INTERNATIONAL JOURNAL OF ADVANCED BIOLOGICAL RESEARCH

www.scienceandnature.org

THE ADVERSE EFFECTS OF CHEMOTHERAPEUTIC AGENTS IN IRAQI PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA DURING THE INDUCTION PHASE

[a]Mohammed khudair Hassan, [a]Jaafar Jabir Ibrahim, [b]Mohammed Salem Abbas
[a]Department of Clinical Pharmacy, College of Pharmacy, University of Baghdad, Baghdad, Iraq
[b]Department of Hematology, College of Pharmacy, University of Baghdad, Baghdad, Iraq

ABSTRACT
Acute lymphoblastic leukemia (ALL) is a malignant transformation of a clone of cells from lymphoid progenitor cells. The aim of the present work was to study some of the adverse effects of the chemotherapeutic agents' methotrexate, vincristine, L-asparaginase, cytarabine and doxorubicin in Iraqi patients with acute lymphoblastic leukemia during the induction phase. Beside, special emphasis was made for the evaluation of adverse effect of L-asparaginase. Sixty Iraqi patients of different ages and gender with acute lymphoblastic leukemia (ALL) attended Baghdad teaching hospital (8 patients) and central teaching hospital of pediatrics (52 patients) and treated by the chemotherapeutic agent's methotrexate, vincristine, L-asparaginase, cytarabine and doxorubicin were followed for one month. Blood samples were taken from all the sixty patients to study the effect of these chemotherapeutic agents on; AST, ALT, serum uric acid, blood urea, total serum bilirubin, and hemoglobin; before beginning of the induction phase and after end of the induction phase. However, for special emphasis on evaluating the adverse effects of L-asparaginase, blood were sampled from twenty patients only to study the effect of the drug on PT, a PTT, plasma fibrinogen, serum amylase and blood sugar. The adverse effects of the above mentioned agents; during the induction phase of therapy; on gastrointestinal tract, central nervous system, immune system and some other miscellaneous adverse effect (pain and edema at the administration site, fever, back pain, joint pain and fungal infection) were reported for all the sixty patients involved in the study. The result showed that patients with ALL treated with the chemotherapeutic agents methotrexate, vincristine, L-asparaginase, cytarabine and doxorubicin had statistically significant ($p<0.05$) elevation in AST, ALT, blood urea, total serum bilirubin, and hemoglobin after end of the induction phase. However, statistically non-significant ($p>0.05$) reduction in serum uric acid was observed after end of the induction phase. The parameters PT, a PTT, serum amylase and blood sugar showed statistically significant ($p<0.05$) elevation after end of the induction phase. Besides, there was statistically significant ($p<0.05$) reduction in plasma fibrinogen after end of the induction phase. Adverse effects of these agents during the induction phase on gastrointestinal tract, central nervous system, immune system, and other miscellaneous adverse effect (pain and edema at the administration site, fever, back pain, joint pain and fungal infection) were also reported.

KEY WORDS: acute lymphoblastic leukemia, chemotherapeutic agents, adverse effects.

INTRODUCTION

Leukemia is malignant hematopoietic disease characterized by an uncontrolled proliferation and block in differentiation of hematopoietic cells these malignant cells can spread to the lymph nodes, spleen, liver and other tissues. Leukemia is broadly classified as acute or chronic referring to the type of cell affected and by the rate of cell growth and of myeloid or lymphoid according to the type of cell that is multiplying abnormally [1]. Leukemia divided into acute myeloid leukemia or Acute Myelogenous Leukemia (AML) which characterized by the malignant transformation of myeloid stems cells in the bone marrow, which are in capable of normal differentiation and maturation [2]. Chronic Myeloid Leukemia (CML) is a clonal disease that results from an acquired genetic change in a pluripotential hemopoietic stem cell [2]. Chronic Lymphocytic Leukemia (CLL) is also known as chronic lymphatic leukemia. Its typically consists of clonal expansion of mature, long-lived, functionally deficient B-lymphocytes that express high levels of the anti-apoptotic protein BCL-2 [3]. acute lymphoblastic Leukemia (ALL) that result from a monoclonal proliferation and expansion of immature B or T lymphocyte progenitor in the bone marrow, blood, and other organs [4,5]. Most ALL cases occur in children, with an incidence of 3 to 4/100,000 in patients 0 to 14 years of age and w1/100,000 in patients older than 15 years, in the United States [6]. In children, ALLs represent 75% of all acute leukemia (which in turn represent 34% of all cancers in this age group), with a peak incidence at 2 to 5 years of age [7]. This percentage is much lower in adults, in whom acute myeloid leukemia (AMLs) and chronic lymphocytic leukemia are more common [7, 8]. Epidemiological studies of acute leukemia in children have examined a number of possible risk factors (e.g., environmental, genetic, or infectious) in an effort to determine the etiology of the disease. Only two environmental risk factors (ionizing radiation and benzene) has been significantly linked with ALL; most environmental risk factors [e.g., electromagnetic fields,

cigarette smoking] have been weakly or inconsistently associated with either form of childhood leukemia[9]. Only a few cases (<5%) are associated with inherited, predisposing genetic syndromes [10]. Patients with trisomy 21, Klinefelter syndrome, and inherited diseases with excessive chromosomal fragility such as Fanconi anemia, Bloom syndrome, Nijmegen breakage syndrome and ataxia-telangiectasia have a higher risk of developing ALL [4, 10]. The clinical onset of ALL is most often acute, although a small percentage of cases may evolve insidiously over several months [11]. The most common symptoms include fever (caused by leukemia or a secondary infection secondary to neutropenia), fatigue and lethargy (as a result of anemia), bone and joint pain, and a bleeding diathesis (related to thrombocytopenia).Patients with precursor T-cell ALL/LBL often present with a mediastinal mass with or without associated pleural effusions, which may lead to respiratory distress and other signs of superior vena cava syndrome, Common extra medullary sites of involvement include lymph nodes, liver, spleen, and meninges, whereas less commonly, ALL may infiltrate orbital tissues, testes, tonsils, and adenoids[12]. Diagnosis of ALL depends on physical examination and various laboratory tests which include complete blood cell counts , peripheral blood smear and bone marrow morphological examination .Once a diagnosis of leukemia has been made further test are performed on bone marrow cells which include cytochemistry , immunophenotyping , cytogenetic and molecular analysis [13].

1.2Treatment of Acute Lymphoblastic Leukemia (ALL)

1.2.1 General care

Supportive care including the use of packed red cells, platelet transfusions and human recombinant granulocyte colony-stimulating factor (G-CSF), are required fairly frequently, especially when aggressive multiagent chemotherapy is employed, resulting in temporary bone marrow failure. When high fever and possible septicemia occur in the presence of neutropenia, antibiotic therapy should be started after taking appropriate blood cultures and chest radiographs, Platelet transfusions allopurinol in divided doses is given in all cases before the commencement of antileukemic drugs [14].

1.2.2 Chemotherapy

The choice of treatment of ALL is based on the estimated clinical risk of relapse in the patient, which varies widely among the subtypes of ALL. Three of the most important predictive factors are the age of the patient at the time of diagnosis, the initial leukocyte count, and the speed of response to treatment (i.e., how rapidly the blast cells can be cleared from the marrow or peripheral blood) [15].

Treatment is generally divided into 3 phases, namely, induction phase, intensification (consolidation) phase, and maintenance phase

1.2.2.11Induction phase

During this phase, therapy is usually given for 4 weeks and consists of vincristine weekly, a corticosteroid such as dexamethasone or prednisone, and either repeated doses of native L-asparaginase or a single dose of a long-acting asparaginase preparation. Intrathecal cytarabine or methotrexate, or both, may also be given. Patients at higher risk also receive daunomycin or doxorubicin at weekly intervals. With this approach, 98% of patients are in remission, as defined by less than 5% blasts in the marrow and a return of neutrophil and platelet counts to near-normal levels after 4-5 weeks of treatment. Intrathecal chemotherapy is usually given at the time of diagnosis and once more during induction [15].

1.2.2.1Consolidation/Intensification phase

Once remission has been achieved, systemic treatment in conjunction with central nervous system (CNS) therapy follows. Intensification may involve use of the following agents: Intermediate-dose or high-dose methotrexate (1–5 g/m^2) with leucovorin rescue or escalating-dose methotrexate without rescue [16]. Drugs similar to those used to achieve remission (reinduction or delayed intensification) [17]. L-asparaginase for an extended period of time [18]. Combinations of the above [18].

1.2.3 Maintenance (continuation therapy)

Patients with ALL generally require prolonged continuation therapy, for reasons that are still poorly understood. A combination of methotrexate administered weekly and mercaptopurine given daily constitutes the basis of most continuation regimens [19]. Studies have shown that adding intermittent pulses of vincristine and a glucocorticoid (prednisone) or dexamethasone to the methotrexate / 6-mercaptopurine combination is beneficial [15, 20].

1.2.4Management of CNS leukemia

Although cranial irradiation effectively prevents overt CNS relapse, concern about subsequent neurotoxicity and brain tumors has led many investigators to replace irradiation with intensive intrathecal and systemic chemotherapy. Systemic treatment including high dose methotrexate, intensive L-asparginase and dexamethasone .Triple intrathecal therapy with methotrexate cytarabine and hydrocortisone is more effective than intrathecal methotrexate alone in preventing CNS relapse [20].

1.2.5 Allogeneic haemopoietic stem-cell transplantation

Allogeneic haemopoietic stem-cell transplantation is the most intensive form of treatment for acute lymphoblastic leukemia. allogeneic transplantation clearly benefit to several subgroups of patients with high-risk ALL, such as individuals with Philadelphia chromosome-positive disease (even when treated with a tyrosine kinase inhibitor) and those with a poor initial response to treatment [21,22].

1.2.6 Radiation therapy

Radiation therapy is the use of high energy x-rays to kill cancer cells. It is sometimes used to treat leukemia that has spread to the brain and spinal cord or to the testicles. It might also be used to reduce pain when the leukemia has spread to a bone if chemotherapy hasn't helped [23, 24].

2. PATIENTS & METHODS

2.1Study design

Sixty newly diagnosed patients with ALL during a period of about 7 months (from November 2012 to July 2013) participated in this study. Eight patients were collected from Baghdad teaching hospital and 52 patients were collected from Central Teaching Hospital of Pediatrics. The patients were 39 males and 21 females. The ages of children range from 7 months to 15 years, and the ages of adults range from 18 to 52 years.

2.2Clinical and Laboratory Evaluation

Clinical evaluation of patients for the adverse effects of chemotherapeutic agents on gastrointestinal tract, central nervous system, immune system and on other miscellaneous adverse effects during induction phase was done by specialized hematologist during one month.

Blood specimen collection and laboratory analysis (before the induction phase and after the induction phase) of AST, ALT, total serum bilirubin, blood urea, serum uric acid and Hb. Before treatment with L-asparaginase, after 4th dose and after end of L-asparaginase dosing for PT, aPTT, plasma fibrinogen, serum amylase and random blood sugar was done by specialized laboratory researchers who did not participate in this study.

2.3 Chemotherapy

L-asparaginase protocol: In Central Teaching Hospital of Pediatrics, L-asparaginase was given as IM injection in 9 doses every other day according to United Kingdom acute lymphoblastic leukemia 2003 (UKALL2003) for pediatrics protocol. In Baghdad teaching hospital, L-asparaginase was given as IV infusion during 3 hours for 9 doses according to UKALL 2003 protocol for adults [25].

Vincristine protocol: In Central Teaching Hospital of Pediatrics, Vincristine was given intravenously as a single dose 1.5- 2 mg/m^2 weekly according to UKALL 2003 protocol. In Baghdad teaching hospital, Vincristine was given intrathecally as a single dose 2 mg/m^2 weekly according to UKALL 2003 protocol for adults [25].

Methotrexate protocol: In Central Teaching Hospital of Pediatrics, Methotrexate was given as weekly dose intrathecally according to the age: 6 mg (age <1 yr.), 8 mg (age 1 yr.), 10 mg (age 2 yrs.), 12 mg (age > 3 yrs.) according to UKALL2003 protocol as prophylactic from CNS leukemia [25]. In Baghdad teaching hospital, MTX (12.5 mg) was given intrathecally in adults as prophylactic from CNS leukemia according to UKALL 2003 protocol for adults [26].

Cytarabine protocol: In Central Teaching Hospital of Pediatrics, Cytarabine was given intrathecally only one dose in day 1 of the induction phase according to the age: <1 year 20 mg, 1-2 years 30 mg, 2-3 years 50 mg, >3years 70 mg, according to UKALL 2003 protocol [25]. In Baghdad teaching hospital, Cytarabine100 mg was given to adults' intrathecally only as one (single) dose in day 1 of the induction phase according to UKALL 2003 protocol for adults [25].

Doxorubicin protocol: In Central Teaching Hospital of Pediatrics, Doxorubicin was given weekly as intravenous dose 20 mg/m^2 over 3-5 hours to pediatrics according to UKALL 2003 protocol [25]. In Baghdad teaching hospital, Doxorubicin was given intravenously on weekly doses of 30-60 mg/m^2 to adults according UKALL 2003 protocol for adults [25].

The duration of the induction phase in UKALL 2003 protocol for adults and UKALL 2003 protocol for pediatrics is one month.

UKALL 2003 pediatrics protocol: The chemotherapeutic agents were given as follow: L-asparaginase was given in 9 doses by IM route every other day starting from day 7 of beginning the induction phase. Vincristine was given by IV route on weekly basis, 4 doses given during the induction phase starting from day 1. Intathecal methotrexate was given on weekly basis, 4 doses given during the induction phase starting from day 1. Intrathecal Cytarabine was given as single dose in day 1 only. Doxorubicin was given intravenously 4 doses starting from day 1 of beginning the induction phase. Doxorubicin was added to the above chemotherapeutic agents only for patients with high risk group such as high percentage of blast cells (more than 25%) and Down syndrome. Only four pediatric patients treated as high risk group in this study. All adults treated with doxorubicin.

UKALL 2003 protocol for adults: The chemotherapeutic agents were given as follow: L-asparaginase was given as IV infusion in 9 doses from day 7 every other day. Vincristine was given by IV infusion on weekly basis, 4 doses given during the induction phase starting from day1. Intathecal methotrexate was given on weekly basis, 4 doses given during the induction phase starting from day1. Intrathecal Cytarabine was given as single dose in day 1 only. Doxorubicin was given intravenously 4 doses starting from day 1 of beginning the induction phase. Doxorubicin was given to all adults patients with or without risk factors when compared to pediatrics regimens.

For the above two protocols; the chemotherapeutic agents administered IV, IM and intrathecal should not be given in the same time, rather, 12-24 hour interval between them.

2.4 Statistical Analysis

Data were analyzed by using Med Calc program v.6. This Software is developed for medical and statistical software solutions.

Differences between means were tested by pair t-test, whereas differences between proportions were tested by Chi-square.

Differences in findings (two variables) with P value less than 0.05 were considered significant. The difference with P values less than 0.01 were considered highly significant, and P values less than 0.0001 were considered very highly significant.

1. Demographic data and base line characteristics of the patient

This study included sixty patients treated with chemotherapeutic agents (L-aparaginase, MTX, vincristine, cytarabine and doxorubicin) for ALL. Demographic data and base line characteristics of the patients were shown in table (3-1) A and (3-1) B:

TABLE (3-1) A: Demographic data of the patients

Means ± SD and (percentages)				Parameters
8.7217±8.55671				Age
26.8133±19.05694				Weight
0.8968±0.38401				B.S.A
20 (34%)	female	40 (66%)	male	Gender

TABLE (3-1) B: Patients baseline characteristics

Numbers and (percentages)				Parameters
35 (58. %)	ALL-L2	25 (41%)	ALL-L2	Diagnosis
60 (100%)		0 (0%)		Hx. of bleeding%
60 (100%)		0 (0%)		Hx. of thrombosis%
60 (100%)		0 (0%)		Presence of H.T%
59 (99%)		1 (1.6%)		Presence of D.M%
60 (100%)		0 (0%)		Family Hx. of bleeding%
60 (100%)		0 (0%)		Family Hx. of thrombosis%
57 (95%)		3 (5%)		Family Hx. of leukemia%
59 (99%)		1 (1%)		Family Hx. of other cancers%

IM= Intramuscular, IV= Intravenous
H.T= Hypertension, D.M= Diabetes mellitus
B.S.A=Body surface area Hx= History

TABLE (3-2): Effect of the chemotherapeutic agents (L-asparaginase, MTX, vincristine, cytarabine and doxorubicin) on biochemical parameter

P-value	After induction phase	Before induction phase	Parameter
<0.0001 P	35.31 ± 23.60***	14.61 ±7.19	AST (U/L)
<0.0001 p	31.67 ± 17.09***	12.23 ± 8.09	ALT(U/L)
0.187	197.77 ± 96.581*	231.12 ± 105.30	Serum uric acid (Umol/l)
0.0001 P<	5.89 ± 1.7521***	3.82 ± 0.9162	Blood urea (mmol/l)
0.0001 < p	16.96 ± 8.0512***	8.31 ± 3.5339	Total serum bilirubin (mmol/l)
P<0.012	9.85 ± 1.36*	7.71 ± 2.29	Hemoglobin% (g/dl)
0.0001 P <	15.68 ± 3.79***	12.78 ± 0.8955	PT (seconds)
P < 0.0001	38.05 ± 3.94***	29.95 ± 1.54	a PTT (seconds)
P < 0.0001	135.20 ± 56.22 ***	216.50 ± 61.18	Plasma Fibrinogen (mg/dl)
P = 0.0027	51.1 ± 23.60**	32.15 ± 8.9650	Serum amylase (U/L)
P < 0.0001	5.10 ± 0.88***	4.02 ± 0.50	Random blood Sugar(mmol/l)

Values are presented as Mean ± SD. * Significant increase compared to pretreatment with the chemotherapeutic agents for all the 60 patients. **high significant increase in PT compared to pretreatment with L-asparaginase for 20 patients from total 60 patients. *** Very high significant increase compared to pretreatment with L-asparaginase for 20 patients from total 60 patients.

TABLE (3.3) Effect of the chemotherapeutic agents (L-asparaginase, MTX, vincristine, cytarabine and doxorubicin) on biochemical parameter before starting L-asparaginase and after 4th dose of L-asparaginase

P-value	After 4th dose of L-asparaginase	Pretreatment with L-asparaginase	Parameter
P =0.0001	13.97 ± 1.51**	12.76 ± 0.90	PT (seconds)
P < 0.0001	33.17 ± 2.59***	29.95 ± 1.54	a PTT (seconds)
P <0.0001	173.10 ± 65.22 ***	216.50 ± 61.18	Plasma Fibrinogen (mg/dl)
P= 0.0396	40.28 ± 14.85*	32.15 ± 8.97	Serum amylase(U/L)
P= 0.0926	4.29 ± 0.56	4.02 ± 0.50	Random blood Sugar (mmol/l)

Values are presented as Mean ± SD. * Significant increase compared to pretreatment with the chemotherapeutic agents for all the 60 patients. **high significant increase in PT compared to pretreatment with L-asparaginase for 20 patients from total 60 patients. *** Very high significant increase compared to pretreatment with L-asparaginase for 20 patients from total 60 patients.

TABLE (3-4): Effect of the chemotherapeutic agents on (L-asparaginase, MTX, vincristine, cytarabine and doxorubicin) biochemical parameter after 4th dose of L-asparaginase and after end of L-asparaginase dosing

P-value	Post treatment with L-asparaginase	After 4th dose of L-asparaginase	Parameter
P = 0.0073	15.68 ± 3.79 **	13.97 ± 1.51	PT (seconds)
P < 0.0001	38.05 ± 3.94***	33.17 ± 2.59	a PTT (seconds)
P<0.0001	135.20 ± 56.22 ***	173.10 ± 65.21	Plasma Fibrinogen (mg/dl)
P= 0.0019	51.14 ± 23.60 **	40.28 ± 14.85	Serum amylase (U/L)
P= 0.0011	5.10 ± 0.88 **	4.29 ± 0.56	Random blood Sugar(mmol/l)

Values are presented as Mean ± SD. * Significant increase compared to pretreatment with the chemotherapeutic agents for all the 60 patients. **high significant increase in PT compared to pretreatment with L-asparaginase for 20 patients from total 60 patients. *** Very high significant increase compared to pretreatment with L-asparaginase for 20 patients from total 60 patients.

TABLE (3-5): The adverse effect of the chemotherapeutic agents (L-asparaginase, MTX, vincristine, cytarabine and doxorubicin) on gastrointestinal

Numbers and (percentages) of occurrence of the adverse effects n=60		Adverse effects
NO	YES	
18 (30%)	42 (70%)	Nausea
18 (30%)	42 (70%)	Vomiting
22 (38%)	38 (62%)	Loss of appetite
31 (52%)	29 (48%)	Diarrhea
57 (94%)	3 (6%)	Constipation
59 (99%)	1 (1%)	Acute pancreatitis
60 (100%)	0 (0%)	Hemorrhagic pancreatitis
13 (22%)	47 (78%)	Abdominal pain
33 (54%)	27(46%)	Wt. loss
58 (96%)	2 (4%)	Wt. gain

tract during the induction phase

TABLE (3-6): The adverse effect of the chemotherapeutic agents (L-asparaginase, MTX, vincristine, cytarabine and doxorubicin) on central nervous system during the induction phase

Numbers and (percentages) of occurrence of the adverse effects n=60		Adverse effects
NO	YES	
16 (26%)	44 (74%)	Agitation
15 (24%)	45 (76%)	Depression
57 (94%)	3 (6%)	Hallucinations
15 (24%)	45 (76%)	Confusion
59 (99%)	1 (1%)	Somnolence
60 (100%)	0 (0%)	Seizures
59 (99%)	1 (1%)	Impaired consciousness
59 (99%)	1 (1%)	Fine tremor of the fingers
60 (100%)	0 (0%)	Coma
60 (100%)	0 (0%)	Seizures
60 (100%)	0 (0%)	unconsciousness

TABLE (3-7): The adverse effect of the chemotherapeutic agents (L-asparaginase, MTX, vincristine, cytarabine and doxorubicin) on immune system during the induction phase

Numbers and (percentages) of occurrence of the adverse effects n=60		Adverse effects
NO	YES	
41(68%)	19(32%)	Local erythema
49(66%)	11 (34%)	Urticaria
46(48%)	14 (42%)	Breathing difficulties
53(88%)	7 (12%)	Bronchospasm
60(100%)	0 (0%)	Anaphylactic shock

TABLE (3-8): The adverse effect of the chemotherapeutic agents (L-asparaginase, MTX, vincristine, cytarabine and doxorubicin) on other miscellaneous adverse effects during the induction phase

Numbers and (percentages) of occurrence of the adverse effects n=60		Adverse effects
NO	YES	
7(12%)	53(88%)	Pain at injection site
58(97%)	2(3%)	Edemas at injection site
38(64%)	22(36%)	Fever
22(36%)	38(64%)	Back pain
8(14%)	52(86%)	Joint pain
8(14%)	52(86%)	Fungal infections

4. DISCUSSION

The present study showed that after end of the induction phase (after treatment), very high significant elevation in AST and ALT was found. The elevation in the AST and ALT is caused by one or combination of the therapeutic agents investigated in this study, namely, L-asparaginase, MTX, Vincristine, Cytarabine and doxorubicin. Concerning L-aspaaginase, the reasons for the considerable elevations in AST and ALT caused by the drug are due to glutamine deficiency, decreased hepatic protein synthesis, oxidative stress, and consequent impairment of mitochondrial b-oxidation [27, 28]. Beside, L-aspaaginase causes instances of macro- and micro vesicular liver steatosis[29]. Herrera *et al.*1984 Show six patients with ALL were treated in induction phase with vincristine, prednisolone and doxorubicin, shortly after the administration showed an increase in AST, ALT activity [30]. Exadaktylos *et al.*,1994 show acute hepatotoxicity with intermediate-dose methotrexate in children with leukemia and non-Hodgkin's lymphoma [31].

In this study, total serum bilirubin concentration before beginning the induction phase (base line) was within normal range. However, after the induction phase there was very high significant elevation in total serum bilirubin. Recent studies show similar found in this investigations Oettgen *et a1*.,1970 reviewed the toxicity of the *E coli* preparation of L-asparaginase in 131 children and 143 adults with various neoplastic diseases, their data suggest that the drug may be more toxic to the adult liver and Increased levels of bilirubin, 29% and 51%, respectively[32].

This study show normal value of blood urea concentration in newly diagnosed patients with ALL before beginning of the induction phase. After the induction phase, there was very high significant elevation in blood urea concentration after the end of induction phase. Several factors are known to contribute to the nephrotoxic potential of antineoplastic drugs in patients with ALL; namely the concomitant use of combination of chemotherapy, urinary infections, intravascular volume depletion, sepsis and other co morbidities. Chemotherapy-induced nephrotoxicity may affect glomeruli, tubules, renal vasculature or excretory system depending on the drugs involved [33]. Kopecna showed improved chance for cure and prolonged survival, especially in childhood leukemia, implies the necessity for long-term follow-up of body systems. Effects of therapeutic approaches and different complications are mostly directly related to the kidney [34].

The results of this study showed an elevation from the baseline level of serum uric acid in patients with ALL before starting the induction phase. This study showed that after end of the induction phase, there was a non-significant reduction in total serum uric acid after end of the induction phase. The increase in uric acid concentration in plasma is constantly present in patients with tumor lysis syndrome (TLS). Hyperuricemia may be already present at time of diagnosis of ALL, or it may develop 2–3 days after initiation of anti-cancer treatment [35]. Recent studies show similar results: Kedar *et al*., 1995 Tumor lysis syndrome (TLS) is a well-recognized complication of leukemia and lymphoma, especially in patients with B-cell or T-cell neoplasms and a large tumor burden [36].

The results of this study show lower concentration of hemoglobin from the normal baseline level in patients with ALL before starting the induction phase. Anemia is common in patients with newly diagnosed ALL[37]. Anemia in children with cancer is associated with decreased erythropoietin activity but not with inadequate erythropoietin production, leading to the assumption that anemia in patients with leukemia mainly results from suppression of normal hematopoiesis in the bone marrow by infiltrating blasts [38, 39] .The current study show that after end of the induction phase, there was a significant increase in hemoglobin concentration. A similar result was shown by Simone. But failed to demonstrate any significance for this factor, although there was a trend towards worse survival over 8 g/dl [40].

The results of this study showed that normal value of plasma fibrinogen concentration in patients with ALL before treatment with L-asparaginase (after one week from starting the other chemotherapy). After 4th dose of L-asparaginase, plasma fibrinogen concentration exhibited very high significant decrease when compared with pretreatment concentration. After 9th dose of L-asparaginase, there was very high significant decline in plasma fibrinogen concentration when compared with after 4th dose. Besides, there was very high significant reduction in fibrinogen concentration when comparing pretreatment concentration and the concentration after 9th doses of L-asparaginase. Recent study show similar result. Vicarioto *et al*., 1986 studied fibrinogen and AT-III sequentially during remission induction in 20 ALL children. There was a significant decrease in the plasma fibrinogen and AT-III in the first 2 weeks [41].

The results of this study showed normal value of PT and aPTT in patients with ALL before starting the treatment with L-asparaginase. After 4th dose of L-asparaginase, PT demonstrated high significant prolongation and aPTT showed very high significant prolongation when compared with pretreatment value. After 9th dose of L-asparaginase (after end of induction phase), there was high significant prolongation in PT and there is very high significant prolongation in a PTT when compared that to after 4th dose of L-asparaginase. In addition, there was very high significant prolongation in PT and aPTT when comparing L-asparaginase pretreatment value with the value after 9th doses of L-asparaginase. Recent study show similar result. Ott *et al*., 1988 show the incidence of thrombotic or hemorrhagic complications following L-Asparaginase therapy for childhood lymphoblastic leukemia [42].

The results of this study showed normal value of serum amylase activity in patients with ALL before starting the treatment with L-asparaginase. After 4th dose of L-asparaginase, serum amylase activity shows a significant elevation when compared with pretreatment activity. After 9th dose of L-asparaginase, there is high significant elevation in serum amylase activity when compared with the activity after 4th dose. Furthermore, there is high significant elevation in serum amylase when compared to pretreatment value with the value after 9th doses of L-asparaginase. The mechanisms of L-asparaginase-induced pancreatitis in humans remain unknown but there are

many reports of L-asparaginase-induced pancreatitis [43]. Recent studies show similar results: Raetz & Salzer show L-asparaginase-associated pancreatitis has been reported in 1–18% of pediatric ALL patients [44].

The results of the current study demonstrated normal value of random blood sugar in patients with ALL before treatment with L-asparaginase. After 4th dose of L-asparaginase, the increase in random blood sugar was non-significant when compared with pretreatment. After 9th dose of L-asparagine, there was high significant elevation in random blood sugar when compared to that after 4th dose. Besides, there is very high significant elevation in random blood sugar when comparing pretreatment concentration and the concentration after nine doses of L-asparaginase. Hyperglycemia is a well-documented complication of L-asparaginase therapy for ALL [45]. Other studies show results similar to this study: Hsu et al., 2002 Show significant relationship between L-asparaginase treatment and hyperglycemia also suggested that some malignancies such as ALL can affect the glucose homeostasis [46].

In the present study, the adverse effects of the chemotherapy on gastrointestinal tract occurred in different number of patients and percentages of occurrence during induction phase as follow: nausea n=42 (70%) , vomiting n=42 (70%), loss of appetite n=38 (62%), abdominal pain n=47 (78%), diarrhea n=29 (48%), constipation n=3 (6%), acute pancreatitis n=1 (1%), Hemorrhagic pancreatitis n=0 (0%), weight loss n=27 (46%) and weight gain n=2 (4%). Severity of nausea and vomiting are responsible for the poor treatment compliance [220]. Recent studies reported similar adverse effects observed in the present Study [25, 47, 48-51]. The adverse effects of chemotherapy on CNS in the present study, appeared in variable numbers of patients and percentages of occurrence during induction phase as agitation n=44 (74%), depression n=45(76%), confusion n=45 (76%), hallucinations n=3(6%), somnolence n=1 (1%), seizures n=0 (0%), impaired consciousness n=1 (1%), fine tremor of the fingers n=1(1%), coma n=0 (0%) and unconsciousness n=0 (0%) occurred rarely. This study show similar results with recent studies [25, 52-54].

In the present study, the effects of chemotherapy on immune system was observed in different numbers of patients and percentages of occurrence during induction phase as follow: local erythema n=19 (32%), urticaria n=11 (34%), breathing difficulties n=14 (42%) occurred frequently, bronchospasm n=7 (12%) less frequent, and anaphylactic shock n=0 (0%) not occurred. Recent studies showed similar results as found in this investigation [55-60].

In the present study, the effect of chemotherapy on other miscellaneous adverse effects in numbers of patients and percentages of occurrence during induction phase as follow: pain at injection site n=53 (88%),oedemas at injection site n=2 (3%), fever n=22 (36%), back pain n=38 (64%), joint pain n=52 (86%), fungal infections n=52 (86%). Recent studies show similar results found in this investigations [61].

REFERENCES

[1]. Lee, S.J., K.H. Kim, J.S. Park, D.W. Kim and K.P. Kim (2007)Comparative analysis of cell surface proteins in chronic and acute leukemia cell lines. ***Biochem. Biophys.*** Res. Comm., 357: 620-626.

[2]. Mughal, T.I. and Goldman, J.M. (2001) Chronic myeloid leukemia. STI 571 magnifies the therapeutic dilemma. ***Eur. J. Cancer***, 37: 161-168.

[3]. Hanada, M., Delia, D., Aiello, A., Stadtmauer, E. and Reed, J. (1993) Bcl-2 gene hypo methylation and high level expression in B-cell chronic lymphocytic leukemia. ***Blood, 82***: 1820-1828.

[4]. Jabbour. E.J., Faderl, S., Kantarjian, H.M. (2005) Adult acute lymphoblastic leukemia. ***Mayo Clin Proc.***80: 1517-1527.

[5]. Jeha, S. (2007) New therapeutic strategies for the treatment of acute lymphoblastic leukemia. ***Nat Rev Drug Discov.*** 6: 149-165.

[6]. National Cancer Institute (2009) SEER Cancer Statistics Review, 1975–2006. Accessed January 23.

[7]. Gurney, J.G., Severson, R.K., Davis, S. (1995) Incidence of cancer in children in the United States. Sex-, race-, and 1-year age-specific rates by histologic type. ***Cancer***; 75(8):2186–95.

[8]. American Cancer Society (2009) ***Cancer facts and figures*** 2008. Accessed January 23.

[9]. Robison, L.L., Look, A. T. (2008) Acute lymphoblastic leukemia, ***Lancet*** ; 371: 1030-1043.

[10]. Hong, D., Gupta, R., An cliff, P., Atzberger, A., Brown, J., Soneji, S. (2008) Initiating and cancer-propagating cells in TEL-AML1-associated childhood leukemia, ***Science***. 319: 336-339.

[11]. Pui, C.H. (2006) Acute lymphoblastic leukemia. In: Pui CH, editor. Childhood leukemias, New York: Cambridge University Press. pp. 439–72.

[12]. Kahwash, S.B., Qualman, S.J. (2002) Cutaneous lymphoblastic lymphoma in children: report of six cases with precursor B-cell lineage. ***Pediatric Dev. Pathol*** . 5(1):45–53.

[13]. Pui, C.H., Robison, L.L., Look, A.T. (2008) Acute lymphoblastic leukemia. ***Lancet***. 22; 371 (9617): 1030-43.

[14]. Whitlock, J.A., Gaynon, P.S. (2009) Acute Lymphoblastic Leukemia in Children. In: Greer JP , Foerster J , Rodgers GM, Paraskevas F , Glader B , Arber DA. Wintrbe's Clinical Hematology 12th ed. Philadelphia: Lippincott Williams & Wilikins publishing, 1 - Chapter 80, p.1897 – 1898.

[15]. Swirsky, D., Bain, B. J. (2006) Erythrocyte and leucocyte cytochemistry. In: Lewis MS, Bain BJ, Bates I. editors. Dacie & Lewis Practical Hematology. 10th. ed., Philadelphia: ***Churchhill Livingstone Elsevier***. Chapter 13, p.323.

[16]. Niemeyer, C.M., Gelber, R.D., Tarbell, N.J. (1991) Low- dose versus high-dose methotrexate during remission induction in childhood acute lymphoblastic leukemia (Protocol 81–01 update). ***Blood***. 78:2514-2519.

[17]. Silverman, L.B., Gelber, R.D., Dalton, V.K. (2001) Improved outcome for children with acute lymphoblastic leukemia: results of Dana-Farber Consortium Protocol 91-01. ***Blood***. 97 (5): 1211-8.

[18]. Hon Pui, C., Evans, W.E. (2006) Treatment of Acute Lymphoblastic Leukemia N. ***Engl. J. Med***. 354:166-178.

[19]. Mahoney, D.H. Jr, Shuster, J.J., Nitschke, R. (2000) Intensification with intermediate-dose intravenous methotrexate is effective therapy for children with lower-risk B-precursor acute lymphoblastic leukemia: A Pediatric Oncology Group study. J Clin Oncol 18 (6): 1285-94.

[20]. Arico, M., Valsecchi, M.G., Camitta, B. (2000) Outcome of treatment in children with Philadelphia chromosome-positive acute lymphoblastic leukemia. ***N Engl J Med*** . 342**:** 998–1006.

[21]. Hunault, M., Harousseau, J.L., Delain, M. (2004) Better outcome of adult acute lymphoblastic leukemia after early genoidentical allogeneic bone marrow transplantation (BMT) than after late high-dose therapy and autologous BMT: ***a GOELAMS trial. Blood***. 104**:** 3028–37.

[22]. Evans, W.E. (2006)Treatment of acute lymphoblastic leukemia. ***N Engl J Med*** .354**:** 166–78.

[23]. Grant Steen and Joseph Mirro (2000) Childhood Cancer: A Handbook from St Jude Children's Research Hospital, Published by Perseus Publishing.

[24]. Pizzo, P., Poplack, D. (2002) Principles and Practice of Pediatric Oncology. Fourth ed. Philadelphia: ***Lippincott Williams & Wilkins***.

[25]. BC Cancer Agency Lymphoma Tumor Group (2004) (LYIT) BCCA Protocol Summary for Treatment of Lymphoma using Intrathecal Methotrexate and Cytarabine. Vancouver, British Columbia: ***BC Cancer Agency*** (39).

[26]. Bodmer, M., Sulz, M., Stallman, S., Droll, A., Terracciano, L., Krahenbuhl, S. (2006) Fatal liver failure in an adult patient with acute lymphoblastic leukemia following treatment with L-asparaginase. ***Digestion.***74:28-32.

[27]. Scheimber, I.B., Pollock, D.J., Collins, P.W. (1995) Pathology of the liver in Leukemia and lymphoma. A study of 110 autopsies. ***Histopathology***. 26: 311-21.

[28]. Fromenty, B., Pessayre, D. (1997) Impaired mitochondrial function in micro vesicular steatosis. Effects of drugs, ethanol, hormones and cytokines. ***J Hepatol***. 26:43-53.

[29]. Herrera, J., Ramos, E., Ambriz, R., Aguirre, J., and Pizzuto, J. (1984) Hepatic injury during doxorubicin therapy. ***Arch pathol Lab Med.*** 108:912-913.

[30]. Exadaktylos, P., Reiss, T., Schobess, R. (1994) Acute hepatotoxicity with intermediate-dose methotrexate inn children with leukemia and non-Hodgkin's lymphoma. ***Klin Padiatr***, 206(4):315-18.

[31]. Oettgen, H.F., Stephenson, P.A., Schwartz, M.K. (1970) Toxicity of E coli L-asparaginase in man. ***Cancer***. 28:253-278.

[32]. De Jonge, M. J. & Verweij, J. (2006) Renal toxicities of chemotherapy. ***Semin Oncol,*** 33, No 1, pp. 68-73.

[33]. Kopecna, L. (2001) Late effects of anticancer therapy on kidney function in children with acute lymphoblastic leukemia. ***Bratisl Lek Listy***. 102:357–360.

[34]. Chasty, R.C., Liu-Yin, J.A. (1993) Acute tumor lysis syndrome. ***Br J Hosp Med*** .49:7-12.

[35]. Kedar, A., Grow, W., Neiberger, R.E. (1995) Clinical versus laboratory tumor lysis syndrome in children with acute leukemia. Pediatr Hematol Oncol. 12(2):129-34.

[36]. Santana, V.M., Dodge, R.K., Crist, W.M., Rivera, G.K., Look, A.T., Boehm, F.G. (1990) Presenting features and treatment outcome of adolescents with acute lymphoblastic leukemia. ***Leukemia***. 4:87-90.

[37]. Dowd, M.D., Morgan, E.R., Langman, C.B., Murphy, S. (1997) Serum erythropoietin levels in children with leukemia. ***Med Pediatric Oncol***. 28:259-67.

[38]. Corazza, F., Beguine, Y., Bergmann, P., André, M., Ferster, A., Devalck, C. (1998) Anemia in children with cancer is associated with decreased erythropoietin activity and not with inadequate erythropoietin production. ***Blood.*** 92. (5):1793-8.

[39]. Simone, J. V. (1975) Prognostic factors in childhood acute lymphocytic leukemia. ***Adv. Biosci***.14: 27-42.

[40]. Vicarioto, M., Rosolen, A., Cappellato, M.G., Zanesco, L., Girolami, A. (1986) Greater decrease of fibrinogen as compared to antithrombin III in L-asparaginase treated leukemia patients. ***Folia Haematol Int Mag Klin Morphol Blutforsch***. 113:663-9.

[41]. Ott, N., Ramsay, N.K., Priest, J.R. (1988) Squeal of thrombotic or hemorrhagic complications following L-asparaginase therapy for childhood lymphoblastic leukemia. ***Am J Ped Hematol Oncol.*** 10:191-195.

[42]. Knoderer, H.M., Robarge, J., Flock hart, D.A. (2007) predicting L-asparaginase- associated pancreatitis. ***Pediatric Blood Cancer***, 49: 634-9.

[43]. Raetz, E.A. & Salzer, W.L. (2010) Tolerability and efficacy of L-asparaginase therapy in pediatric patients with acute lymphoblastic leukemia. ***Journal of Pediatric Hematology/oncology***. 32, 554–563.

[44]. Cetin, M., Yetgin, S., Kara, A., Tuncer, M., Günay, M., Gümrük, F. (1994) Hyperglycemia, ketoacidosis and other complications of L-asparaginase in children with acute lymphoblastic leukemia. ***J Med***. 25:219-29.

[45]. Hsu, Y.J., Chen, Y.C., Ho CL, Kao, W.Y., Chao, T.Y. (2002) Diabetic ketoacidosis and persistent hyperglycemia as long-term complications of L-asparaginase-induced pancreatitis. ***Zhonghua Yi Xue Za Zhi (Taipei)*** . 65(9): 4415.

[46]. Hong, D., Gupta, R., An cliff, P., Atzberger, A., Brown, J., Soneji, S. (2008) Initiating and cancer-propagating cells in TEL-AML1-associated childhood leukemia. ***Science***. 319: 336-339.

[47]. Cheng, K.K.F. (2008) Association of plasma methotrexate, neutropenia, hepatic dysfunction, Nausea/vomiting, and oral mucositis in children with cancer. ***European J Cancer Care*** .17:306-311.

[48]. McLeod, J.G., Penny, R. (1969) Vincristine neuropathy: an electrophysiological and histological study. ***J Neurol Neurosurg Psychiatry***. 32: 297-304.

[49]. Sikorska-Fic, B., Stańczak, E., Matysiak, M. and Kamiński, A. (2008) Acute Pancreatitis during Chemotherapy of Acute Lymphoblastic Leukemia Complicated with Pseudo cyst, ***Medycyna Wieku Rozwojowego***, 12:4, pp. 1051-1055.

[50]. Ho, D.H.W., Yap, H.Y., Brown, N., Benjamin, R.S., Friereich, E.J., Blumenschein, G.R., Bodey, G.P. (1981) Clinical pharmacology of intramuscularly administeredL-asparaginase, ***J. Clin. Pharmacology***. 27: 72-78.

[51]. Ohnuma, T., Holland, J., Freeman, A., Levy, R. (1971) Treatment of adult leukemia with *L*-asparaginase (NSC-109229) Cancer Chemother Rep. *55*:*269–275*.

[52]. Moore, I.M., Miketova, P., Hockenberry, M., Krull, K., Pasvogel, A., Carey, M., and Kaemingk, K. (2008) Methotrexate-induced alterations in beta-oxidation correlate with cognitive abilities in children with acute lymphoblastic leukemia. ***Biol Res Nurs***.9 (4):311-319.

[53]. Johnson, F. L., Bernstein, I. D., Hartmann, J. R., and Chard, R. L. (1973) Seizures associated with vincristine sulphate therapy. ***Journal of Pediatrics***, 82, 699-704.

[54]. Maharaj, K. Raina (2006) Director Medical Information, Enzon Pharmaceuticals. ***Personal communication***.

[55]. Clavell, L.A., Gelber, R.D., Cohen, H.J. (1986) Four-agent induction and intensive asparaginase therapy for treatment of childhood acute lymphoblastic leukemia. ***The New England journal of medicine***.315(11):657–663.

[56]. Alkins, S.A., Byrd, J.C., Morgan, S.K. (1996) Anaphylactic reactions to methotrexate, ***Cancer*** .77:2123–2126.

[57]. John Shepherd, M.D. (2007) Personal communication. BC Cancer Agency ***Leukemia/BMT Tumor Group***.

[58]. Gassel, W.D., Gropp, C., Havemann, K. (1984) Acute allergic reaction due to vincristine sulfate. A case report. ***Oncology*** .41(6):403-5.

[59]. Panosyan, E.H., Seibel, N.L., Martin-Aragon, S. (2004) L-asparaginase antibody and L-asparaginase activity in children with higher-risk acute lymphoblastic leukemia: Children's Cancer Group Study CCG-1961. ***J Pediatric Hematology Oncol***. 26:217-226.

[60]. Koll, B. S., Brown, A. K. (1993) The changing epidemiology of infections at cancer hospitals. ***Clin Infect Dis***.17:S322-8.

[61]. Kannarkat, G., Lasher, E. E. & Schiff, D. (2007) Neurologic complications of chemotherapy agents. ***Curr Opin Neurol***, 20: 6, pp. 719-25.