Evaluation of Some Physiological and Immunological Parameters in Patients with Acute Myeloid Leukemia Before and After Chemotherapy

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Abstract

acute myeloid leukemia (AML) has been commonly observed effect on cxcl8 levels, kidney and liver function. In this study the purpose to estimate a number of parameters of liver, kidney and cxcl8 function in Iraqi patients with acute leukemia before and after Chemotherapy. The study subjects comprised of 60 acute myeloid leukemia patients (male40 and female20) and 30 healthy individuals (15 males and 15females) with an age ranging from (18-68) years were involved in this study and it was performed in Marjan Teaching Hospital (hematology unit) in Babylon Governorate, middle Euphrates cancer center /Najaf province and Medical City Hospital (hematology unit) in Baghdad Governorate/ Iraq. For the purpose of determining levels of the parameters of kidney, liver function and clcx8, blood samples were taken from each patient and control. The result findings that AML patients had significantly higher ($p \leq 0.01$) serum levels of the liver function markers (ALT) and (AST) than the control group ($p \leq 0.01$). Furthermore, as compared to the control, AML patients have significant increases($p \leq 0.01$) in blood urea, creatinine, and uric acid levels . Additionally, as compared to the control group, the level of cxcl8 in the AML patients significant decrease ($p \leq 0.01$).

1. Introduction

Leukemia is a type of blood cancer that develops when a blood cell's life cycle or certain aspects of its division are not adequately controlled (Chaudhari et al.,2014). From a single cell, the cell starts to multiply uncontrollably, creating a large cell population (Stock and Hoffman.,200) . Cancers of the blood, bone marrow, and lymph nodes are known as haematological malignancies. chronic lymphocytic (CLL), acute lymphocytic (ALL), acute myeloid (AML), chronic myeloid (CML), myeloma, and lymphoma are all included in this categorization. (Taylor.,2017) ,(Enad and Al-Amili.,2019).

Progenitor cell proliferation that is uncontrollable and absent of differentiation is a hallmark of leukemia.

When differentiation is blocked, undeveloped cells accumulate, beunsuccessful to mature properly, and eventually death. Immature cells that have ceased d ifferentiating and have escaped immunesurveillance eventually take over the bone marrow and infect ot her tissuesand organs, resulting in death (Hoffbrand and Moss.,2011)

Infiltration of leukemic liver cells has been reported in the portal vein tract and the sinusoid of the liver in AML; particularly extensive infiltration of leukemic liver cells can manifest as fulminant liver failure (Litten et al.,2006) Aminotransferases are generally found in small amounts in the blood.When the liver cell membrane is harmed, the permeability increases , these enzymes are released in higher levels into the bloodstream (Eugene et al.,2001 ; Anderson et al .,2001). The activation of (ALP) and (GGT) is great when leukemia cells infiltrate the liver (Shimizu et al.,2006).

Cxcl8 (Chemokines) are small proteins that regulate a variety of tissue activities, including cell recruitment and activation, in both inflammatory states and homeostatic. CXCL8 is a chemokine that interacts with the CXCR1 and CXCR2 receptors. Many cell types, including mesothelial cells, endometrial cells and peripheral blood monocytes, produce the chemokine CXCL8. CXCL8 has been identified to increase the proliferation of many additional cell types in addition to its chemotactic, angiogenic, and activating effects for granulocytes (Li et al.,2012)

2. Materials and Methods

This study(cases and control) was accompanied during the period from january(2021) to August (2021) and it was performed in Marjan Teaching Hospital(hematology unit) in Babylon Governorate, middle Euphrates cancer center /Najaf province and Medical City Hospital (hematology unit) in Baghdad Governorate/ Iraq

The study subjects comprised of 60 acute myeloid leukemia patients (male40 and female20) , age (ranging from 18-68 years).These patients were suffered from AML and were referred to the Hematology Consultation Clinic . Diagnosis was depended on peripheral blood smear of blood sample revealing at least 10% blast cell and other diagnostic criteria included TSP-1. The study included 40 patients who received first-line chemotherapy as first-line therapy and 20 with newly diagnosed AML. The healthy group, which was composed of 30 people (15 males and 15 females)

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with ages ranging from 18 to 68 that served as a comparison group for the patient group
5 ml disposable needles and syringes were used to draw 3 ml of blood from the vein. The serum was removed from the blood via centrifugation at 3000 rpm for (10-15) minutes and then maintained in a deep freezer at -20 C before analysis. The blood was injected into a gel tube and allowed to coagulate for 10 minutes at room temperature. The collected data were examined using SPSS/PC version 22 of the statistical package for social science. The t-test and Anova test were used to calculate differences between means with a p-value of (≤ 0.05).

3. Result

1.The general characters of study groups
Result show the patients with acute myeloid leukemia are (40.86±15.60) years and the percentage of males was (66.6%) while (33.3%)) are females , (62.5%) of male are hypertension while the proportion (53.33%) of healthy male . also the results of study revealed (60%) of female patient are hypertension while it was (60%) in healthy female , as showing in table (1)

Table 1: General characteristic of the patients and healthy groups.

Character	Healthy Control (N= 30)	Patients (N= 60)
Age (years) (mean ±S.D)	(18-68) (40.73±14.99)	(18-68) (40.86±15.60)
Gender (NO%)		
Male Female	15/30 (50%) 15/30(50%)	40/60(66.6%) 20/60(33.3%)
Hypertension (%، .NO)		
Male with hypertension Female with hypertension Male without hypertension Female without hypertension	8/15(53.33%) 9/15(60%) 7/15(46.66%) 6/15(40%)	25/40(62.5%) 12/20(60%) 15/40(37.5) 8/20(40%)
Residence		
Urban	19/30(63.33%)	42/60(70%)
Rural	11/30(36.66%)	18/60(30%)
Family history		
Present	8/30(26.66%)	13/60(21.66%)
Absent	22/30(73.33%)	47/60(78.33%)

2. Biochemical parameters levels in study groups.

The result in the table (2) showed a significant increase at a level (p≤ 0.00) in level of (urea ,creatinine , AST, ALT) concentrations in leukemia patients compared healthy subjects , and significant in new diagnose patients when compared with treated leukemia . Also the level of uric acid increased significant in both leukemia patients and new diagnose compared with the healthy control groups , and when compared between new and leukemia patients the result showed decrease in uric acid in the treated patients compared to the new diagnosis patients, but there was non-significant (p> 0.05) in both Na and K level in all study groups.

Table (2) : levels of some biochemical parameters in acute myeloid leukemia patients and healthy control group.(Mean ± S.D)

Study groups				Variable
Patient(N=60)			Healthy (N=30)	
Sig level	New diagnose Patients (N= 20)	Treated Patient(N=40)		
0.00	24.02±20.20 c,a	36.29±30.29 b	18.70±6.98 a	ALT(U/L)
0.00	21.19±8.57 c,a	30.49±16.25 b	19.08±5.56 a	AST(U/L)
0.00	0.79±0.29 c,a	1.66±1.79 b	0.87±0.18 a	Creatinine(mg/dl)
0.00	29.01±11.47 c	32.00±12.72 b,c	16.00±3.63 a	Urea (mg/dl)
0.00	9.57±1.60 c	7.66±2.19 b	4.85±1.50 a	Uric acid mg/dl
0.18	137.92±5.28	141.20±16.62	135.96±6.05	Na [mmol/l]
0.10	3.82±0.59	4.07±0.72	3.75±0.56	K + [mmol/l]

Different letters refer to significant difference at level (p≤0.05) between groups

3. Level of immune biomarker between in study groups

In a table (3) that shows the results of the statistical analysis of the immune biomarkers that was included in this work, it was found that there was a significant different (p≤0.01) in the level of immune markers cxcl8 of patients groups when compared with healthy individuals. The results showed the presence significant increase (p≤0.01) in statistically indication of the level (cxcl8) in new diagnose patients when compared with treated patients.

Table (3):levels some of immune biomarkers in acute myeloid leukemia patients and healthy control groups. Mean ± S. D				
Study groups				Variable
Patient(N=60)			Healthy (N=30)	
Sig level	New diagnosis Patients (N=20)	Treated Patients)N= 40(		
0.01	90.01±121.61c	44.80±85.61 b	155.91±201.93 a	Cxcl8 (ng/L)

The levels of biochemical parameters in acute myeloid leukemia patients and healthy groups according to gender (mean ± S.D)

In the table (4) which describe levels of biochemical parameters showing that in acute myeloid leukemia patients markedly rise in level biochemical parameters that measured in the study , where the significant increase (p≤ 0.05) in (AST, ALT, creatinine , urea,) concentration for both genders when compared with healthy control group .while insignificant increase (p≥0.05) in (uric acid , k)level in male patients compared with control groups. while, insignificant increase (p≥0.05) in (Na) level in both genders patient with compared of health control.

Table(4):levels some of biochemical parameters in patient Vs healthy (according to gender)						
P. value (female)	P. value (male)	patients (N=60		Healthy control (N=30)		Groups variable
		female	male	female	Male	
*0.00	0.04*	31.16±27.53	33.39±28.32	17.90±3.61	19.49±9.31	ALT(U/L)
*0.00	*0.00	26.80±16.61	27.74±13.94	18.74±3.88	19.68±4.62	AST(U/L)
0.00*	0.03*	1.17±0.59	1.47±1.82	0.80± 0.16	0.94±0.18	Creatinine(mg/dl)
0.04*	*0.00	28.72±8.39	32.14±13.82	16.53±3.90	15.46±3.39	Urea (mg/dl)
*0.02	0.19	7.67±2.58	8.86±1.75	3.98±1.16	5.72±1.31	Uric acid mg/dl
0.12	0.16	141.76±13.35	139.28±14.30	136.20±5.50	135.73±6.73	Na [mmol/l]
*0.03	0.25	4.08±0.90	3.95±0.57	4.01± 0.58	3.49± 0.42	K + [mmol/l]

Immune parameter level in patients and healthy according to gender (mean ± S.D)

The results recorded a in significant decrease in a level (CXCL8) in patients comparison with healthy group for both gender when compared with healthy controls as shown in table (5)

Table (5): Level of serum immunological parameter in Patients Vs healthy control (according to gender)						
Groups variable	Healthy control (N=30)		patients (N=60		P. sig (male)	P. sig (female)
	Male	female	male	Female		
Cxcl 8 (ng/L)	156.54± 258.49	155.29± 137.09	79.93± 107.81	55.08± 76.87	0.03*	0.00*

4. Discussion

1.Age

The current study shown that acute myeloid leukemia is common in the all ages, but is mainly in elderly patients, as the ages of patients ranged (18.68) years table (1). Agree with (Seer., 2004) show elder patient is common infected with AML. Also (Appelbaum., et al.2006) found that elderly individuals had greater comorbidity and have a lower performance status (PS) upon diagnosis. Less than 5% of AML patients in this age range have a 5-year survival rate, compared to 40% in young people, which is a very bad prognosis (Alibhai.,et al.2009 ; Menzin.,et al.2002) . The causes of poor outcomes in the elderly include patient- and disease-related given that persons in the Western world should expect to live another 20 years after they are 65 and another three years after they turn 80 (WHO. 2016). Frailty and comorbidities are frequently associated with advanced age, and these factors have a significant impact on these patients' tolerance for rigorous treatment methods (Mohammadi et al.,2015). Elderly patients are more likely to have undergone prior cytotoxic treatments or to have previous hematologic disorders, such as myeloproliferative neoplasms, myelodysplastic (MDS), and radiation [Mohammadi., et al. 2015]. In addition to these clinical characteristics, elder AML patients also have a different cytogenetic profile from younger patients, with a higher prevalence of numerous chromosomal abnormalities (Leith.,1997).

5. Gender

Results in this study recorded that males are more affected than females table (1). The reason why males are more likely than females to get acute leukemia at almost any age is unknown, however it's possible that the ABO blood group distributions of males and females with acute myeloid leukemia are different. They suggest that group O women are protected from AML, at least in our population, by the presence of a "sex-responsive" gene close to the

ABO gene locus on chromosome 9 in females with AML. Another reason why males are more prone to acquire acute myeloid leukemia and probably other childhood cancers is that such a gene may exist. Additionally, some risk factors, such smoking or occupational exposure to carcinogens, could contribute to the male preponderance in adults. (Jackson et al., 1999) and could be different according to and may be due to differ in hormones between male and female patients.

6. Biochemical Parameters Levels

Liver function Status indicators (AST and ALT Levels)

Aminotransferase levels are sensitive indications of liver-cell damage, because aminotransferases are generally seen in low concentrations in the blood. When the liver cell membrane is damaged, resulting in increased permeability, these enzymes are released in higher numbers into the bloodstream (Eugene, B.,etal.,2001 and Anderson, S. H.,etal.2001).

When compared to the control table (2), patients with AML had significantly higher serum values of the liver function indicators ALT and AST (p 0.00). These enzymes' increased activity may be caused by hepatic infiltration , according to the findings of (Jumaah et al.,2021) in AML patients. Increased levels of AST are proportional to an infiltrative condition caused by a malfunction in mitochondrial and cytoplasmic membranes. Hepatic damage causes elevated ALT and AST levels in individuals. Additionally, an increase in the quantity of leukemic cells causes the concentration of the transaminase enzyme to rise .

in addition the results of ALT is showing significant increase (p≤ 0.00)after chemotherapy treatment than the value measured before starting chemotherapy in table(2) . Chemotherapy-induced hepatotoxicity was found to be a common cause of abnormal liver function tests in individuals with acute leukemia, according to prior studies (Jahalla and Alamin .,2017) (Kim et al.,2008) (Satter et al.,2016).

In this study also showed the mean level of serum AST in acute myeloid leukemia patients was significantly higher (p ≤ 0.00) than the value measured before starting chemotherapy. This finding was accorded with previous studies as showed that chemotherapy-induced hepatotoxicity is common in patients with acute myeloid leukemia (Jahalla and Alamin., 2017) (Rasool, M., etal.2015).

3.2. Renal Status indicators (Urea, uric acid and Creatinine Levels)

When compared to the control in table (2), the mean levels of serum urea and uric acid in the patient with AML increased in a highly significant (p 0.00) manner. I agreement with (Al-Kazzaz., 2011), which discovered that AML patients' serum uric acid and urea concentrations were significantly greater than those of the control group. This is because uric acid in the blood is the result of leukemia cells' nucleic acids breaking down, and it could be a sign of disease aggression (Alvarez-Lario. and Macarron-Vicente.,2010; Yamauchi et al.,2013). Multiple complications, including Tumor Lysis Syndrome (TLS), an oncologic emergency caused by massive tumor cell lysis with the release of large amounts of potassium, phosphate, and nucleic acids into the systemic circulation (Das et al.,2015), drug adverse reactions, and renal dysfunction, were also discovered to cause clinically advanced hyperuricemia. According to additional research the under excretion in certain patients due to renal impairment was the source of the rise in serum uric acid levels (Yamauchi et al.,2013).

Hyperuricemia is caused by the catabolism of nucleic acids to uric acid, which can cause uric acid precipitate in the renal tubules, renal vasoconstriction, poor auto regulation, decreased renal flow, oxidation, and inflammation, culminating in acute kidney injury (Davidson et al.,2004). When compared to the control groups, people with AML had significantly higher levels of creatinine than healthy individuals in table (2) . This finding is agree with a previous study (Rasool et al.,2015), which found that creatinine levels were substantially higher (p0.01) in AML patients. Furthermore, because creatinine is an endogenous substance, its metabolism varies based on a variety of circumstances (Beddhu et al., 2003). Creatinine is still the most generally used criterion for diagnosing renal failure, but it's important to remember that its significance reflects the kidney's function rather than the presence of real injury (Walaa .,2017) found that an increase in creatinine was linked to an increase in the rate of catabolism and the clogging of renal tubules, all of which resulted in the buildup of creatinine in the bloodstream and, ultimately, an increase in creatinine level.

3.3. electrolyte level (Na, K)

in the current study the level of sodium and potassium were high in patients compered to healthy people while there was no significant (P>0.05) difference in table (2). Hyperkalemia can be caused by leukemic infiltration of the kidneys, severe leukostasis, microvascular insufficiency, and tumor-lysis syndrome (Lundberg et al.,1977). While central diabetes insipidus causes hypernatremia (Nakamura F., et al., 2004), urea-induced osmotic diuresis causes hypernatremia (Dickenmann et al.,1998). Also the mean of sodium and potassium which showed significant increase in their concentration after chemotherapy as shown in Table (2) . Hyperkalaemia (an rise in blood K+ level) is caused by the first lysis of tumor cells and is aggravated by the development of uraemia (renal failure), which is often caused by excessive iatrogenic potassium injection during induction therapy. Severe arrhythmias and sudden death can ensue from a fast spike in serum potassium (Mitchell and Michael.,2004). Some anti-leukemic medications can produce hyperkaluria (an rise in K+1 levels in the urine), implying that the killing of leukemic cells releases toxins that are harmful to the

kidney (Salman et al.,2013).

4.CXCL8 (ng/L)

CXCL8 has long been known to be a pro-inflammatory cytokine and a potent neutrophil chemoattractant. In addition to this physiological function, environmental factors such as hypoxia, acidosis, chemotherapy, and others have been linked to IL-8 production in tumor tissue. Furthermore, higher CXCL8 levels have been found in several malignancies, including prostate, colorectal, and non-small cell lung cancer (Kuett et al.,2015).

In this study that show the level of cxcl8 level was significantly increase ($p \leq 0.05$) in control group compared with treated patients in table (3), Much research have found that serum levels of IL-8 are increased in patients with acute myeloid leukemia when compared to healthy controls. Patients with AML, myelodysplastic syndrome, and non-Hodgkin lymphoma have also been found to have higher serum CXCL8 levels than healthy control participants (Denizot, Y, etal.1996). AML cells penetrate the supporting stroma in the BM microenvironment and promote niche remodeling by decreasing endosteal vasculature and osteoblasts. CXCL8 overexpression in tumor cells is linked to enhanced tumorigenesis and angiogenesis, as well as a poor clinical outcome and relapse (Sharma et al.,2013 and Du et al.,2013). However, the effect of CXCL8 produced from the microenvironment on tumor growth, particularly in hematologic malignancies, remains poorly understood.

And the results agree with (Von der Heide et al.,2017) CXCL8 expression was shown to be 5-fold higher in healthy donors' BM-MSCs compared to individuals with AML in one study . When serum levels of IL-8 in AML patients undergoing intensive chemotherapy (with sequential high-dose AraC and mitoxantrone as induction chemotherapy (Braess et al., 2009) were examined, it was interesting to see that serum levels of IL-8 were lowest at initial diagnosis with high leukemic burden and granulocytopenia, increased during aplasia, and then decreased to lower levels after achieving CR and recovery of peripheral blood count.

7. Conclusions

It can be concluded from the results of the present study that there were negative effects on the functions of liver and kidney as well as the serum levels of cxcl8 in acute myeloid leukemia patients.

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