INTRODUCTION

Leukemia is a cancer that involves the blood forming tissue of the bone marrow, spleen and lymph nodes. The bone marrow starts producing large numbers of abnormal white blood cells. These abnormal immature cells called lymphoblast or blasts, crowed out other blood cells in the bone marrow, blood stream and lymph system. Although overall incidence is rare, leukemia is the most common type of childhood cancer. It accounts for 30% in all cancers diagnosed in children younger than 15 years. Within this population, acute lymphoblast leukemia (ALL) accounts approximately five times more frequently than acute myelogenous leukemia (AML) and accounts for approximately 78% of all childhood leukemia diagnosis. Epidemiological studies of acute leukemias in children have examined possible risk factors including genetic, infectious, environmental and nutritional, in an attempt to determine the etiology ***(Martin et al., 2006).***

In Egypt, the incidence of childhood cancers overall is approximately 78,010 new patients (as documented in the years 2002-2005), seen at the NCI (National Cancer Institute, Cairo, Egypt), among which leukemia represents the most common childhood cancer, representing almost 35% of all cases (34.6% boys and 33.3% girls) ***(Elattar et al., 2006).***

Children with newly diagnosed leukemia seemed to present significant nutritional depletion. Thus nutritional indices should be monitored in children with leukemia as treatment may intensify malnutrition, which might be prevented by early adequate nutritional intervention through providing nutrients needed to maintain health while fighting cancer ***(Uderzo et al, 1996).***

Good nutritional status is very important in patients with malignant diseases, especially during chemotherapy. It is important to avoid cachexia. One should avoid factors that may cause it or feed the patient by tube or intravenously if not possible orally and if necessary to give total parenteral nutrition. The target is to ensure that the children with malignant diseases during chemotherapy will retain optimal nutritional condition, which helps the children's growth and makes them tolerate the treatment better ***(Bodánszky, 1997).***

The impact of Undernutrition in the outcome of treatment in children with acute leukemia has been analyzed by several authors who have highlighted undernutrition as another relevant prognostic factor in children with acute leukemia. Undernutrition by itself and without interacting with other variables may be a significant prognostic factor in the long term outcome of treatment of pediatric patients with acute leukemia. After identifying this variable as important, imaginative approaches to the treatment of cancer in childhood, in the years

ahead may lead into the improvement of results of treatments ***(Lobato et al., 2003).***

Chemotherapy and radiotherapy seem to be an important nutritional risk factor due to the numerous side effects associated along the course; loss of appetite (anorexia), myositis, sore mouth or throat, dental and gum problems, changes in taste or smell, nausea, vomiting, diarrhea, constipation, fatigue and depression. Contributing in the disability to eat, leading to the decrease of food intake, nutrient loss, and thus weight loss and malnutrition. Children with cancer are at risk of suffering from undernutrition which can affect tolerance of therapy and may influence their overall survival. The goals of the nutritional support in the cancer patient are to achieve and maintain desirable weight and to prevent or correct nutritional deficiencies. Parentral nutrition should be considered if the gut is not functioning adequately to allow the normal absorption and digestion of nutrients or if oral nutritional support is not sufficient to meet nutritional needs ***(Sala et al., 2003).***

Inadequate oral food intake and manifest malnutrition are indications for artificial nutrition, the indication of nutritional therapy should be based on the guidelines for entral/parentral nutrition. However, the individual life situation of patient and any disease specific changes in the digestive capacity should also be considered ***(Schneider et al., 2007).***

AIM OF THE WORK

The aim of the study was to evaluate the nutritional status of Egyptian leukemic children with intolerance to oral feeding at the first (1st) presentation, as well as to reassess their nutritional status after nutritional supplementation in the form of partial parentral nutrition for 2 weeks followed by oral nutritional supplementation for another 10 weeks starting with giving the induction therapy.

CHILDHOOD LEUKEMIA

Classification of Leukemia:

Leukemia can be classified into:

1- Acute Lymphocytic leukemia (ALL).

2- Acute Myelogenous Leukemia (AML).

3- Chronic Myelogenous Leukemia (CML).

4-Hybrid or mixed Lineage Leukemia.

1-Acute Myelogenous Leukemia (AML)

- ***Definition and History:***

Acute myelogenous leukemia (AML) is a clonal malignant disease of hematopoietic tissue that is characterized by accumulation of abnormal (leukemic) blast cells, principally in the marrow and impaired production of normal blood cells. Thus, the leukemic cell infiltration in marrow is accompanied by anemia and thrombocytopenia. The absolute neutrophil count may be low or normal, depending on the total white blood cells count ***(Zipf et al., 2000).***

The first well-documented case of acute leukemia is attributed to Friedreich, but Ebstein was the first to use the term acute leukemia in 1889 ***(Ebstein, 1889).***

Neumann (1878) proposed that marrow was the site of blood cells production and suggested that leukemia originated

in the marrow and used the term *myelogene* (myelogenous) leukemia.

- ***Etiology:***

Although the cause of AML is unknown in most patients, several factors may associated with its development:

1-Radiation exposure:

A great deal of evidence has implicated radiation in leukemogenesis in many patients, as evidenced in Japan after the atomic explosions at Hiroshima and Nagasaki. Most of the leukemias arose within the first 5 years after exposure, although some developed as much as 15 years after exposure ***(Lichtenstein et al., 2000).***

2-Exposure to toxins and drugs:

- Exposure to toxic chemicals that cause damage to the bone marrow, such as benzene and toluene used in the leather, shoe and dry cleaning industries, is associated with leukemia in adults. Direct evidence of this effect in children has not been established. Exposure to pesticides has been noted to increase the risk of AML ***(Snyder, 2002).***
- A compelling association has been observed after treatment with antineoplastic cytotoxic agents, particularly alkylating agents such as procarbazine, the nitrosoureas, cyclophosphamide, melphalan and most recently epipodophyllotoxins etoposide and teniposide. Patients

receiving these agents to treat malignancies (eg: Hodgkin lymphoma) especially if the agents are administered with radiation therapy, have a significantly increased risk of developing a preleukemic syndrome that ultimately transforms into overt AML ***(Greaves, 2002).***

3-Genetic factors and syndromes:

- Children with Down syndrome (trisomy 21) have a 15-fold increased risk of developing leukemia, most commonly acute megakaryoblastic leukemia, compared with the general population ***(Spirito et al., 2003).***
- Approximately 8% of children with Fanconi anemia develop AML in their adolescent years ***(Alter, 2003).***
- Patients with inherited disorders such as Shwachman, Bloom or Diamond-Blackfan syndromes, also have an elevated risk of developing leukemia. These syndromes share features of poor DNA repair that are believed to predispose affected individuals to leukemogenic stimuli ***(Mitsui et al., 2004).***
- Children with neurofibromatosis type I and Kostmann neutropenia (severe congenital neutropenia) also appear to be at increased risk for developing AML ***(Vlachos et al., 2001).***

- ***Pathogenesis:***

AML results from a series of somatic mutations in either a hematopoietic multipotential cell or occasionally a more differentiated lineage-restricted progenitor cell. Some cases of

monocytic leukemia, promyelocytic leukemia and AML in younger individuals more likely arise in a progenitor cell with lineage restrictions (progenitor cell leukemia) ***(Luca and Almanaseer, 2003).***

Somatic mutation results from a chromosomal translocation in the majority of patients. The translocation results in rearrangement of a critical region of a protooncogene. Fusion of portions of two genes usually does not prevent the processes of transcription and translation; thus, the fusion gene encodes a fusion protein that, because of its abnormal structure, disrupts a normal cell pathway and predisposes to a malignant transformation of the cell ***(Shumacher, 2002).***

- ***Incidence:***

AML accounts for 15 to 20 percent of the acute leukemias in children it is slightly more common in males ***(Martin et al., 2007).***

- ***Classification:***

Variants of AML can be identified by morphologic features of blood films using polychromatic stains and histochemical reactions, monoclonal antibodies against surface markers or by the presence of specific chromosome translocations. The epitopes on the progenitor cells of several phenotypic variants overlap, and several monoclonal antibodies are required to make specific distinctions among cell types ***(Greaves, 2002).***

Correlation between morphologic and immunologic phenotyping of AML is poor. However, poor correlation is expected because the morphological phenotyping method is more subjective, given to observer variation, and is based on qualitative factors, whereas the method which characterizes surface molecular features is more accurate and reproducible ***(Greaves, 2002).***

Immunologic Phenotypes of AML:

Phenotypes	**Usually Positive**
Myeloblastic	CD11, CD13, CD15, CD33, CD117, HLA-DR
Myelomonocytic	CD11, CD13, CD14, CD15, CD32, CD33, HLA-DR
Erythroblastic	Glycophorin, spectrin, ABH antigens, carbonic anhydrase I, HLA-DR
Promyelocytic	CD11, CD13, CD15, CD33
Monocytic	CD11, CD13, CD14, CD33, HLA-DR
Megakaryoblastic	CD34, CD41, CD42, CD61, von Willebrand factor

(Greaves, 2002)

Morphologic Variants of AML:

Variant	Cytologic Features	Special Clinical Features	Special Laboratory Features
Acute myeloblastic leukemia (M0, M1, M2)	1. Myeloblasts are usually large; nuclear cytoplasmic ratio 1:1. Cytoplasm usually contains granules and occasionally Auer bodies. Nucleus shows fine reticular pattern and distinct nucleoli.	1. Most frequent variety in infants.	
	2. Blast cells are sudanophilic. They are positive for myeloperoxidase and chloroacetate esterase, negative for nonspecific esterase, and negative or diffusely positive for PAS (no clumps or blocks).	2. Three morphologic-cytochemical types (M0, M1, M2)	1. M0 type blast cells positive with antibody to myeloperoxidase and anti-CD34 and CD13 or CD33 coexpression. *AML1* mutations in 25%.
	3. Electron microscopy shows primary cytoplasmic granules.		2. M1 expresses CD13 and CD33. Positive for myeloperoxidase by cytochemistry.
			3. (M2) AML with maturation often associated with t (8; 21) karyotype.
Acute promyelocytic leukemia (M3, M3v)	1. Leukemic cells resemble promyelocytes. They have large atypical primary granules and a kidney-shaped nucleus. Branched or adherent Auer rods are common.	1. Not common in children.	1. Cell contains t (15; 17) or other translocation involving chromosome 17
	2. Peroxidase stain intensely positive.	2. Hypofibrinogenemia and hemorrhage common.	2. Cells are HLA-DR negative.
	3. A variant has microgranules (M3v), otherwise the same course and prognosis.	3. Leukemic cells mature in response to all-*trans*-retinoic acid.	
Acute myelomonocytic leukemia (M4, M4Eo)	1. Both myeloblastic and monoblastic leukemic cells in blood and marrow.	1. Similar to myeloblastic leukemia but with more frequent extramedullary disease.	1. Eosinophilic variant has inversion or translocation of chromosome16.
	2. Peroxidase, Sudan-, chloroacetate esterase-, and nonspecific esterase-positive cells.	2. Mildly elevated serum and urine lysozyme.	
	3. M4Eo variant has marrow eosinophilia.		
Acute monocytic leukemia (M5)	1. Leukemia cells are large; nuclear cytoplasmic ratio lower than myeloblast. Cytoplasm contains fine granules. Auer rods are rare. Nucleus is convoluted and may contain large nucleoli.	1. Seen in children or young adults.	1. t (4; 11) common in infants.
	2. Nonspecific esterase-positive inhibited by NaF; Sudan, peroxidase and chloroacetate esterase negative. PAS occurs in granules, blocks.	2. Gum, CNS, lymph node, and extramedullary infiltrations are common.	2. Rearrangement of q11; q23 very frequent.
		3. DIC occurs.	
		4. Plasma and urine lysozyme elevated.	
		5. Hyperleukocytosis common.	
Acute erythroleukemia (M6)	Abnormal erythroblasts are in abundance initially in marrow and often in blood. Later the morphologic findings may be indistinguishable from those of AML.	Pancytopenia common at diagnosis.	Cells reactive with antihemogloblin antibody. Erythroblasts usually are strongly PAS and CD71-positive, expresses ABH blood group antigens, and reacts with antihemoglobin antibody.
Acute megakaryocytic leukemia (M7)	Small blasts with pale agranular cytoplasm and cytoplasmic blebs. May mimic lymphoblasts of medium to larger size.	1. Usually presents with pancytopenia. 2-Common phenotype in the AML of Down syndrome.	Antigens of von Willebrand factor, and glycoprotein Ib (CD42), IIb/IIIa (CD41), IIIa (CD61) on blast cells.

(Pui at al., 2004)

- ***Clinical Features:***

❖ *Signs and symptoms that signal the onset of AML include:*

1- Pallor, fatigue, weakness, palpitations, and dyspnea on exertion. These signs and symptoms reflect the development of anemia; however, weakness, loss of sense of well-being and fatigue on exertion can be out of proportion to the severity of anemia ***(Pui et al., 2004).***

2- Easy bruising, petechiae, epistaxis, gingival bleeding, conjunctival hemorrhages and prolonged bleeding from skin injuries reflect thrombocytopenia they are frequent early manifestations of the disease ***(Pui et al., 2004).***

3- Very infrequently, gastrointestinal, genitourinary, broncho-pulmonary or central nervous system (CNS) bleeding occurs at the onset of the disease ***(Greaves, 2002).***

4- Pustules or other minor pyogenic infections of the skin are most common. Major infections, such as sinusitis, pneumonia, pyelonephritis and meningitis are uncommon presenting features of the disease, partly because absolute neutrophil counts less than 500 (0.5 x 10^9/liter) are uncommon until chemotherapy starts. With intensification of neutropenia and monocytopenia after chemotherapy, major bacterial, fungal or viral infections become frequent ***(Pui et al., 2004).***

5- Anorexia and weight loss are frequent findings ***(Pui et al., 2004).***

6- Fever is present in many patients at the time of diagnosis ***(Pui et al., 2004).***

7- Palpable splenomegaly or hepatomegaly occurs in approximately one third of patients ***(Pui et al., 2004).***

8- Lymphadenopathy is extremely uncommon except in the monocytic variant of AML ***(Greaves, 2002).***

- ***Special Clinical Features:***

1- Hyperleukocytosis

Approximately 5 percent of patients with AML develop signs or symptoms attributable to a markedly elevated blood blast cell count, usually greater than 100 x 10^9/liter ***(Greaves, 2002).***

2- Hypoplastic Leukemia

Approximately 10 percent of patients with AML present with a syndrome that includes pancytopenia, often with inapparent blood blast cells, and absence of hepatic, splenic or lymph nodal enlargement ***(Greaves, 2002).***

3- Neonatal Myeloproliferation and Leukemia

Four myeloproliferative syndromes related to AML have been identified in the neonate: transient myeloproliferative disorder, transient leukemia, congenital leukemia and neonatal leukemia ***(Greaves, 2002).***

Transient myeloproliferative disease (TMD) can be present at birth or occur shortly thereafter in approximately 10 percent of infants with Down syndrome ***(Pui et al., 2004).***

- ***Investigations:***

1- Blood counts and blood smears

The hallmark of leukemia is a reduction or absence of normal hematopoietic elements.

Anemia is usually normocytic, with a reticulocyte count lower than expected for the level of the hemoglobin. The decrease in hemoglobin levels can range from minimal to profound ***(Zipf et al., 2000).***

Platelets count are usually low and generally commensurate with the degree of bleeding. Patients with spontaneous petechiae usually have platelet counts of less than 20 X 10^9/L ***(Zipf et al., 2000).***

WBCs count may be decreased or elevated. Hyperleukocytosis with WBCs count of more than 100 X 10^9/L are occasionally observed; with high numbers, the blood specimen appears white ***(Zipf et al., 2000).***

Upon careful examination of the blood smears, Auer rods (characteristic cytoplasmic inclusions) are revealed in specimens of circulating blood obtained from many patients with AML ***(Zipf et al., 2000).***

2- Blood chemistries and other blood work

Both serum uric acid and lactic dehydrogenase levels are frequently elevated as a consequence of increased cell proliferation and destruction. Other signs of tumor lysis including hyperkalemia, hypocalcemia and lactic acidosis, may be present. Blood and urine cultures should always be obtained in a child with fever and leukemia ***(Greaves, 2002).***

3- Bone marrow examination

Bone marrow aspirates and biopsy samples demonstrate the characteristic replacement of normal marrow elements with the monotonous sheets of leukemic blasts ***(Greaves, 2002).***

4- Tests of cytogenetic markers, histochemical staining, and immunophenotyping

Monoclonal antibodies specific for different cell lineages and stages of development are routinely used to further characterize the leukemic cells. The most common myeloid markers are CD13, CD14, CD15 and CD33, with more than 90% of leukemic cells demonstrating positivity to some of these antigens. CD34 is frequently found in AML blasts ***(Greaves, 2002).***

5- Lumbar puncture and CSF examination

Although the CSF is less frequently involved in AML than in ALL, leukemic infiltration can occur. CSF samples

should be obtained before any therapy is begun. Fluid should be sent for cytologic evaluation in addition to the usual cell counts and chemical tests ***(Luca and Almanaseer, 2003).***

6- Typing of human leukocyte antigen

Human leukocyte antigen (HLA) matched family donors should be identified because bone marrow (or hematopoietic stem cell) transplantation may be considered in high-risk patients ***(Luca and Almanaseer, 2003).***

7- Imaging Studies

Although radiographic studies are not helpful in confirming the diagnosis, they can be important when leukemic complications are suspected. Routine chest radiography should be performed to rule out mediastinal masses, particularly in patients with respiratory symptoms.

CT and MRI is also done for staging of the disease diagnosis of the complications ***(Luca and Almanaseer, 2003).***

8- Bone marrow aspirate and biopsy

Bone marrow examination is necessary to establish the diagnosis of AML ***(Zipf et al., 2000).***

9- Lumbar puncture

Lumbar puncture is necessary for diagnostic and therapeutic reasons. Even if the marrow is not involved at the