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بالرسالة صفحات لم ترد بالاصل

EFFECT OF CIS-RETINOIC ACID ON BCL-2 AND SOME MITOCHONDRIAL ENZYMES IN PATIENTS WITH ACUTE MYELOID LEUKEMIA

Thesis

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Contents

List of Abbreviations

AIDS	Aquired immunodificiency syndrome
AIF	Apoptosis inducing factor
AL	Acute leukemia
ALL	Acute lymphocytic leukemia
AML	Acute myeloid leukemia
ANOVA	Analysis of variance
APL	Acute promyelocytic leukemia
ATRA	All trans retinoic acid
ATP	Adenosine triphosphatase
BCL-2	B Cell lymphoma leukemia 2
BM	Bone marrow
CD	Cluster of differentiation
CR	Complete remission
CRA	Cis –retinoic acid
Cyt o. C.O	Cytochrome C Oxidase
CNS	Central nervous systeme
DNA	Deoxyribonucleic acid
EDTA	Ethylene diamine tetra-acetic acid
ER	Endoplasmic reiculum
FAB	French-American-Britich
Igs	Immunoglobulins
Hb	Haemoglobin.
IF	Immunoflluorscence
INF	Interferon
KCL	Potasium chloride
KD	Kelo dalton
MDS	Myelodysplastic Syndrome
MFI	Mean fluorescence index
NS	Insignificant
PBS	Phosphate buffer saline
PCD	Programed cell death
PT	Permeability transision
RA	Retinoic acid
RBCs	Red blood cells
RARs	Retinoic acid receptors
RAS	Retinoic acid syndrome
RNA	Ribonucliec acid
ROS	Reactive oxygen species
RXRs	Retinoid x receptors
SPSS	Statistical package for social science
TdT	Terminal deoxynucleotidyl transferase
VDAC	Voltage-dependent anion channel
WBCs	White blood cells count
Apaf-1	Apoptosis-activating factor 1

INTRODUCTION

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1. Acute myeloid leukemia

Acute myeloid leukemia (AML) is a malignant disease of the bone marrow in which hematopoietic precursors are in an early stage of development.[1] It is also called acute nonlymphocytic leukemia, acute myeloblastic leukemia or acute granulocytic leukemia.[2]

AML is characterized by progressive accumulation of relatively immature, poorly functioning myeloid blasts in the bone marrow, and peripheral blood. It eventually leads to inhibition of the production and differentiation of cells within the normal hematopoietic compartments.[3]

This developmental arrest results in Two disease processes. First, a marked decrease in the production of normal blood cells occurs, resulting in varying degrees of anemia, thrombocytopenia and neutropenia. Second, the rapid proliferation of these cells, along with a reduction in their ability to undergo programmed cell death (apoptosis), results in their accumulation in various organs most commonly the spleen and liver.[4]

1.1. Incidence of acute leukemia

The acute leukemias account for approximately 10% of all human cancer. The yearly incidence in the United States is 3.5%/100,000.[5]

The incidence of acute leukemia in Egypt accounts for 54% of all leukemia.[6]

The acute myeloid leukemia accounts for 12% of cases of leukemia in children under age of ten years, 28% between ages of 10 to 15 years. In adults it accounts for 80 to 90% of cases of acute leukemia, particularly as chronic myeloproliferative disorders and preleukemic conditions such as myelodysplasia usually progress to AML rather than ALL. The incidence increases with age and the median age is at 60 years.[7]

AML is more common in men than in women. The difference is even more apparent in older patients. This is likely due to the fact that myelodysplastic syndromes (MDS) are more common in men, and advanced MDS frequently evolves into AML.[8]

1.2. Pathogenesis of AML

The pathogenesis of AML is uncertain, but involves chromosomal abnormalities in most patients which include t(7;20) translocation.[9] and t(3;6) translocation.[10]

Also environmental, occupational and genetic factors play a role in the pathogenesis of AML.[11] High dose radiation exposure, chronic benzene exposure and alkylating agents, are the only three well documented environmental factors.[12] The leukemogenic risk was five to six times higher in workers exposed to benzene than in general population and the average latency was 11.4 years.[13]

Also there is increased incidence of leukemia in workers involved in organic synthesis and paint manufacturing.[14] Smoking is also associated with leukemia, AML is two to three times higher in male smokers .[15]

There is also increased risk of leukemia associated with isolated events in which large amounts of radiation have been released to the atmosphere.[16] Alkylating agents cause point mutations, which result in activation of oncogenes such as retinoic acid (RA), as well as chromosomal deletions and unbalanced translocations involving chromosomes 5 and 7.[17]

Maternal alcohol consumption during pregnancy has also been associated with an increased risk of AML particularly in young children.[18]

AML may develop from progression of other clonal disorders of hemopoietic stem cells, including chronic myelogenous leukemia, polycythemia vera, idiopathic myelofibrosis, primary thrombocytopenia and the pre-leukemic syndromes, to a more malignant state. Although this can occur spontaneously in each disorder, the frequency of clonal progression to AML is enhanced by radiation or chemotherapy, especially in polycythemia vera.[19]

Patients who develop AML may have an incident predisposing disease, either acquired as AIDS,[20] or inherited conditions characterized by chromosomal abnormality or instability such as Down syndrome, Fanconi anemia or Bloom's syndrome.[21]

Also AML is accompanied by further genetic change.[22] Perhaps involving one or more oncogenes or antioncogenes, often reflected in

chromosomal abnormalities. Mutation of the retinoic acid syndrome (RAS) gene is the most commonly detected abnormality in AML.[23]

1.3. Symptoms and signs

The early signs of AML can look very much like the flue or other common illness .Manifestations of anemia as pailor, fatigue, weakness, palpitations and dyspnea on exertion usually signal the onset of AML.[24] Manifestations of thrombocytopenia are easy bruising, epistaxis, gingival bleeding, and prolonged bleeding from skin injuries. Other constitutional symptoms as fever, anorexia and weight loss are frequent.[25] Organomegaly of liver and spleen occur in about 30% of cases,[25] while lymphadenopathy is extremely rare except in monocytic variant of AML.[26]

1.4. Classification

Acute myeloid leukemia (AML) is classified morphologically according to the French-American-British (FAB) criteria by the degree of is it only morphologic and histochemical differentiation along different cell lines and the extent of cell maturation.[27]

Myeloblastic leukemia with no differentiation is (M0).They lack definite myeloid differentiation by conventional morphologic or cytochemical analysis. Myeloid differentiation must be demonstrated by immunophenotyping, with reactivity to at least one lineage-specific myeloid antigen, such as CD33 or CD34, or by ultrastructural evidence of peroxidase-positive granules.[28]