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ABSTRACT

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Physiological and Molecular Studies on Apoptosis in Leukemia

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Keywords: Cancer, Leukemia, Acute Leukemia, Acute Myeloid Leukemia, Acute Lymphoblastic Leukemia, Leukemia Immunophenotyping, Chemotherapy, Apoptosis, DNA Damage.

Cancer is a term used for diseases in which abnormal cells divide without control and are able to invade other tissues. Leukemia is cancer of the blood characterized by the production of irregular white blood cells in the bone marrow. Immature leukemic stem cells also have rapidly proliferating cell cycles and usually a resistance to apoptosis. Acute leukemias are generally aggressive diseases in which cancerous

transformation occurs at early stages in the development of the affected blood cell. If untreated, these diseases can be rapidly fatal. The goal of this project was to study the anti-tumor effect of chemotherapy drugs Cytarabine (Ara-C) plus to Daunorubicin and vincristine plus to dexamethasone as inhibitors of leukemic cells expressing the oncogene, which causes AL. The drugs were also tested *in vivo* establishing their toxicity in AL patients that induced apoptosis, and determining their efficacy in a leukemia. The acute leukemia treatment strategies with chemotherapy drugs (D4 and D14). However, our research shows that two important factors in decreasing the toxicity and increasing the efficacy of AL treatment (apoptosis) are the amount of the concentration of drug dose. These therapeutic techniques may be used to expand our treatment options for AL. AML cases show no response to the treatment, while; ALL show a good response and easily recovered.

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AIM OF THE WORK

This work aims to study apoptosis physiologically and molecularly in acute leukemia. Leukemia disease is dangerous and can lead to death.

The treatment strategy aims to destroy cancer cells by activating their apoptotic signaling pathways, ideally to induce selective apoptosis cell death on cancer cells, and exert no harmful effects on normal cells.

Apoptosis form of cell death is chosen to eliminate cancer cells instead of other alternative mechanism because it is a series of regulated cell events that perform cellular suicide without triggering inflammatory response, and neither harmful to neighboring cells.

Most importantly, apoptotic form of cell death is occasionally altered in cancer cells. The understanding of apoptosis unfolds a gate to tumor specific apoptosis therapy.

LIST OF ABBREVIATIONS

11q23	Chromosome Rearrangement
AKt/PKB	Serine/Threonine-Specific Protein Kinase/ Protein Kinase B
AL	Acute Leukemia
AIEOP	Associazione Italiana di Ematologia e Oncologia Pediatrica
ALL	Acute Lymphoblastic or Lymphoid Leukemia
ALL-L2	Acute Lymphoblastic or Lymphoid Leukemia-Lymphocitic2
AML	Acute Myeloid or Myelogenous Leukemia
AMLL	Acute Mixed-Lineage Leukemias
AML-M0	Acute Myeloid or Myelogenous Leukemia-Myeloid

AML-M1	Acute Myeloid or Myelogenous Leukemia-Myeloid1
AML-M2	Acute Myeloid or Myelogenous Leukemia-Myeloid 2
AML-M3	Acute Myeloid or Myelogenous Leukemia-Myeloid 3
AML-M4	Acute Myeloid or Myelogenous Leukemia-Myeloid 4
AML-M5	Acute Myeloid or Myelogenous Leukemia-Myeloid 5
AML-M6	Acute Myeloid or Myelogenous Leukemia-Myeloid 6
AML-M7	Acute Myeloid or Myelogenous Leukemia-Myeloid 7
ANLL	Acute Non Lymphoblastic Leukemia
APL	Acute Promyelocytic Leukemia
ATP	Adenosine Triphosphate

ATM	ataxia Teleangectasia-mutated
ATRA	All Trans-Retinoic Acid
BI	Vpreb Proteins - is a B Cell-Specific Maturation Marker (Pro-B)
BII	Vpreb Proteins - is a B Cell-Specific Maturation Marker (Pre-B)
BIII	Vpreb Proteins - is a B Cell-Specific Maturation Marker (Cortical-B)
B12	Monoclonal Antibody -Based Immunofluoroassay That Detects Both Monomers And Tetramers of Alpha- And Beta-Tryptases
B-ALL	B- Acute Lymphoblastic or Lymphoid Leukemia
BASO	Basophils
Bcl-2	B-Cell Lymphoma 2 Protein Regulate Cell Death

BM	Bone Marrow
BMT	Bone Marrow Transplantation
bp	Base Per
BSA	Body Surface Area
CBF	Core Binding Factor
cCD79a	Cytoplasmic Cluster Of Differentiation 79a
CD4+	Cluster Of Differentiation 4+
CD10	Cluster Of Differentiation 10 ALL
CD13	Cluster Of Differentiation 13 AML
CD14	Cluster Of Differentiation 14 AML
CD15	Cluster Of Differentiation 15 AML
CD19	Cluster Of Differentiation 19 ALL
CD20	Cluster Of Differentiation 20 ALL

CD22	Cluster Of Differentiation 22 ALL
CD33	Cluster Of Differentiation 33 AML
CD34+	Cluster Of Differentiation 34+
CD36	Cluster Of Differentiation 36 AML
CD38	Cluster Of Differentiation 38 AML
CD41	Cluster Of Differentiation 41 AML
CD42	Cluster Of Differentiation 42 AML
CD61	Cluster Of Differentiation 61 AML
CD117	Cluster Of Differentiation 117 AML
cIg	Cytoplasmic Immunoglobulin
Cm	Centimeters
Cmm	Cubic Milliliter = Microliter
c-Myc	Myc is a regulator gene that codes for a transcription factor

CNS	Central Nervous System
CR	Complete Remission
CRD	Completely Randomized Design
CVAD	Cytoxan, Vincristine, Adriamycin and Dexamethasone Chemotherapy Complex
DC	Direct Current
DDR	DNA Damage Response
DFS	Disease-Free Survival
DNA	Deoxyribonucleic Acid
DNase	Deoxyribonuclease
DNMT	DNA methyltransferase inhibitor
DMs	Dichroic Mirrors
EDTA	Ethylendiamine Tetra Acetic Acid
EMF	Electromagnetic Fields

EMR	Electromagnetic Radiation
FAB	French-American-British Classification
FACS	Fluorescence Activated Cell Sorting
FACScan	Fluorescence Activated Cell Scan
FLT-3	Fms-like tyrosine kinase 3
FLT3-ITD	Fms- Related Tyrosine Kinase 3 Gene-Internal Tandem Doplications
FSC	Forward Scatter
gpIIIa	Glycoprotein IIIa
gpIIb/IIIa	Glycoprotein IIb/IIIa
gp IX/Ib	Glycoprotein IX/Ib
HCT	Hematocrit
HGB	Hemoglobin
HLA-B27	Human Leukocyte Antigen-Subtypes B 27

HLA-DR	Human Leukocyte Antigen Complex With Its Ligand
HLS	Hematopoietic Lymphoid System
Ht	Height
HTLV	Human T Cell Leukemia Virus
Ig	Immunoglobulin
IgM	Immunoglobulin M
IMT	Immune-Mediated Thrombocytopenia
Int-DAC	Intermediate-Dose Cytarabine
ITDs	Internal Tandem Duplications
Kg	Kilogram
LCD Screen	Liquid-Crystal Display Screen
LDH	Lactate Dehydrogenase
M^2	Cubic Meters