INTRODUCTION

Approximately 20% of childhood leukemias are of myeloid origin and they represent a spectrum of hematopoietic malignancies. The majority of myeloid leukemias are acute, and the remainder include chronic and/or subacute myeloproliferative disorders such as chronic myelogenous leukemia (CML) and juvenile myelomonocytic leukemia (JMML), as well as myelodysplastic syndromes ***(Karen, 2011).***

Acute myeloid (AML) shows 2 peaks in occurrence in early childhood and later adulthood, with an incidence of 3.7 per 100,000 persons and an age-dependent mortality of 2.7 to nearly 18 per 100,000 persons ***(Deschler and Lübbert, 2006).***

AML is a clonal disorder caused by malignant transformation of a bone marrow-derived, self-renewing stem cell or progenitor, which demonstrates a decreased rate of self-destruction as well as aberrant differentiation. These events lead to increased accumulation in the bone marrow and other organs by these malignant myeloid cells ***(Karen, 2011).***

AML shows great variability in clinical course and response to therapy, as well as in the genetic and molecular basis of the pathology. Besides these major cytogenetic

abnormalities, gene mutations also constitute key events in AML pathogenesis. Mutations affecting genes that contribute to cell proliferation (*FLT3, c-KIT, RAS, protein tyrosine standard phosphatase non receptor 11*), mutations affecting genes involved in myeloid differentiation (*AML1* and *CEBPA*), and mutations affecting genes implicated in cell cycle regulation or apoptosis (*P53, NPM1*) ***(Renneville and Roumier, 2008).***

The recent WHO 2008 classification of AML contains most, but not all, cytogenetic subgroups specific to children. Compared with previous classifications (European Group of Immunologic Characterization of Leukemias [EGIL]), the new WHO classification introduced a defined subclass of acute leukemias of ambiguous lineage (mixed phenotype acute leukemias [MPALs]), mainly on the basis of detailed immunophenotypic criteria ***(Creutzig and Van den Heuvel, 2012).***

The mainstay of the therapeutic approach in AML is systemically administered combination chemotherapy. Treatment is ordinarily divided into two phases induction (to attain remission), Postremission consolidation / intensification. Postremission therapy may consist of varying numbers of courses of intensive chemotherapy and/or allogeneic hematopoietic stem cell transplantation (HSCT) **(*Abrahamsson, 2011).***

The 5-year survival rate for children with AML has increased over time, and is now in the range of 60% to 70% ***(Creutzig, 2012).***

Compared with all other subtypes of AML, 5-year survival rate was most favorable for AML with t(15;17), AML with inv(16), and AML with t(8;21) among individuals less than 20 years of age ***(Curtis, 2012).***

Aim of the Work

The aim of this work is:

To evaluate the clinico-epidemiological and risk factors of pediatric AML, and assesse the overall survival and event free survival and their relations to different prognostic factors.

ACUTE MYELOID LEUKEMIA

Definition:

Leukemia is the most common malignancy in those under the age of 15 years, accounting for one out of three cases of childhood cancer. The two major subtypes of leukemia seen in children are acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML), which account for 80 and 17% of leukemias diagnosed, respectively ***(Metayer and Milne, 2013).***

Acute myeloid leukemia (AML) is a heterogeneous group of leukemias that arise from clonal disorder caused by malignant transformation of a bone marrow-derived, self-renewing stem cell or myeloid progenitor, which demonstrates a decreased rate of apoptosis as well as aberrant, and usually limited, differentiation capacity ***(Smith, 2014).***

The cell of origin in AML is a blast that most often show myeloid or monocytic differentiation. In approximately 5 to 10% of patients blasts have erythroid or megakaryocytic differentiation. For this reason, acute non-lymphoblastic leukemia (ANLL) has been considered a more precise term but AML is more common and recommended term ***(Cheson et al., 2003).***

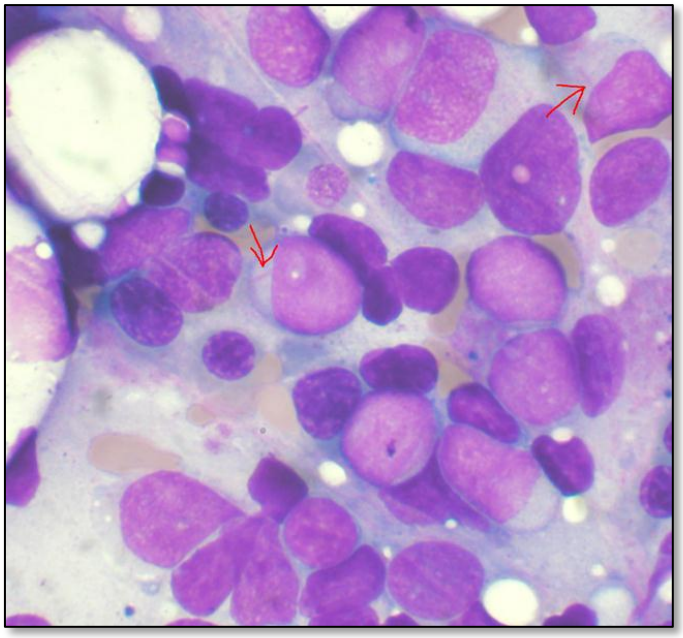

Fig. (1): Bone marrow aspirate showing acute myeloid leukemia. Arrows indicate Auer rods

Epidemiology:

Acute myeloid leukemia accounts for 15%-20% of childhood acute leukemias all over the world ***(Liesveld and Lichtman, 2006).*** And for 25%-35% among Egyptian children ***(Adel, 2015).***

AML has incidence in infants of 1.5 per 100,000 individuals per year, the incidence decreases to 0.9 per 100,000 individuals aged 1-4 and 0.4 per 100,000 individuals aged 5-9 years, after which it gradually increases into adulthood, up to an incidence of 16.2 per 100,000 individuals aged over 65 years ***(Howlader and Krapcho, 2012).***

Little difference in incidence is seen between individuals of African or European descent at any age, while a lower incidence is seen in persons of Asians descent. An increase in frequency of AML is seen in Jews, especially those of Eastern European descent ***(Liesveld and Lichtman, 2006).***

AML contributes to about 50% of all deaths of pediatric leukemia in the United States. The age-adjusted incidence rate of childhood AML in the US has been increasing at 1% per year between 1975 and 2011 and is currently estimated to be 8.5 cases per million ***(Howlader and Krapcho, 2012).***

PREDISPOSING FACTORS

The underlying cause of AML is unknown, and childhood AML generally occurs de novo ***(Seif, 2012).***

Genetic Predisposition:

Chromosomal instability:

In children, the occurrence of AML is preceded by clonal evolution of preleukemic myeloproliferative diseases, such as MDS or juvenile myelomonocytic leukemia (JMML), is rare. Germline affected individuals, such as those with Fanconi anemia or Bloom syndrome, have an increased risk for developing AML as a secondary malignancy ***(Seif, 2011; Tonnies and Huber, 2003).***

Several autosomal dominant conditions can lead to AML, including Fanconi's anemia, ataxia-telangiectasia, neurofibromatosis which results from mutations in the neurofibromin tumor suppressor gene on chromosome 17q11.2 and is associated with the development of juvenile CML, ALL, lymphomas, and a disproportionately high rate of MDS evolving into AML in young patients and Bloom's syndrome in which AML occur in about 25 percent of affected individuals ***(Cucuianu et al., 2005).*** Also Li-Fraumeni syndrome (consequence of dominantly inherited germline mutations of the p53 tumor suppressor genes), and is associated with the development of multiple types of tumors, occasionally including leukemia, Kostmann's syndrome (associated with mutations in the G-CSF receptor on chromosome 1p35-p34.3) and Diamond Blackfan anemia (congenital hypoplastic anemia) ***(Christ et al., 2007).***

Germline mutations:

Recently, germ-line mutations in several genes, such as TP53, RUNX1, GATA2 and CEBPA, have been found in families with an unexplained high risk of AML, suggesting a familial predisposition to develop AML ***(Hahn and Chong, 2011).***

Congenital immunodeficiency disorders:

Wiskott-Aldrich syndrome, an X-linked immunodeficiency syndrome is associated with the occasional development of lymphomas and AML. X-linked agammaglobulinemia and Down syndrome, have also been associated with an increased incidence of AML ***(Hunter et al., 2000).***

Children with Down syndrome classically present with a unique megakaryoblastic subtype of AML, classically following a transient myeloproliferative disorder in the neonatal period, which is characterized by somatic mutations in the GATA1 gene ***(Link and Schuettpelz, 2011).***

Environmental Risks

Significant exposure to ionizing irradiation results in a 10 to 20 fold increase in the incidence of AML. The incidence peaked between 6 to 8 years following the exposure but remained significantly higher over the next 20 years when compared to unexposed individuals ***(Hiddemann et al., 2003).***

There is no convincing evidence that prenatal or postnatal exposure to ultrasound or the effects of electrical power lines increases the risk of AML ***(Kauneet al., 2000).***

Prenatal exposures to genotoxic chemicals have been reported to result in increased risk of the development of AML in these offspring, for instance; prenatal exposure to maternal cigarette smoking, marijuana and alcohol. Excess maternal ingestion of foods and vegetables with high contents of topoisomerase II inhibitors has been reported to be associated with the development of AML in exposed offspring ***(Hiddemann et al., 2003).***

AML may occur following previous radiotherapy or chemotherapy containing alkylating agents. These are typically characterized by either MLL-rearrangements or by monosomy 7 ***(Sandler and Friedman, 1997; Weiss and Vora, 2003).***

A growing area of concern that is, in part, a result of the success of cancer treatments, involves the increased incidence of secondary leukemia following treatment of primary malignant and nonmalignant conditions. For example, treatment with alkylating agents, such as (ifosfamide, melphalan, nitrogen mustard, and cyclophosphamide) is linked to an increased incidence of MDS and AML, with a peak incidence at 4 to 5 years after initial treatment (some cases may occur 10- 12 years later). Leukemogenic effect of epipodophyllotoxins, such as etoposide (VP-16), is now well established ***(McKenzie et al., 2005).***

Acquired Predisposition

The development of MDS should also be considered a predisposing condition for AML. In this context, the acquisition of certain somatic chromosomal abnormalities, often associated with MDS, may predispose individuals to develop AML ***(Tooze et al., 1999).***

For example, the development of monosomy 7 in bone marrow precursors may be associated with an increased frequency of disorders of the myeloid lineage, including MDS and AML. The acquisition of a variety of other genetic alterations, most commonly translocations, involving genes that regulate cell growth, differentiation, and apoptosis, also plays a fundamental role in the etiology of AML ***(Crisan, 2000).***

Pathogenesis:

Acute myeloid leukemia is believed to begin in a single somatic hematopoietic progenitor that transforms to a cell incapable of normal differentiation. Many of these cells no longer possess the normal property of apoptosis resulting in a cell with prolonged life-span and unrestricted clonal proliferation. A Major cause of morbidity and mortality is the deficiency of normal functioning mature hemopoietic cells, rather than the presence of numerous malignant cells ***(Zhou et al, 2000; Estey and Döhner, 2006)***.

Genetic Factors:

AML is thought to arise from at least two classes of cooperating genetic events ***(Kelly and Gilliland, 2002).***

Type I abnormalities result in increased, uncontrolled proliferation and/or survival of the leukemic cell and are often activating mutations of genes involved in signal transduction pathways, such as *FLT3*, *KIT*, *N-RAS*, *K-RAS* and *PTPN11****(Ahmed and Sternberg, 2004; Hollink, 2011).***

Type II abnormalities impair differentiation and mainly result from genetic aberrations in hematopoietic transcription factors, due to, the AML-characteristic translocations t(8;21) (q22;q22) /*AML1-ETO* and 11q23 / *MLL* rearrangements or from mutations in genes, such as *NPM1* and *CEBPA* ***(Hollink, 2009; Balgobind, 2011).***

The most common cytogenetic abnormalities in children are t(8;21)(q22;q22), inv(16)(p13.1q22) (together referred to as core binding factor (CBF)-AML), t(15;17) (q22;q21) and 11q23/ *MLL*-rearranged abnormalities ***(Grimwade, 2001; Betts and Ammann, 2007).***

Some translocations, for example t(1;22)(p13;q13), t(7;12)(q36;p13) and t(11;12)(p15;p13), are specific for children and are rarely or never found in adults ***(Hollink, 2011; Von Bergh, 2006).***

The somatic mutation results from a chromosomal translocation in nearly 80% of patients. The translocation results in rearrangement of a critical region of a proto-oncogene. The fusion of portions of two genes usually doesn't prevent the process of transcription and thus the fusion gene encodes a fusion protein that, because of its abnormal structure, disrupts a normal cell pathway and leads to malignant transformation of the cell. This protein product is often a transcription factor that disrupts the regulatory sequences that control differentiation, growth rate or survival of blood cell progenitors ***(Kelly and Gilliland, 2002).***

These primary mutations are not sufficient to cause AML. Addition activating mutations, for example, in hematopoietic tyrosine FLT3 and KIT or N-Ras and K-Ras are required to induce a proliferative advantage in the affected primitive cell. Other mutations occur in leukemic cells involving, myeloproliferative leukemia virus oncogene (MPL), Retinoblastoma (Rb), Wilm's tumor gene (WT1) and P53 ***(Liesveld and Lichtman, 2006).***

Hematopoietic growth factors and cytokines:

Leukemic cells exhibit a proliferative response to many of the endogenous hematopoietic growth factors critical for normal hematopoiesis such as G-CSF, GM-CSF, M-CSF, SCF, IL-3 1L-4, IL-5,IL-6, IL-7, FLT3 and KIT

ligand which are mediated through specific growth factor receptors that are frequently expressed on the surface of AML cells ***(Rosenfeld and List, 2001).***

It appears that a combination of these factors can produce a synergistic growth response. In particular, stem cell factor can enhance by some of 10-20 folds the proliferation of leukemic blasts induced by G-CSF, GM-CSF and IL-3 ***(Giles et al., 2002)***.

Activation of surface membrane receptors leading to the proliferation of ANLL cells may occur in multiple ways:

A. Over expression of growth factors receptors and their interactionwith normal endogenous hematopoietic growth factors:

The interaction with specific hematopoietic growth factors with their corresponding receptors presumably triggers a cascade of molecular events that leads to the stimulation of cells division ***(Rosenfeld and List, 2001)***.

Hepatocyte growth factor is a pleiotropic cytokine involved in hepatocyte morphogenesis is secreted by stromal cells**.** In conjunction with other growth factors (GM-CSF, IL-3), it can augment the growth of committed progenitors through interaction with its receptors found on CD34+ cells ***(Matsuda-Hashii et al., 2004)***.

B. Interaction with autocrine growth factors:

Autonomous growth has been reported to occur as a result of autocrine or paracrine stimulation of a number of these hematopoietic growth factors. The acquisition of autonomous growth capability allows AML cells to be more aggressive by making them independent of stromal cell production of essential growth factors ***(Ward, 2007)***.

There is evidence that secretion of IL-1 can stimulate the release of G-CSF, GM-CSF from endothelial cells which in turn may affect the proliferation of leukemic blasts (autocrine growth factor) ***(Giles et al.,2002)***.

C. Activation of mutation within the receptors themselves:

Disruption of normal hematopoietic growth factors signal transduction pathways and mutations in hematopoietic growth factors receptor genes that interfere with normal receptor complex formation may lead to their activation in absence of specific ligands. Mutation the G-CSF, FLT3 and c-KIT receptor genes have been described in AML ***(Lowenberg and Burnett, 2005)***.

Adhesion molecules:

Primitive HSCs express a wide range of cell adhesion molecules, which include members of the integrin, selectin and immunoglobulin families ***(Wang et al., 2007).***