

## Levels of interleukins 12 (IL-12) and 13 (IL-13), hepatitis B and C serology, and blood cultures among acute myeloid leukemia (AML) patients in Egypt

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**Abstract:** There is an interest in the use of IL-12 as a possible anti-cancer drug to induce immune responses and anti-IL-13 formulations to treat the undesirable effects of IL-13. Thus, the present study aimed at analyzing IL-12 and IL-13 profiles, viral hepatitis serology and blood cultures in acute myeloid leukemia (AML) patients. Forty individuals (20 without septicemia – Group A, and 20 with septicemia – Group B) and 20 healthy controls were evaluated. Hepatitis B virus antigens (HBsAg) and hepatitis C virus antibodies (HCV Ab) were quantified using commercial ELISA kits. IL-12 and IL-13 levels were estimated in culture supernatant of mitogen-stimulated peripheral blood mononuclear cells by ELISA. Significantly low IL-12 values were observed among AML patients compared to controls whereas the opposite was observed regarding IL-13. IL-12 levels were found to be elevated in the follow-up cases. M4 and M5 subtypes of AML presented higher IL-12 levels than M1 and M2 subtypes. The isolated organisms from AML with septicemia were *Staphylococcus aureus* (35%), *Esherichia coli* (25%), coagulase-negative staphylococci (25%), and *Candida* (15%). Fungemia cases showed higher IL-12 values than bacteremia cases. In conclusion, IL-12 and IL-13 should be further tested in large-scale studies to provide future immunotherapy against AML.

**Key words:** acute myeloid leukemia, IL-12, IL-13, HBsAg, HCV, ELISA.

### INTRODUCTION

Acute myeloid leukemia (AML) is a cancer of the myeloid line of blood cells. The myeloid stem cells in AML develop into myeloblasts (1).

Although conventional cancer treatments (surgery, chemotherapy, and radiation) have greatly enhanced patients' survival rates, the manipulation of the immune response to cancer cells in order to promote their destruction remains an important and increasingly realistic goal for physicians. The ideal result of immunotherapy would be the specific eradication of cancer cells with minimal damage to normal host cells (2).

Cytokines have been used as vaccine adjuvants in antitumor vaccines. Interleukin 2 (IL-2) and interleukin 12 (IL-12) have been promising in

conferring improved T-helper 1 (TH1) type immune responses to various tumor antigens (1).

In cancer therapy, cytokines are used to enhance immunity. Cytokines regulate both the innate and adaptive immune system. They appear to have applications in the treatment of hematological malignancies. The major cytokines currently in use or under evaluation for cancer therapy are: interferon- $\alpha$ , IL-2, granulocyte macrophage-colony stimulating factor (GM-CSF), and IL-12(3).

IL-12 is a very exciting cytokine. It is a heterodimeric protein that promotes NK and T cell activity and is a growth factor for B cells. IL-12 shows promise in immunotherapy, both as an adjuvant therapy and in combination with other cytokines (4).

IL-13 stimulates growth and differentiation of B-cells, inhibits TH1-cells and the production of macrophage inflammatory cytokines (e.g. IL-1, IL-6), and decreases the production of IL-8, IL-10 and IL-12 (5). Studies have shown that IL-13 release by activated T cells increased in the presence of AML blasts. Formulations suitable for treatment of disorders associated with undesirable expression or activity of IL-13 are provided in different forms of anti-IL-13 antibody formulations (6, 7).

The present study aimed at analyzing cytokine profiles, viral hepatitis serology and blood cultures among AML patients in pursuit of future effective immunotherapy.

## PATIENTS AND METHODS

The study was carried out on 40 patients suffering from AML admitted to Alexandria Main University Hospital during the years of 2008 and 2009. A group comprising 20 healthy subjects of matched age and sex served as controls. Group A consisted of 20 AML patients without septicemia whereas Group B was composed of 20 AML patients with septicemia.

Patients were subjected to the following: history taking, full clinical assessment, bone marrow examination, and abdominal ultrasound. Both patients and controls were subjected to: complete blood count (CBC); liver and renal function tests; and detection of HBsAg and HCV Ab using enzyme linked immunosorbant assay (ELISA) kits (Ortho Antibody to HBsAg ELISA Test System 2<sup>o</sup>, Ortho-Clinical Diagnostics, USA; Ortho HCV version 3.0 ELISA<sup>o</sup>). Conventional blood cultures for patients suffering from septicemia were performed. Cases and controls positive for human immunodeficiency virus (HIV) were excluded from the study.

Estimation of IL-12 and IL-13 levels was achieved by isolation of peripheral blood mononuclear cells (PBMC) from heparinized venous blood by Ficoll-hypaque (Sigma Aldrich, Australia) density layer centrifugation and cultured at  $2 \times 10^5$  cells per 500  $\mu$ L RPMI-1640 (Roswell Park Memorial Institute medium, Sigma Aldrich, Australia) medium supplemented with antibiotics and 5% fetal calf serum (FCS). For stimulation, 5  $\mu$ g/mL phytohemagglutinin (PHA, Wellcome Pharmaceuticals, UK) mitogen

was used. Incubation of cultures was performed at 37°C in a humidified atmosphere of 5% CO<sub>2</sub>. After two days of culturing, supernatants were collected from each tube and stored at -20°C to be assayed using commercial ELISA kits [Human IL-12 (P70)<sup>o</sup>, Human IL-13<sup>o</sup>, RayBio, UK] (8). For HBsAg and HCV Ab a third generation ELISA (Ortho-Clinical Diagnostics, USA) (9, 10) was performed according to the manufacturers' instructions. Bacteremia was detected by the conventional blood culture technique (11).

## Statistical Analysis

The statistical package for social science (SPSS version 9.0 for Windows<sup>o</sup> Microsoft, USA) was used for data analysis. Comparison between patients and controls was made using the t-test for quantitative data and  $\chi^2$ -test for qualitative data. The Kruskal-Wallis test was used to test for differences among the three studied groups. The Mann-Whitney test was used to ascertain any differences between control and other groups. The 5% level of significance was adopted, so that  $p \leq 0.05$  was considered significant. Data were shown as mean  $\pm$  standard deviations (SD).

## RESULTS

The studied subjects were three different groups: a healthy control group (n = 20); Group A - AML patients without septicemia (n = 20); and Group B: AML patients with septicemia (n = 20).

Complete blood count (CBC) showed significantly higher white blood cell (WBC) count among cases compared to controls. The reverse was observed in hemoglobin level and platelet counts (Table 1).

Liver function tests showed mean values of 70.90 U/L for aspartate aminotransferase (AST) and 76.20 U/L for alanine aminotransferase (ALT) among Group A. Group B showed means of 110.05 U/L for AST and 109.3 U/L for ALT. Both values were significantly higher than the controls (AST: 18.37 U/L and ALT: 13.92 U/L).

Concerning renal function, groups A and B showed respective means of 18.15 mg/dL and 36.45 mg/dL for blood urea and 0.94 mg/dL and 2.82 mg/dL for serum creatinine. The values in both groups were higher than the controls (blood urea: 13.28 mg/dL and serum creatinine: 0.87 mg/dL).

**Table 1.** Comparison of WBC count, hemoglobin values (Hb) and platelet count among the studied groups

	Controls		Group A		Group B		$\chi^2$ (p)
WBC (x 10 <sup>9</sup> /L)							
Range	4.50-9.80		0.46-40.00		14.40-40.00		(< 0.001)
Mean ± SD	7.87 ± 1.42		19.17 ± 9.85		22.00 ± 7.17		
Z1 (p)			(< 0.001)		(< 0.001)		
Hb (g/dL)							
Range	12.00-17.70		4.0- 11.60		6.20-10.40		(< 0.001)
Mean ± SD	14.76 ± 1.79		6.97 ± 1.53		8.06 ± 1.24		
Z1 (p)			(< 0.001)		(< 0.001)		
Z2 (p)					(0.006)		
Platelets (x 10 <sup>9</sup> /L)							
Range	210.00-324.00		90.00- 340.00		90.00-290.00		(< 0.001)
Mean ± SD	282.45 ± 32.71		211.50 ± 72.71		190.00 ± 59.91		
Z1 (p)			(0.001)		(< 0.001)		

$\chi^2$ : chi-square for Kruskal Wallis test; Z1: Z for Mann Whitney test between controls and other groups; Z2: Z for Mann Whitney test between Group A and Group B; p: statistically significant at  $p \leq 0.05$

**Table 2.** Comparison of the three study groups according to hepatitis B and C serological markers

	Controls		Group A		Group B		$\chi^{21}$ (p)
	N	%	n	%	n	%	
HBsAg							
Absent	20	100.0	13	65.0	14	70.0	(0.015)
Present	0	0.0	7	35.0	6	30.0	
FEp			0.008*		0.020*		
Anti-HCV Ab							
Absent	20	100.0	12	60.0	13	65.0	(0.006)
Present	0	0.0	8	40.0	7	35.0	
FEp			0.003*		0.008*		
HBsAg and anti-HCV Ab							
Absent	20	100.0	14	70.0	15	75.0	(0.032)
Present	0	0.0	6	30.0	5	25.0	
FEp			0.020*		0.047*		

$\chi^{21}$ : chi-square test between the different studied groups; FEp: p value for Fisher Exact test between control and other groups; \*: statistically significant at  $p \leq 0.05$ .

**Table 3.** IL-12 and IL-13 levels among the studied groups

	Controls	Group A	Group B	$\chi^2$ (p)
IL-12 (pg/dL)				
Range	10.03-69.11	8.03-58.39	8.03-50.37	(0.491)
Mean $\pm$ SD	24.48 $\pm$ 14.33	20.89 $\pm$ 14.36	22.06 $\pm$ 14.14	
IL-13 (pg/dL)				
Range	2.56- 19.72	0.0-0.2	0.0-0.0	(< 0.001)
Mean $\pm$ SD	10.58 $\pm$ 4.91	0.002 $\pm$ 0.01	0.001 $\pm$ 0.0001	
Z1 (p)		(< 0.001)	(< 0.001)	

$\chi^2$ : chi-square for Kruskal Wallis test; Z1: Z for Mann Whitney test between control and other groups.

Thirty percent (30%) of Group A and 25% of Group B were positive for both hepatitis B and hepatitis C serological markers. They were significantly higher than the controls. The levels of IL-12 and IL-13 in the patients' serum as well as those of the control group are shown in Table 3.

Microorganisms isolated from blood culture of AML cases (Group B) were *Staphylococcus aureus* (n = 7, 35%), *Escherichia coli* (n = 5, 25%), coagulase-negative staphylococci (n = 5, 25%) and *Candida albicans* (n = 3, 15%).

IL-12 levels were higher among cases positive for hepatitis B, C, or both. Their respective mean values were 24.57, 23.86, and 26.71 pg/dL. As to IL-13, the levels were higher in cases negative for hepatitis B, C, or both. The mean values were 4.50, 4.70, and 4.32 pg/dL, respectively.

Correlating interleukin levels and the isolated organisms from Group B revealed the highest IL-12 value with *Candida albicans* (34.38 pg/dL) compared to 23.45 pg/dL with *Staphylococcus aureus*, 21.02 pg/dL with *Escherichia coli*, and 13.74 pg/dL with coagulase-negative staphylococci.

## DISCUSSION

The manipulation of the immune response to cancer cells in order to promote their destruction remains an important and increasingly realistic goal for physicians (3). Our results showed an inverse relation between platelets and IL-12 in the control group. Group A showed an inverse relation between IL-13 and hemoglobin values, and a positive correlation with platelet count. In another study, IL-12-induced PAF synthesis played a critical role in triggering the events

involved in the mitogenic response of PMN and NK to IL-12 (12).

Anti-inflammatory cytokines – such as IL-13 – expression promote heme degradation and iron storage in monocytes and thereby contribute to iron storage in the reticuloendothelial system (13). Transmission of HBV infection through donated blood is reportedly very common, particularly in the developing world (14). Similarly, 26.6% among 188 blood donors were confirmed anti-HCV positive by RIBA test in a study done in Cairo (15).

In developing countries, the primary sources of HCV infection are unsterilized injection equipment and infusion of inadequately screened blood and blood products (16). In our study, 35% of the cases in Group A as well as 30% of the cases in Group B tested positive for hepatitis B surface antigen. Forty percent of the cases in Group A and 35% of Group B cases tested positive for Hepatitis C virus antibodies. The percentages of cases positive for both hepatitis B and hepatitis C were 30% of Group A and 25% of Group B. All the cases in the study had a history of blood transfusion. One of the hazards of blood transfusion is infection with HBV or HCV (17). This could explain the significantly elevated liver enzymes detected in the present study. Furthermore, the fact that renal function tests were significantly elevated may constitute a side effect of chemotherapy (18).

The only positive significant correlation was between IL-12 and serum creatinine in Group B. In a study performed in Osaka, Japan, to assess the influence of IL-12 on several physicochemical characteristics of nephritogenic IgA molecules

in HIGA mice, IL-12 administration caused slight increases in serum creatinine (19). Interleukin-12 plays a central role in the immune response as a cytokine whose functions bridge innate resistance and antigen-specific adaptive immunity. IL-12 is a T-cell-stimulating factor; it stimulates the production of IFN- $\gamma$  and TNF- $\alpha$  from T and NK cells, and reduces IL-4-mediated suppression of IFN- $\gamma$  (20). IL-12 also presents anti-angiogenic activity. Because of its ability to induce immune responses and its anti-angiogenic activity, there has been an interest in testing IL-12 as a possible anti-cancer drug (21). The subjects associated with elevated levels of serum IL-12 may express an immune response against tumor cells. The decrease in serum IL-12 in our cases may be attributed to immunosuppression after chemotherapy (22).

Direct injection of IL-12 has previously shown some effectiveness in the treatment of leukemia in animal models; however, human trials with this approach have not proven successful. Research at University Health Networks (UHN) has demonstrated that IL-12 delivered via transduced leukemia cells has a powerful anti-cancer effect. A key finding of this research is that a remarkably small number of IL-12-producing cells are required for effective therapy (23). IL-12 has been shown to exert potent immunostimulatory effects on certain helper T cells, as well as on cytotoxic T lymphocytes and NK cells. Preclinical studies suggest that IL-12 may prove useful in the treatment of several human diseases, including HIV infection and cancer (24-26). These properties suggest that IL-12 may play an important role in the immune response to many viruses, including HBV. It has been shown that HBV-specific cytotoxic T lymphocytes inhibit HBV replication in the livers of transgenic mice by a non-cytolytic process that is mediated in part by IFN-gamma. IL-12 may have therapeutic value as an antiviral agent for the treatment of chronic HBV infection (27).

T cell responses, including interferon- $\gamma$  production, are severely suppressed in chronic HCV patients. Researchers examined IL-12 production, which is critical for the induction of interferon- $\gamma$  synthesis, in lipopolysaccharide-stimulated human monocyte/macrophages. It was found that core protein binds the gC1qR displayed on the cell surface of monocyte/macrophages and inhibits the production of IL-12p70 upon

lipopolysaccharide stimulation. These results suggest that the HCV core-gC1qR interaction may play a pivotal role in establishing persistent infection by dampening TH1 responses (28).

The role of IL-13 has been demonstrated to be prominent in malignancy. High levels of IL-13 provoke reduced tumor immunosurveillance resulting in an uninhibited tumor progression. IL-13 has been applied in cancer treatment by the technology of Targepeutics, which involves genetically engineering the IL-13 molecule that is naturally present in the body to a modified form that binds the normal IL-13 receptor, but does not activate the signaling from the receptor. Thus, Targepeutics' compounds should effectively negate the role of endogenous IL-13 by a double mechanism of blocking receptors and inhibiting signaling. Neutralizing natural IL-13 has demonstrated a marked increase in the body's ability to fight off cancer cells and tumors (29). It had been reported that IL-13 had a direct and nontoxic inhibitory effect on constitutive AML blast cytokine secretion, and that the release of IL-13 by activated T cells was elevated in the presence of AML blasts (30).

A research study performed in Norway by Bruserud (31) evaluated the effects of the cytokines IL-4, IL-10 and IL-13 on AML and found them to have divergent effects on AML blast proliferation *in vitro*, and their final effect (enhancement/inhibition/no effect) depended on individual differences among patients and the presence of other exogenous cytokines. In contrast to these divergent effects on blast proliferation, all three cytokines were found to inhibit constitutive AML blast cytokine secretion independent of their effects on spontaneous blast proliferation. Bruserud (31) concluded that although exogenous G-CSF, GM-CSF and IL3 can modulate the effects of IL-4, IL-10, and IL-13 on AML blast proliferation, the IL4/IL10/IL13-induced inhibition of AML blast cytokine secretion is not modulated or reversed by the presence of these exogenous hematopoietic growth factors (31).

In the present study, however, we detected a significant decline in IL-13 levels in cases compared to controls. This result may be due to the initiation of chemotherapy, or to cross infection with hepatitis B or hepatitis C. Seventy-five percent of the cases in Group A and 45% of the cases in Group B were subjected to chemotherapy.

IL-13 predominance in chronic HCV infection was found to have a role in the etiology of liver damage in which IL-13 was found to be one of the driving forces in fibrogenesis (32).

In the present study, blood culture specimens from Group B (AML with septicemia) yielded *Staphylococcus aureus* (35%), *Esherichia coli* (25%), coagulase-negative staphylococci (25%), and *Candida albicans* (fungemia) (15%). These results are in agreement with another study performed in Saudi Arabia which concluded that gram-positive microorganisms were the most common blood isolates followed by gram-negative bacteremic infections (33). Similarly, another study in Spain showed that gram-positive microorganisms were found to be the cause in 70% of the episodes, with coagulase-negative staphylococcus (35%) being the most frequently isolated microorganism, followed by *Staphylococcus aureus* (11%) (34). According to another research study carried out in Japan that studied septicemia associated with AML, 52.3% of the total isolates were gram-negative bacilli, 26.8% were gram-positive cocci, 17.2 % were fungi, and 3.5% were anaerobic bacteria (35).

The variability in results in different studies could be attributed to environmental or geographical factors involved in the greater prevalence of certain microorganisms relative to others. The innate immune system plays a key role in immune surveillance against pathogens, particularly during the early phase of infection. The killing activity presented by NK cells has been shown to be up-regulated by several cytokines: e.g. IL-2, IL-12, IFN- $\alpha/\gamma$  and TNF (36, 37). To conclude, IL-12 and /or IL-13 can be exploited and tested on a large scale as future immunotherapy in AML.

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### CONFLICTS OF INTEREST

There is no conflict.

### ETHICS COMMITTEE APPROVAL

The present study was approved by the Ethics Committee of Alexandria University, Egypt.

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