Journal of Health, Medicine and Nursing
ISSN 2422-8419 An International Peer-reviewed Journal
Vol. 13 2015

Effect of some anticancer drugs on the growth of children with Acute Lymphoblastic Leukemia in Iraq

[1*]Marwan G. Oleiwi; [2]Bahir A. R. Mshemish; [2]Inam S. Arif; [3]Sawsan S. Abbas; [4]Mowafaq M. Ghareeb
[1*]Health directorate of Wasit, Ministry of Health, Wasit, Iraq
[2]Dep. of Pharmacology and Toxicology, College of Pharmacy, Almustansiriah University, Baghdad, Iraq
[3]Dep. of Pediatric medicine, College of Medicine, Alnahrain University, Baghdad, Iraq
[4]Dep. of Pharmaceutics, College of Pharmacy, Baghdad University, Baghdad, Iraq
[1*]E-mail of the corresponding author: hardline83@gmail.com

ABSTRACT

Acute Lymphoblastic Leukemia (ALL) is the most common type of leukemia in children. It represents about 75% of all leukemia types in children less than 15 years old and peak incidence at (2-5) years old. The study was designed to evaluate the effect of chemotherapeutic regimens used for Iraqi children with ALL by assessing anthropometric parameters, oxidative state markers, and metabolic state. This prospective randomized clinical study was carried out on (30) newly diagnosed children with ALL (6 months – 8 years old) in Iraq. According to the FAB-classification, the patients grouped as L1 group (n=16) and L2 group (n=14). A healthy children (n=14) were involved and considered as a control group to compare their normal data with these of patients groups. The IGF-I, albumin, total serum protein, BMI, TAS, and LDH were determined at baseline, 1st, 2nd, and 3rd months of the treatment regimen. The results showed that the mean level of serum IGF-I in both patient groups was significantly lower than that of control children at baseline, and it is increased significantly after receiving treatment while no significance difference between patients of both groups. Serum albumin, total serum protein, and BMI showed no significant differences in both patient groups when compared with the control group at baseline and after receiving treatment, also, between patients of both groups. TAS showed a significant reduction at baseline and after receiving treatment of both patients' groups when compared with the control children, and there was a significant difference between patients of both groups. For LDH, there was a significant elevation in the mean level at baseline for both patients' groups when compared with the control children, while after receiving treatment a significant reduction noticed in both groups when compared with control children and no significance difference between patients of both groups. These results can give indication for the effect of chemotherapy on the growth and nutrition of ALL children through their effects on IGF-I, which has a direct effect on GH and the reduction in the levels of total proteins and albumin, which may affect BMI, while the reduction in TAS during chemotherapy treatment may result in disruption of cells metabolism which will affect the normal body homeostasis.

Keywords: ALL, Growth, IGF-I, Chemotherapy.

INTRODUCTION

Leukemia is a malignant hematopoietic disease characterized by an uncontrolled proliferation and block in the differentiation of hematopoietic cells [1]. These malignant cells can spread mostly to the lymph nodes, liver, spleen, and other tissues. Leukemia largely classified as acute or chronic (according to the type of affected cells and by the rate of cells growth) and of myeloid or lymphoid according to the type of cell that is multiplying abnormally [2]. Acute lymphoblastic leukemia (ALL) is a group of heterogeneous lymphoid disorders that result from a monoclonal proliferation and expansion of immature B or T lymphocyte progenitor in the bone marrow, blood, and other organs [3]. ALL is a most common type of leukemia in children [4] with a peak incidence of age between 2-5 years of age and cure rate for about more than 80% [5].

In most patients, the main cause of ALL is unknown [3], the possible risk factors are genetics, environmental and infectious [6]. ALL classified to L1, L2, and L3 according to FAB-classification or to B-cell and T-cell neoplasm according to WHO-classification [7, 8]. ALL can diagnose by laboratory and pathological tests such as blood test, bone marrow aspirate, lymph node biopsy, cytogenetic test, lumbar puncture, and Immunophenotype [9, 10]. Treatment for ALL can include blood transfusion, chemotherapy, radiation therapy, steroids, intensive combined treatments (including bone marrow or stem cell transplants), and growth factors. The main treatment for children with ALL is a chemotherapy, which is usually divided into 3 phases (induction phase, consolidation or intensification phase, and maintenance phase) [11].

Under normal conditions, IGF is responsible for growth and development of children, and it continues to mediate autocrine and paracrine functions throughout adulthood. In the endocrine system, IGF-I serum concentration is directly associated with growth hormone (GH) concentration; growth hormone stimulates the synthesis of IGF-I in the liver, which in turn stimulates growth and development. The deficiency of IGF-I in humans results in short stature [12]. Over the past two decades, greater evidence had accumulated to show that the growth factors play a vital role in maintaining or supporting the progression of neoplastic growth. A numbers of epidemiological evidence showed that it might also be an important determinant of cancer incidence [13].

Oxidative stress defined as an imbalance between the production of free radicals and reactive metabolites, called oxidants or reactive oxygen species (ROS) [14]. Oxidative stress is closely concerning to all aspects of cancer, from carcinogenesis to the tumor-bearing state, and from the treatment to the prevention. When such oxidative stress exceeds the capacity of the oxidation-reduction system of the body, this may lead to result gene mutations or intracellular signal transduction and transcription factors may be affected directly or via antioxidants, leading to carcinogenesis [15].

AIM OF STUDY

The study was designed to evaluate the effect of ALL – therapeutic regimen for Iraqi children patients by assessment of anthropometric parameters, growth, oxidative state markers, and metabolic state.

PATIENTS AND METHODS

This prospective case-control clinical study was carried out by (30) children patients (18 male, and 12 female) newly diagnosed with ALL. Those children were with an age range of (6 months – 8 years), and BMI range of (12.5-19.2 kg/m^2). The mean of age was (4.32 years). Those child patients were diagnosed and treated in Child Center Hospital/ Unit of oncology/ AL-Iskan/ Baghdad, Iraq. Patients were allocated into two subgroups according to FAB – classification to L1 group (n=16) which include children with ALL – L1 subtype and a mean of age (3.81±0.535 years), and L2 group (n=14) which include children with ALL – L2 subtype and a mean of age (4.89±0.515 years). A healthy children (n=14) (8 female, and 6 male) with mean of age (3.85±0.606 years) were involved and considered as a control group to compare their normal data with that of patients groups.

The blood samples were obtained and centrifuged to get the serum and then assayed. The BMI, IGF-I, albumin, total serum protein, TAS, and LDH were determined at baseline before receiving any chemotherapy and after 1st, 2nd, and 3rd month of treatment for both patient groups.

Statistical analysis

All data were presented as Mean ± SEM (Standard error of mean). Data were analyzed by two ways analysis of variance with (ANOVA), and (t-test), and the level of significance was *($p<0.05$)*.

RESULTS

The results of this clinical study showed that the mean level of serum IGF-I in both patient groups was significantly *($P<0.05$)* lower than that of control children at baseline, and it is increased significantly *($P<0.05$)* after receiving chemotherapeutic agents at induction and consolidation phases and no significance difference *($P>0.05$)* between patients of both groups. For serum albumin, total serum protein, and BMI value, there were insignificant differences *($P>0.05$)* in mean of these parameters in both patient groups when compared with those of control group at baseline and after receiving treatment at induction and consolidation phases and also, in comparison between patients of both groups, but, there was a slight reduction in the mean level of these parameters at baseline and after receiving treatment. The oxidative state marker (TAS) showed a significant reduction *($P<0.05$)* in its mean level at baseline and after receiving treatment at induction and consolidation phases of both patient groups when compared with the control children. Also, there was a significant difference *($P<0.05$)* when compared between patients of both groups. For LDH, there was a significant elevation *($P<0.05$)* in its mean level at baseline for both patient groups when compared with the control children, while after receiving treatment at induction and consolidation phases, a significant reduction *($P<0.05$)* noticed in both groups when compared with control children, and no significance difference *($P>0.05$)* in comparison between patients of both groups. See tables and figures (1, 2, 3, 4, 5, and 6, respectively).

Table (1): Effect of chemotherapy protocols on BMI value in ALL patients at induction and consolidation phases

BMI value (kg/m^2)				
Groups	**Baseline**	**1st month**	**2nd month**	**3rd month**
Control (n=14)	**15.89 ± 0.5906**			
L1 group (n=16)	**15.29 ± 0.5324[a]**	**15.11 ± 0.5259[a]**	**15.00 ± 0.5874[a]**	**14.88 ± 0.6443[a]**
L2 group (n=14)	**15.72 ± 0.5341[a]**	**15.64 ± 0.4739[a]**	**15.41 ± 0.4570[a]**	**15.26 ± 0.4583[a]**

Results are expressed as mean ± SEM Result with identical superscript (a) within the same group considered no significant difference (*P>0.05*)

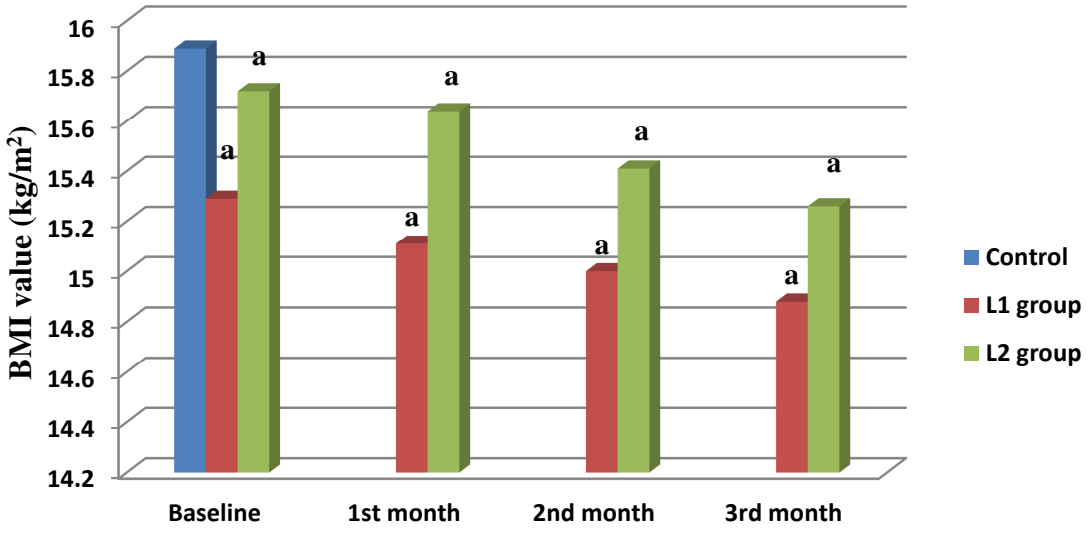

Figure (1): Effect of chemoyherapy protocols on BMI value in ALL patients at induction and consolidation phases

Table (2): Effect of chemotherapy protocols on IGF-I level in ALL patients at induction and consolidation phases

IGF-I level (ng/ml)				
Groups	**Baseline**	**1st month**	**2nd month**	**3rd month**
Control (n=14)	**107.8 ± 8.285**			
L1 group (n=16)	**57.40 ± 8.176 a***	**69.71 ± 7.771 a**	**86.38 ± 8.974 b**	**104.7 ± 10.17 c**
L2 group (n=14)	**48.84 ± 7.824 a***	**66.37 ± 9.246 a**	**80.92 ± 7.679 b**	**92.41 ± 8.734 c**

Results are expressed as mean ± SEM *
Significant difference ($P<0.05$) compared with the control group at the baseline level.

Result with non-identical superscript (a, b, c) within the same group considered significant difference ($P<0.05$)

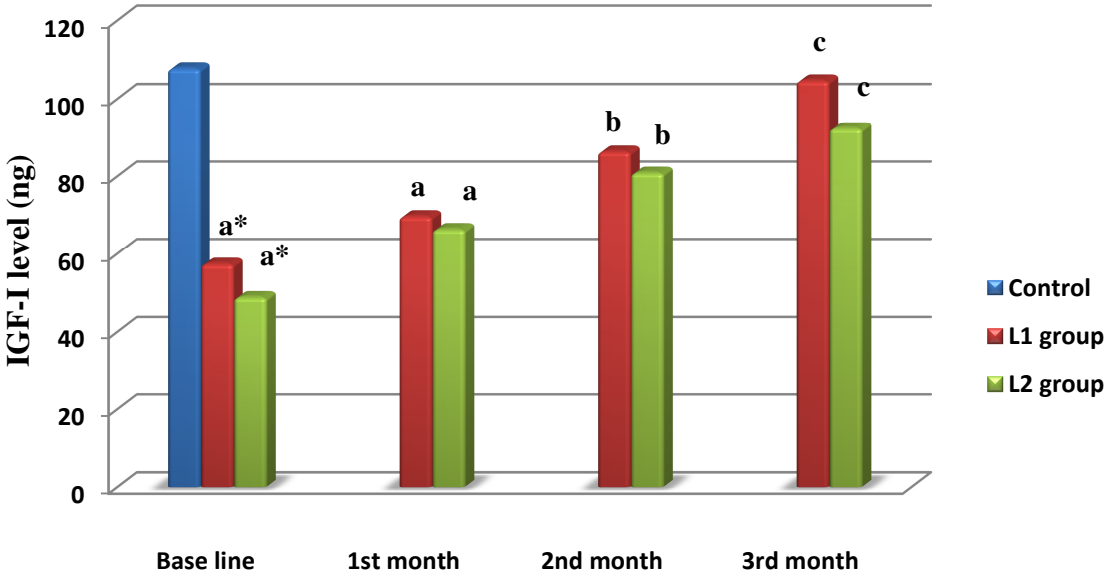

Figure (2): Effect of chemotherapy protocols on IGF-I level in ALL patients on induction and consolidation phases

Table (3): Effect of chemotherapy protocols on Albumin level in ALL patients at induction and consolidation phases

Albumin level (g/dL)				
Groups	**Baseline**	**1st month**	**2nd month**	**3rd month**
Control (n=14)	**4.740 ± 0.2032**			
L1 group (n=16)	**4.409 ± 0.1908[a]**	**4.256 ± 0.1278[a]**	**3.979 ± 0.1200[a]**	**3.933 ± 0.1182[b]**
L2 group (n=14)	**4.401 ± 0.1779[a]**	**4.286 ± 0.1603[a]**	**4.123 ± 0.1239[a]**	**4.010 ± 0.1611[a]**

Results are expressed as mean ± SEM Result with non-identical superscript (a, b) within the same group considered significant difference (*P<0.05*)

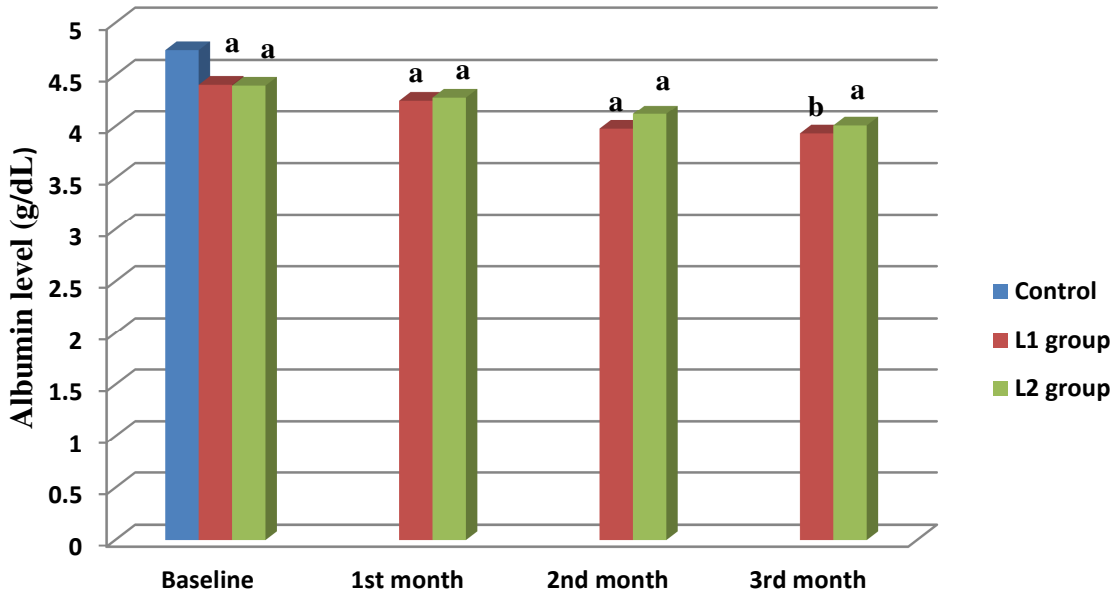

Figure (3): Effect of chemotherapy protocols on albumin level in ALL patients at induction and consolidation phases.

Table (4): Effect of chemotherapy protocols on total serum protein level in ALL patients at induction and consolidation phases

Total serum protein level (g/dL)				
Groups	**Baseline**	**1st month**	**2nd month**	**3rd month**
Control (n=14)	**10.10 ± 0.1760**			
L1 group (n=16)	**9.864 ± 0.3575[a]**	**9.616 ± 0.2488[a]**	**9.232 ± 0.2374[a]**	**8.731 ± 0.2805[b]**
L2 group (n=14)	**9.981 ± 0.3900[a]**	**9.514 ± 0.3847[a]**	**9.292 ± 0.3661[a]**	**9.132 ± 0.4282[a]**

Results are expressed as mean ± SEM

Result with non-identical superscript (a, b) within the same group considered significant difference (*P<0.05*)

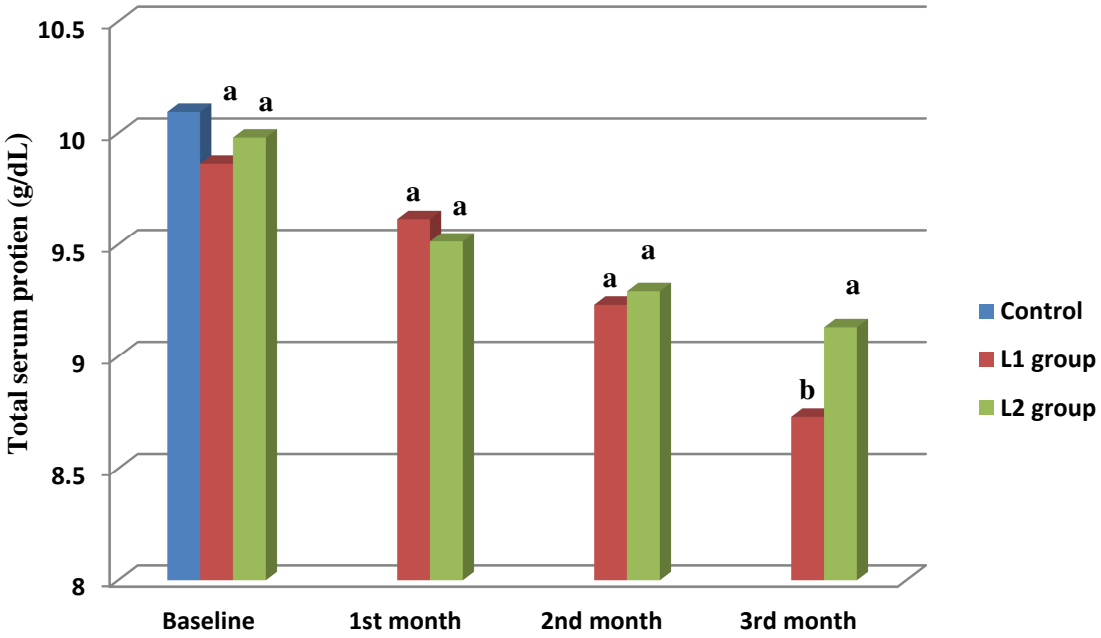

Figure (4): Effect of chemoyherapy protocols on total serum protien level in ALL patients at induction and consolidation phases.

Table (5): Effect of chemotherapy protocols on TAS level in ALL patients at induction and consolidation phases

TAS level (mmol/L)				
Groups	**Baseline**	**1st month**	**2nd month**	**3rd month**
Control (n=14)	**2.183 ± 0.06921**			
L1 group (n=16)	**1.519 ± 0.1289^{a*}**	**1.596 ± 0.09910^{a}**	**1.624 ± 0.1398 ^{a}**	**1.603 ± 0.1377 ^{a}**
L2 group (n=14)	**2.096 ± 0.1661^{a†}**	**1.745 ± 0.08289^{a†}**	**1.531 ± 0.09220^{b†}**	**1.419 ± 0.07564^{c†}**

Results are expressed as mean ± SEM *
Significant difference ($P<0.05$) compared with the control group at the baseline level

Result with non-identical superscript (a, b, c) within the same group considered significant difference ($P<0.05$)
† Significance difference ($P<0.05$) between two ALL patient groups

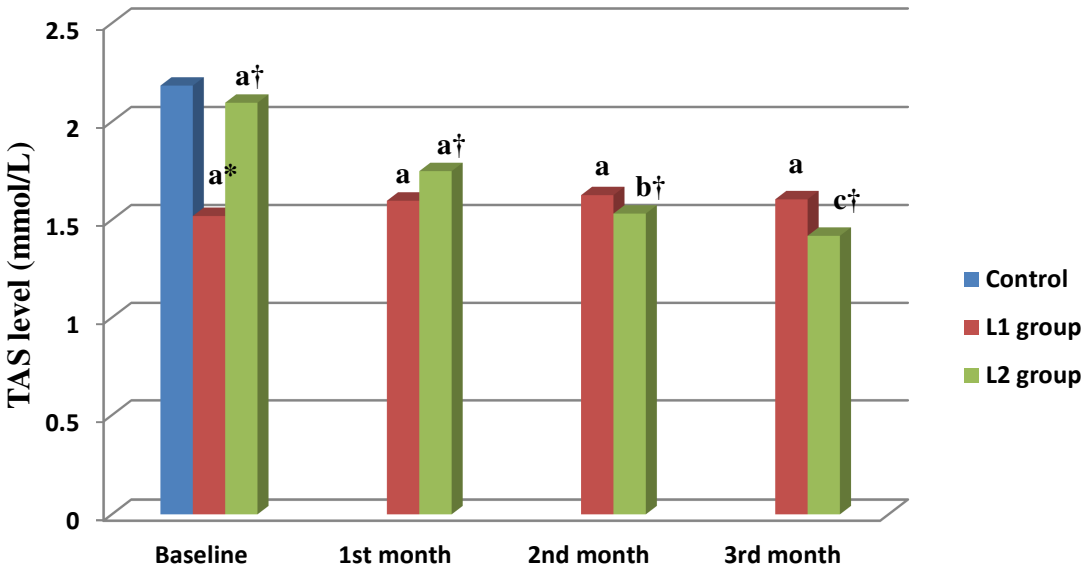

Figure (5): Effect of chemotherapy protocols on TAS level in ALL patients at induction and consolidation phses.

Table (6): Effect of chemotherapy protocols on LDH level in ALL patients at induction and consolidation phases

LDH level (IU/L)				
Groups	**Baseline**	**1st month**	**2nd month**	**3rd month**
Control (n=14)	**374.3 ± 13.58**			
L1 group (n=16)	**500.3 ± 34.24^{a*}**	**459.3 ± 29.70^{a}**	**411.4 ± 27.32^{a}**	**347.6 ± 32.56^{b}**
L2 group (n=14)	**482.5 ± 18.94^{a*}**	**405.4 ± 27.88^{b}**	**370.6 ± 23.30^{c}**	**359.2 ± 24.38^{d}**

Results are expressed as mean ± SEM *
Significant difference (*P<0.05*) compared with the control group at the baseline level

Result with non-identical superscript (a, b, c, d) within the same group considered significant difference (*P<0.05*)

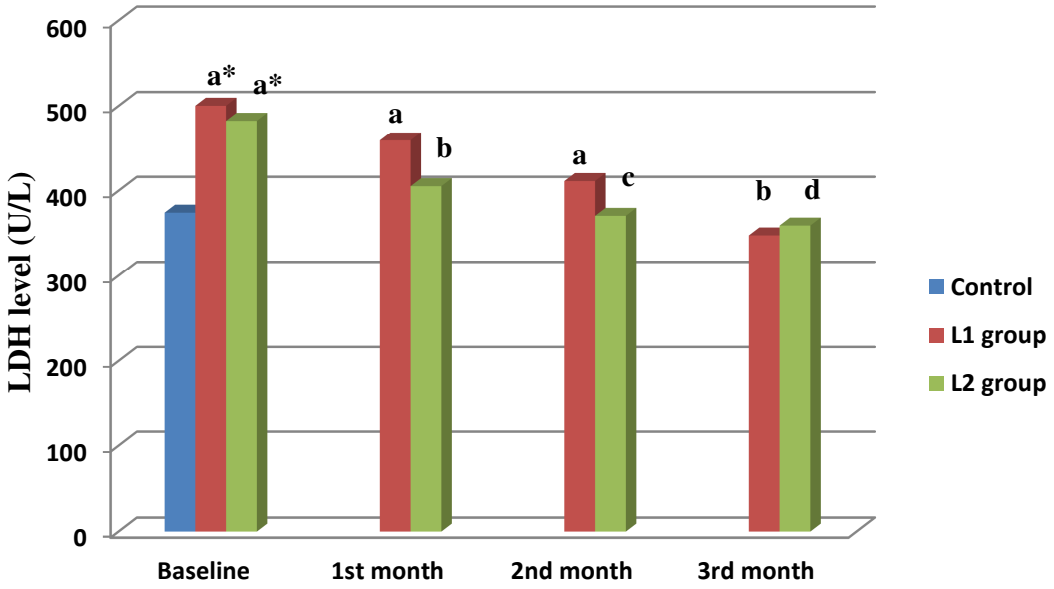

Figure (6): Effect of chemotherapy protocols on LDH level in ALL patients at induction and consolidation phases.

DISCUSSION

The BMI results were supported by many studies and inconsistent with others. The studies that consistent with the current study had shown that the BMI of children with ALL disease was significantly decreased due to the effect of several factors like catabolic state by the disease itself or chemotherapeutic agents, reduced energy intake, infections, poor nutrition , and cranial irradiation [16, 17], while the studies that inconsistent with current results study showed that the BMI was increased due to the effect of corticosteroids which increase food intake and fats in adipose tissue [18], but the increase after chemotherapy suspension, also observed by other researchers, indicating an effect of treatment on body composition or progression in nutrient intake and capacity when therapy is removed [19].

The IGF-I results of the present clinical study showed that there was a significant reduction in the mean level of serum IGF-I at diagnosis of ALL in both patient groups (L1 and L2) compared with the control group. This significant reduction was supported by previous observation, which showed that there was a reduction in the level of serum IGF-I at diagnosis stage due to the disease itself, malnutrition, and other catabolic effects as trauma, sepsis, and organs failure, but this reduction may increase gradually after receiving chemotherapy protocols [20, 21]. The exact reason or mechanism for this decline in serum level of IGF-I was still unknown [22], but some studies suggest that the ALL children have an elevated IGFBP-2/IGF-I ratio at diagnosis and at 6 months after treatment and these may lead to severely catabolic state which may alter the IGF signaling pathway which in turn cause diminish in the level of IGF-I inside the body through the alteration in (GH/IGF-I) axis [23, 24].

Within L1 and L2 group patients, the present study results showed that there was no significant difference in the mean level of serum IGF-I after 1st month of treatment compared with baseline level, while after 2nd, and 3rd months of treatment there was significant elevation in the mean level of serum IGF-I compared with baseline level. The significant elevation in serum level of IGF-I supported by some studies which showed that there was an increase in the level of IGF-I after receiving chemotherapy protocol treatment when compared with IGF-I level at diagnosis stage, and these elevation appear after receiving chemotherapy but not reach normal level until 6 months of treatment or more, but sometimes there was a catch-up period (mainly in maintenance phase), suggested that the intensive chemotherapy may involve directly in growth retardation [23], and there was other reports suggested that chemotherapy had a negative effect on growth [24, 25]. The mechanism of alteration in the (GH/IGF-I axis) in children with ALL was multifactorial. Children with malignancy were severely catabolic, as shown by an increase in protein breakdown and protein synthesis. In addition, malignant diseases lead to alterations in the IGF-I signaling pathway, and IGF-II and express high levels of IGFBP-2 messenger ribonucleic acid, and protein were secreted by leukemic T cell [25]. Finally, there were some studies suggest that cytotoxic drugs impair the synthesis and production of IGF-I by the liver and its action on the cartilage growth plate [26].While there was no significant difference in the mean level of serum IGF-I at baseline, and after 1st, 2nd and 3rd months of treatment between L1 and L2 group patient.

The albumin showed no significant difference in it is mean levels in L1 and L2 group patients when compared with the control group at the baseline level. Also there were non-significant differences found in the mean levels of serum albumin after 1st and 2nd months of treatment when compared with baseline level and within L2 group patients after 1st, 2nd, and 3rd months of treatment when compared with baseline level. These results were inconsistent with many studies which had shown that there was a significant decrease in serum albumin level and this decrease either from an increased loss or depressed synthesis of albumin. A reduction in synthesis of albumin mainly reflects end-stage liver disease, intestinal malabsorption syndromes and protein calorie malnutrition. The continuous decrease in serum albumin result in a shift of fluids from the intravascular to the interstitial space, resulting in depletion of intravascular volume and formation of edema [27, 28]. Few studies showed that there were no significant differences in the level of serum albumin, but sometimes there was a slight decrease due to the effect of chemotherapeutic agents especially L- asparaginase [29]. While within L1 group, there was significant reduction in the mean level of serum albumin in 3rd month after treatment when compared with baseline level, and this result was consistent with many studies which had shown that there were significant reductions in serum albumin levels after chemotherapy regimen [27, 28].When compared between L1 and L2 group patients, there were no significant differences in the mean levels of serum albumin at baseline, and after 1st, 2nd, and 3rd months of treatment.

The total serum protein showed that there was no significant difference in it is mean levels of total serum protein in L1 and L2 group patients when compared with the control group at the baseline level. Also within L1 group patients, there were no significant differences in the mean levels of total serum protein after 1st and 2nd months of treatment when compared with baseline level, and within L2 group patients, there were no significant differences in the mean levels of total serum protein after 1st, 2nd, and 3rd months of treatment when compared with baseline level. These results were inconsistent with most studies which had shown that there were significant decreases in the levels of total protein due to the effect of ALL on patient groups when compared with healthy children [28, 30, 31]. These studies and others showed a significant reduction in total serum protein due to the effect of disease and low intake of protein [32]. To some extent, there were some studies consistent with the current study which showed that the level of total serum protein not affected or there were a slight decrease in its level due to the effect of corticosteroid which cause increase food intake and metabolism alteration [33]. While after 3rd months of treatment, for L1 group patients there was significant reduction in total serum protein mean level when compared with baseline level, this result was supported by many studies which had shown that there were significant reductions in the levels of total serum protein, and this reduction was due to malnutrition or acute loss of protein because of side effect of cancer therapy, reduced protein intake coupled with a hypermetabolic state, resulting in rapid depletion of visceral protein, and this indicate a catabolic protein status

[27, 34].When compared between L1 and L2 group patients, there were no significant differences in the mean levels of total serum protein at baseline, and after 1st, 2nd, and 3rd months of treatment.

For TAS the present clinical study showed a significant reduction in the mean level of serum TAS in L1 group patients when compared with control group at baseline level, while there was no significant difference in the mean level of serum TAS in L2 group patients when compared with control group at baseline level. This result was proved accordingly by some studies which showed that the level of serum TAS lowered in patients with ALL than the healthy children [35] and this reduction may be due to an imbalance between oxidative and antioxidant status (the reduction of antioxidant status in plasma with ALL children was probably associated with increased ROS as indicated by the decrease in the antioxidant activity) [36, 37].Within L1 group patients, there was no significant difference in the mean level of serum TAS after 1st, 2nd, and 3rd months of treatment when compared with the baseline level. These results were inconsistency with most studies, but there were a certain study prove that, which its depending on the fact that the clearance of chemotherapeutic agents occur within hours or few days, and one of the reasons to decrease the level of TAS was the presence of chemotherapy inside the body [38]. Regarding L2 group, the present clinical study showed no significant difference in the mean level of serum TAS after 1st month of treatment compared with baseline level, while after 2nd and 3rd months of treatment there was significant reduction in the mean level of serum TAS when compared with baseline level. These results were supported by a lot of studies which report that during initiation or starting with chemotherapy treatment there was a decrease in the level of serum TAS due to affecting on dietary intake [39, 40]. Also, some studies showed that the cortisol can decrease the serum TAS level through inhibition of nuclear factor- κB [41]. Emotional and biological stressful condition may be contributed to increasing cortisone level which in turn leads to decrease in serum TAS level [42].

When compared between L1 and L2 group patients, the current study showed significant differences in the mean levels of serum TAS at baseline, and after 1st, 2nd, and 3rd months of treatment due to difference in intensity of chemotherapeutic regimen and sometimes there was simple difference due to difference in sex, age, dietary supplement, geographical location [43].

The current clinical study had shown a significant elevation in the mean level of serum LDH in L1 and L2 group patients when compared with the control group at the baseline level. This result was consistent with many studies which showed that, in ALL patients, there was marked elevation in serum concentration of LDH due to tissue damage and rapid cell turnover, this elevation in cellular LDH activity reflects a shift toward anaerobic metabolism and increased glycolysis in the cytoplasm of malignant cells accompanied by high cellular turnover rate (LDH involved in tumor initiation and metabolism) [44]. This increase in LDH concentration represents a prognostic marker for disease [45, 46]. Also, LDH considered a marker for oxidative state inside the human body, so the elevation of LDH concentration lead to increasing generation of ROS which in turn increase genesis of cancer and increase the cardiotoxicity especially with anthracycline and cyclophosphamide [47]. The mechanism for cardiotoxicity caused by anthracycline was through generation the ROS and leads to myocyte injury. Cardiac myocytes were highly susceptible to oxidative damage due to their intensive oxidative metabolism and relatively poor antioxidant defense [48, 49]. Within L1 group patients, there were no significant differences in the mean levels of serum LDH after 1st and 2nd months of treatment, while after 3rd months of treatment there was significant reduction in mean level of serum LDH when compared with baseline level. In L2 group patients, there were significant reductions in the mean levels of serum LDH after 1st, 2nd, and 3rd months of treatment when compared with the baseline level. The insignificant results during 1st and 2nd months in L1 group were supported by some studies which showed that some patients not responded to usual doses of chemotherapy because of the difference in individual biology of cancer cell or the malignant cells may acquire additional characteristics of invasiveness and reduce sensitivity due to increasing genetic instability that result from decreasing cell cycle control mechanism [50, 51]. Other results which had shown a decrease in LDH concentration were observed by many studies, where the concentration of LDH was dropped gradually until reach normal value because of lympholysis following chemotherapy regimen. The reduction in the level of LDH means that there is clinical and hematological remission [44, 50, 52]. When compared between L1 and L2 group patients, there were no significant difference in the mean level of serum LDH at baseline, and after 1st, 2nd and 3rd months of treatment.

CONCLUSION

Chemotherapy affect the growth and nutritional status of ALL children through their effects on the pathway of IGF-I synthesis, which in turn had a direct effect on GH and also, reduction in the levels of total proteins and albumin, which in turn effect on BMI of patients. The antioxidant level decreased significantly during chemotherapy treatment and led to cells metabolism alteration due to increased oxidative damage and metastasis of the disease, and these might lead to long term complications like nutritional and metabolic dysfunctions.

AKNOWLEGMENT

The present work was abstracted from MSc. thesis submitted to the Department of Clinical Pharmacy, College of Pharmacy, Al-Mustansiriyah University. The authors gratefully thank the College of Pharmacy, Al-Mustansiriyah University and The Child Hospital Center, Oncology Unit, Baghdad, Iraq for supporting the project.

REFERENCES

1. Lee S.J., K.H. Kim, and J.S. Park, *et al*. Comparative analysis of cell surface proteins in chronic and acute leukemia cell lines. *Biochemist. Biophys. (2007)*; Res. Comm., (357), pp.: 620-26.
2. Leonard, B., Leukemia: *A Research Report*. (2nd edition). DIANE Publishing, (1998); p.: 63.
3. Jeha S: New therapeutic strategies for the treatment of acute lymphoblastic leukemia. *Nat Rev Drug Discov*. (2007); 6, pp.: 149-65.
4. Gustafson, G., A. Kreuger, and N. Clausen, *et al*., Intensified treatment of acute childhood lymphoblastic leukemia has improved prognosis, especially in non-high-risk patients: The Nordic experience of 2648 patients diagnosed between (1981 and 1996), *Nordic Society of Pediatric Hematology and Oncology (NOPHO). Acta Pediatric*. (1998); 87, pp.: 1151-61.
5. Gurney JG, Severson RK, and Davis S, *et al*. Incidence of cancer in children in the United States, Sex-, races-, and 1-year age-specific rates by histologic type. *Cancer*; 75 (1995); (8), pp.:2186–95.
6. Freedman MD, Stewart P, and Kleinerman RA, *et al*. Household solvent exposures and childhood acute lymphoblastic leukemia. *Am J Public Health*. (2001); 91, pp.:564–67.
7. Seiter, K., Anand, J, and Harris, JE. *et al*. "Acute Myeloid Leukemia Staging". *Medscape Reference*. New York, USA: WebMD 2014.
8. Varian JW, Thiele J., and Bunning RD., *et al*: The revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes, *Blood journal hematology library*, (2009); p.:937 – 51.
9. Longo, D; Fauci, A; and Kasper, D, *et al*. *Harrison's Principles of Internal Medicine* (18th edition), 2011. New York: McGraw-Hill Professional.
10. Greer JP, Foerster J, and Rodgers GM, *et al*. Paraskos's Clinical Flow cytometer. In: *Lippincott Williams & Wilkin's publishing*. Winter be's Clinical Hematology. (12th edition) Philadelphia (2009); Vol.1, p.: 27.
11. Campana D and Hon Pui C. Childhood acute lymphoblastic leukemia. In: Hoff brand AV, Catovsky D, and Edward GD, et al., *Postgraduate Hematology*, (6th edition) U.K: Wiley –Blackwell Publishing. (2011), pp.:448 - 58.
12. Backeljauw P, Bang P, and Clayton PE, *et al*. Diagnosis and management of primary insulin-like growth factor-I deficiency: Current perspectives and clinical update. *Pediatr Endocrinol Rev* (2010); 7 Suppl 1: pp.:154-71.
13. Holly JM, Gunnell DJ, and Smith DG: Growth hormone, IGF-I, and cancer. Less intervention to avoid cancer? More intervention to prevent cancer? *J Endocrinol*. (1999), 162, pp.: 321-30.
14. Halliwell, B.: Can oxidative DNA damage be used as a biomarker of cancer risk in humans Problems, resolutions and preliminary results from nutritional supplementation studies. *Free Radical Res*. (1998); 29, pp.: 469–86.
15. Noriko NODA and Hiro WAKASUGI. Cancer and Oxidative Stress, National Cancer Center Research Institute, *JMAJ* (2001) 44 (12), pp.:535–39.
16. MaÂ rky I, Mellander L, and Lannering B., *et al*. A longitudinal study of growth and growth hormone secretion in children during treatment for acute lymphoblastic leukemia. *Medical Pediatric Oncology* 1991, 19, pp.:258-64.
17. Brauner R and Rappaport R. Pituitary hormone secretion and growth after cranial irradiation. Therapeutic consequences. In: *Hormonal Regulation of Growth*, Eds H Frish & MO Thorner. New York: Raven Press, 1989, pp.: 245-53.
18. Van Dongen-Melman JEWM, Hoekken-Kolega ACS, and Hählen K, *et al*. Obesity after successful treatment of acute lymphoblastic leukemia in childhood. *Pediatr Res*, 1995; 38, pp.: 86–90.
19. Odame Y, Reilly JJ, and Gibson BES, *et al*. Patterns of obesity in boys and girls after treatment for acute lymphoblastic leukemia. *Arch Dis Child*. (1994) 71, pp.:147–49.
20. ZHAO Dong-Ju, ZHANG Wen-Lin, and SHI Tai-Xin. Serum levels of insulin-like growth factor-1 and growth factor binding protein-3 in children with acute lymphocytic leukemia. *Zhongguo Dang Dai Er Ke Za Zhi.* 2011 Feb; 13(2), pp.: 101-30.
21. Rosen CJ, Donahue LR, and Hunter SJ. Insulin-like growth factors and bone: the osteoporosis connection. *Proc Soc Exp Biol Med* (1994), 206, pp.: 83–102.
22. Argente J, Caballo N, and Barrios V, *et al*. Multiple endocrine abnormalities of the growth hormone and insulin-like growth factor axis in patients with anorexia nervosa: effect of short and long-term weight recuperation. *J Clin Endocrinol Metab*. (1997), 82, pp.: 2084 –92.
23. Attard-Montalto SP, Camacho-Hubner C, and Cotterill AM, *et al*. Changes in protein turnover, IGF-I and IGF binding proteins in children with cancer. *Acta Paediatr*. (1998), 87, pp.: 54 – 60.
24. Mohnike K, Do¨ rffel W and Timme J. Final height and puberty in 40 patients after antileukemic treatment during childhood. *Eur J Pediatr*. (1997), 156, pp.: 272–76.

25. Sklar C, Mertens A, and Walter A, *et al*. Final height after treatment for childhood acute lymphoblastic leukemia: comparison of no cranial irradiation with 1800 and 2400 centigrades of cranial irradiation. *J Pediatr*. (1993), 123, pp.: 59 – 64 .
26. Bar-On E, Beckwith JB, and Odom LF, *et al*. Effect of chemotherapy on the human growth plate. *J Pediatr Orthop*. (1993), 13, pp.: 220 –24.
27. Halton JM., Atkinson SA., and Barr RD. Growth and body composition in response to chemotherapy in children with acute lymphoblastic leukemia. *Int J Cancer Suppl* (1998), 11, pp.: 81–84.
28. Khan AU., Sheikh MU., and Intekhab K. Effect of hypoproteinemia on treatment outcome in children with acute lymphoblastic leukemia. *J Ayub Med Coll Abbottabad* (2006), 18(2), pp.:53-56.
29. Gokhale CD., Udipi SA., and Ambaye RY., *et al*. Post-Therapy Profile of Serum Total Cholesterol, Retinol and Zinc in Pediatric Acute Lymphoblastic Leukemia and Non-Hodgkin's Lymphoma. *J Am Coll .Nutr* (2007), 26(1), pp.: 49–56.
30. Khan, A., Moeen-ul-Haq Sheikh, and Kiran Intekhab. Effect of hypoproteinemia on Treatment Outcome in Children with Acute Lymphoblastic Leukemia. *J. Ayub Medical College*, (2006). pp.: 2-18.
31. Mehdi, W., and A. Abdul bari Study the activity of Acid, Alkaline RNase and 5 ′-nucleotidases in sera of Child with Acute lymphoblastic Leukemia. *Australian Journal of Basic and Applied Sciences*, (2013). 7(9), pp.: 72-76.
32. Attard- Montalo Sp, Hadly J, and Kingston JE, *et al*. Ongoing assessment of nutritional status in children with malignant disease. *Pediatric Hematol Oncol*.1998 Sep-Oct; 15(5), pp.:393-403.
33. Skoczen S., Surmiac M, and Strojny W. Survivors of acute lymphoblastic leukemia and body mass changes. *Expert Opin. Drug Saf.* 2010; 9(1), PP.: 65-77.
34. Yu LC, Kuvibidila S, and Ducos R., *et al*. Nutritional status of children with leukemia. *Med pediatrics Oncol*. 1994; 22 (2), pp.: 7-73. *Med Pediatr Oncol*. 1997 April 28(4), pp.: 2- 321.
35. Klaunig JE, Kamendulis LM, and Hocevar BA. Oxidative stress and oxidative damage in carcinogenesis. *Toxicol Pathol* 2010; 38, pp.: 96–109.
36. Halliwell, B., Oxidative stress and cancer: have we moved forward? *Biochem J*., (2009), 401, pp.: 1-11.
37. Devlin, T., *Textbook of biochemical with clinical correlation*. (7th edition), John Wiley and sons. Inc. USA, (2011), pp.:1084-87.
38. Peji ć, S., Todorovi ć, A., and Stojiljkovi ć, V., *et al*. Superoxide dismutase and lipid hydro peroxides in blood and endometrial tissue of patients with benign, hyperplastic and malignant endometrium. *Annals of the Brazilian Academy of Science*, (2008), 80, pp.: 515-22.
39. Durken M, Herrnring C, and Finckh B, *et al.* Impaired plasma anti-oxidative defense and increased non-transferrin-bound iron during high-dose chemotherapy and radio-chemotherapy preceding bone marrow transplantation. *Free Radic Biol Med* 2000, 28, pp.: 887-94.
40. Bhuvarahamurthy V, Balasubramanian N, and Govindasamy S: Effect of radiotherapy and chemoradiotherapy on circulating antioxidant system of human uterine cervical carcinoma. *Mol Cell Biochem* 1996, 158, pp.:17-23.
41. Almawi, W.Y. and Melemed jian, O.K. Negative regulation of nuclear factor-kappa B activation and function by glucocorticoids. *Journal of Molecular Endocrinology*, (2002), 28, pp.:69-78.
42. Swaab, D.F., Raadsheer, F.C., and Endert, E., *et al*. Increased cortisol levels in Aging and Alzheimer's disease in postmortem cerebrospinal fluid. *Journal of Neuroendocrinology*, (2006) 6, pp.: 681-87.
43. Paris, J.J., Franco, C., and Sodano, R., *et al*. Sex differences in salivary cortisol in response to acute stressors among healthy participants, in recreational or pathological gamblers, and in those with posttraumatic stress disorder. *Hormones and Behaviour*, (2010) 57, pp.: 35-45.
44. Kornberg A and Polliack A. Serum lactic dehydrogenase levels in acute leukemia: Marked elevations in lymphoblastic leukemia. *Blood* 1980; 56, pp.: 351-55.
45. Field M, Block JB, and Levin R, *et al*. Significance of leukemia and other neoplastic proliferative disorders. *Am J Med*. 1966; 40, pp.: 528-47.
46. Ghosh K and Malik KK: Serum and leukocyte lactate dehydrogenase activity in leukemia. *Haem-Budap*. 1998:21(4), pp.: 227-32.
47. Šimůnek T, Štërba M, and Popelowá O, *et al.* Anthracycline induced cardiotoxicity: Overview of studies examining the roles of oxidative stress and free cellular iron. *Pharmacol Reports*. 2009; 61, pp.:154–71.
48. Yarnold J and Brotons MC. Pathogenetic mechanisms in radiation fibrosis. *Radiotherapy Oncology*. 2010: 97, pp.:149–61.
49. Trachtenberg BH, Landy DC, and Franco VI, *et al*. Anthracycline associated cardiotoxicity in survivors of childhood cancer. *Pediatric Cardio.* 2011; 32, pp.:342–53.
50. Wagner HP. Biology of cancer cells. In: *International seminar and CME program in pediatric hematology and oncology*. 1st international Society of Pediatric Oncology (SIOP). Dhaka, Bangladesh, 2001.
51. Erickson RJ and Morales DR. Clinical use of lactic dehydrogenase. *New Eng. J Med*. 1961; 265, pp.: 478 -82.
52. Salem M and Omar MN: Lactate dehydrogenase and alpha hydroxyl butyrate dehydrogenase: Sensitive indicators of disease status and responsiveness to therapy in adult acute lymphoblastic leukemia. *Saudi Medical Journal* 1995: 16(2), pp.: 99-101.

The IISTE is a pioneer in the Open-Access hosting service and academic event management. The aim of the firm is Accelerating Global Knowledge Sharing.

More information about the firm can be found on the homepage:
http://www.iiste.org

CALL FOR JOURNAL PAPERS

There are more than 30 peer-reviewed academic journals hosted under the hosting platform.

Prospective authors of journals can find the submission instruction on the following page: http://www.iiste.org/journals/ All the journals articles are available online to the readers all over the world without financial, legal, or technical barriers other than those inseparable from gaining access to the internet itself. Paper version of the journals is also available upon request of readers and authors.

MORE RESOURCES

Book publication information: http://www.iiste.org/book/

Academic conference: http://www.iiste.org/conference/upcoming-conferences-call-for-paper/

IISTE Knowledge Sharing Partners

EBSCO, Index Copernicus, Ulrich's Periodicals Directory, JournalTOCS, PKP Open Archives Harvester, Bielefeld Academic Search Engine, Elektronische Zeitschriftenbibliothek EZB, Open J-Gate, OCLC WorldCat, Universe Digtial Library , NewJour, Google Scholar