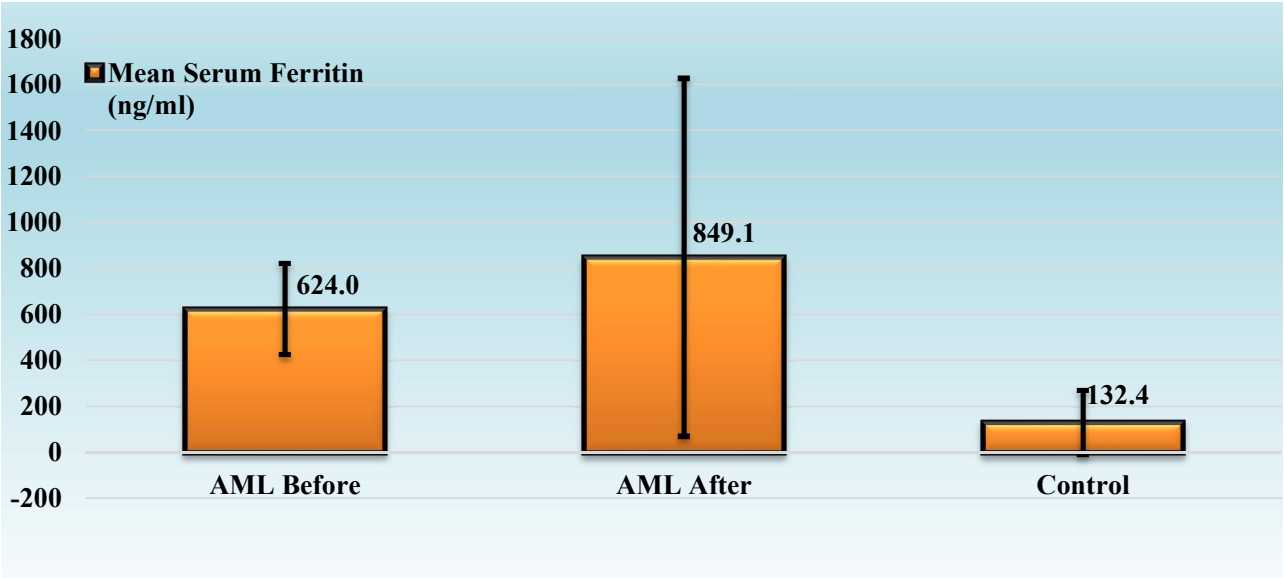
Table (2): Mean C - reactive protein Levels for Studied Groups.

		AML Before treatment		AML After treatment	
		No.	%	No.	%
CRP (mg/L)	0	8	18.6	3	7.0
	6	6	14.0	1	2.3
	12	-	-	2	4.7
	24	7	16.3	4	9.3
	48	22	51.2	33	76.7
P value comparing (CRP=<6 x >6)	0.014*				
P value comparing (CRP=<12 x >12)	0.045*				
P value comparing (CRP=<24 x >24)	0.013*				
*Significant difference between proportions using Pearson Chi-square test at 0.05 level					

Table (3): Mean Serum Ferritin Levels for Studied Groups

Serum Ferritin (ng/ml)	AML Before treatment	AML After treatment	Controls
Number	43	43	43
Mean+SD	624.0±197.68	849.1±777.6	132.4±138.7
Standard Error of Mean	30.146	118.588	21.157
Range	300-1200	410-5704	40.9-982
P value compared to Control	0.015*	0.0001*	-
P value compared to AML After	0.002*	-	-

*Significant difference between



two independent means using Student-t-test at 0.05 level

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Table (4): Mean Serum Iron Levels for Studied Groups:

Serum Iron (mmol/L)	AML Before	AML After	Controls
Number	43	43	43
Mean±SD	15.11±2.32	12.57±1.98	23.19±2.66
Standard Error of Mean	0.354	0.301	0.406
Range	10.60-20.10	8.81-16.30	19.02-28.00
P value compared to Control	0.0001*	0.0001*	-
P value compared to AML After	0.0001*	-	-
*Significant difference between two independent means using Student-t-test at 0.05 level			

Table (5): Mean Serum TIBC Levels for Studied Groups.

TIBC (mmol/L)	AML Before	AML After	Controls
Number	43	43	43
Mean±SD	51.32±4.78	37.63±7.63	58.24±5.27
Standard Error of Mean	0.729	1.163	0.804
Range	42.00-69.00	15.00-60.20	49.00-69.00
P value compared to Control	0.0001*	0.0001*	-
P value compared to AML After	0.0001*	-	-
*Significant difference between two independent means using Student-t-test at 0.05 level			