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Acute leukemia in children with Down syndrome

An Essay

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By

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"قالوا سبحانك لا علم لنا إلا ما علمتنا إنك أنت العليم الحكيم"

صدق الله العظيم

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List of Abbreviations

ABC	**ATP-binding cassette**
AdoHyc	**S-adenosylhomocysteine**
AdoMet	**S-adenosylmethionine**
AICAR	**aminoimidazolecarboxamide ribonucleotide**
AIEOP	**Italian Association of Pediatric Hematology and Oncology**
ALL	**Acute lymphocytic leukemia**
ALL-NDS	**Acute lymphoblastic leukemia in children without Down syndrome**
AMKL	**Acute megakaryoblastic leukemia**
AML	**Acute myeloid leukemia**
AML1-ETO	**Acute myeloid leukemia1_Eight twenty one**
AML-DS	**Acute myeloid leukemia in children with Down syndrome**
AML-NDS	**Acute myeloid leukemia in children without Down syndrome**
Ara C	**Cytarabine**
ASD	**Atrial septal defect**
AUC	**Area under the curve**
BACH1	**Basic leucine zipper transcription factor 1**
BCP	**B-cell precursor**
BCR/ABL1	**Breakpoint cluster region/ Abelson murine leukemia viral oncogene homolog1**
BMT	**Bone marrow transplantation**
BSA	**Body surface area**
C-ABL	**Cellular Abelson tyrosine kinase**
c-kit	**Tyrosine-protein kinase Kit**
C-MYC	**Myelocytomatosis viral oncogene homolog**
Ca(2+)	**Calcium**

CBC	**Complete blood count**
CBR	**Carbonyl reductase**
CBS	**Cystathionine synthase**
CCG	**Children cancer group**
CCR	**Continuous complete remission**
CD	**Cluster of differentiation**
CHD	**congenital heart diseases**
CNS	**Central nervous system**
COG	**Children Oncology Group**
CR	**Complete remission**
CRLF2	**Cytokine receptor-like factor 2**
CTC	**Common Toxicity Criteria**
DCOG	**Dutch children oncology group**
DFS	**Disease-free survival**
DIC	**Disseminated intravascular coagulopathy**
DHFR	**Dihydrofolate reductase**
DNA	**Deoxyribonucleic acid**
DS	**Down syndrome**
DSCR1	**Down syndrome critical region 1**
DSCR2	**Down syndrome critical region 2**
dUMP	**Deoxyuridine-5-monophosphate**
DYRK1A	**Tyrosine-phosphorylation-regulated kinase 1A**
EFS	**Event-free survival**
ERG	**Ets related gene**
Ets	**E twenty-six**
FAB	**French-American-British**
FAICAR	**Formyl-aminoimidazolecarboxamide ribonucleotide**

FISH	**Fluorescent in situ hybridization**
FLT3	**Fms-like tyrosine kinase-3**
FPGS	**Folylpolyglutamyl synthetase**
GATA1	**Globin transcription factor 1**
GGH	**Glutamyl hydrolase**
GvHD	**Graft versus host disease**
Gy	**Gray**
HD-Ac	**High dose cytarabine**
HD-MTX	**High dose Methotrexate**
HHD	**Hyperdiploidy**
Hsa21	**Homo sapiens 21**
HSC	**Hemopoietic stem cells**
iBFM	**International Berlin-Frankfurt-Münster**
ID	**Intellectual disability**
IgH	**Immunoglobulin heavy locus**
inv	**Inversion**
JAK	**Janus kinase**
LTS	**Life-threatening symptoms**
MDS	**Myelodysplastic syndrome**
MEP	**Megakaryocyte-erythroid progenitors**
MIR	**MicroRNA**
ML	**Myeloid leukemia**
MLL	**Mixed lineage leukemia gene**
mmol	**Millimolar**
MNNG	**N methyl- N-nitro-N-nitrosoguanidyne**
MPD	**Myeloproliferative disorders**
MR	**Mental retardation**

MRC	**Medical Research Council**
MRD	**Minimal residual disease**
mRNA	**Messenger ribonucleic acid**
MTHFD1	**Methylene tetrahydrofolate dehydrogenase**
MTHFR	**Methylene Tetrahydrofolate Reductase**
MTR	**Methionine synthetase**
MTRR	**Methionine synthase reductase**
MTX	**Methotrexate**
MTXPG	**Methotrexate polyglutamates**
NCI	**National Cancer Institute**
NFATc1	**Nuclear factor of activated T-cells, cytoplasmic 1**
NOPHO	**The Nordic Society of Pediatric Hematology**
OS	**Overall survival**
PAC	**Proteasome Assembling Chaperone**
PDNS	**Purine de novo synthesis**
Ph+	**Philadelphia chromosome positive**
PK	**Pharmacokinetics**
PML/RARA	**Promyelocytic leukemia / retinoic acid receptor alpha**
POG	**Pediatric Oncology Group**
PPHN	**Persistent pulmonary hypertension of the neonate**
PR	**Partial Remission**
RBM15/MKL1	**RNA-binding motif protein-15/ megakaryocytic leukemia-1**
RCAN1	**Regulator of Calcineurin A**
RFC	**Reduced folate carrier**

RFS	**Relapse-free survival**
RIC	**Reduced intensity conditioning**
RNA	**Ribonucleic acid**
SCT	**Stem cell transplantation**
SHMT	**Serine hydroxymethyltransferase**
SLC19A1	**Solute carrier family 19**
SOD	**Superoxide dismutase**
SR-ALL	**Standard risk acute lymphoblastic leukemia**
STAT	**Signal Transducers and Activators of Transcription**
T21	**Trisomy 21**
TAM	**Transient abnormal myelopoiesis**
TBI	**Total body irradiation**
TCR	**T cell receptor**
TCR3-Pbx1	**Transcription factor 3/pre-B-cell leukemia homeobox 1**
TEL/AML1	**Ets leukemia/acute myeloid leukemia 1**
TL	**Transient leukemia**
TMD	**Transient myeloproliferative disease**
TS	**Thymidylate synthase**
TSLP	**Thymic stromal lymphopoietin**
UKALL	**Medical Research Council of the United Kingdom Acute Lymphoblastic Leukemia**
VSD	**Ventricular septal defect**
WBC	**White blood cell**
WHO	**World Health Organization**

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Introduction

Down Syndrome (DS) is the consequence of trisomy of human chromosome 21 (Hsa21) and is the most common genetic form of intellectual disability, occurring in approximately 1 in 700 live births **(Gardiner, 2010)**. Many risk factors are suggested to cause DS. The only well established risk factor is advanced maternal age and so age –specific rates have been documented. Other factors include higher socioeconomic status, which is due in part to maternal age, advanced paternal age (more than 49 years) and birth order **(Hecht and Hook, 1996)**.

Children with Down syndrome (DS) have an elevated risk of developing acute leukemia 10–20 times higher than the general population **(Ross, 2005).** Children with DS have an increased risk of developing both acute myeloid leukemia (AML), as well as acute lymphoblastic leukemia (ALL) **(Whitlock et al., 2005)**. The relative risks of ALL/AML and acute megakaryoblastic leukemia (AMKL) in DS patients have been estimated to be approximately 20 and 400 to 500, respectively **(Hasle et a.l, 2000)**. It is important to note that DS is not a classic genomic instability syndrome as the overall risk of developing cancer, in particular solid tumors, is lower in these people **(Hasle, 2001)**.

DS-ALL patients differ in presenting characteristics from ALL patients without DS (non-DS-ALL). For instance, a lower frequency of T-cell ALL **(Zeller et al., 2005)** and CD10-negative ALL (pro-B-cell ALL) is found in DS-ALL **(Dordelmann et al., 1998)**. Moreover, there are differences in the distribution of genetic abnormalities, with lower frequencies of unfavorable characteristics such as MLL-AF4 and the Philadelphia-chromosome, as well as lower frequencies of favorable characteristics such as high hyperdiploidy and TEL-AML1 in DS-ALL cases **(Forestier et al., 2008)**.

Both DS-AMKL and the transient myeloproliferative disorder (TMD) that often precedes it are consistently associated with acquired mutations in the erythroid transcription factor (GATA1) gene **(Wechsler et al., 2002)**. These mutations arise in utero and are responsible for the congenital transient leukemia present in up to 10% of DS newborns **(Rainis et al., 2003)**.

One of the key agents used in the treatment of ALL is methotrexate. It is well known that Down syndrome patients are more susceptible to methotrexate-induced side-effects than non Down syndrome patients **(Taub and Ge, 2005)**. Plausible explanation for the observed methotrexate toxicity in DS patients could be a gene dosage effect for enzymes found on chromosome 21 **(Zwaan et al., 2008)**.

The key drugs for the treatment of AML-DS are anthracyclines, cytarabine, and etoposide; it was also confirmed by in vitro studies that AMKL-DS blasts were significantly more sensitive to these drugs than non-DSAMLcells **(Zwaan et al., 2002)**. AMKL-DS blasts are especially sensitive to cytarabine, possibly to the effect of the GATA1 mutations and trisomy 21 on the levels of cytarabine-metabolizing enzymes **(Ge et al., 2005).**

With the advent of risk-adapted treatment protocols, children with acute lymphoblastic leukemia have a very good prognosis. However, among patients with standard risk ALL (SR-ALL), those with DS (ALL-DS) have been shown to have a worse prognosis than children without DS (ALL-NDS) despite similar treatment **(Levitt et al., 1990 and Chessells et al., 2001)**. Recently, it is recommended that DS-ALL should be treated without dose reduction of chemotherapy, if possible. The dose of MTX is the exception, and 3 g/m2 seemed to be an overdose in DS-ALL patients **(Maloney et al., 2010)**.

Before the 1990s, most patients with DS-AML were treated outside of clinical studies and received suboptimal therapies, resulting in poor outcomes **(Levitt et al., 1990).** Following the recognition of the favorable outcome when treated with protocols of the collaborative study group for AML **(Ravindranath et al., 1992),** there has been an increase in recruitment into protocol studies. It has become apparent that resistant disease is rare but treatment-related deaths are frequent in most series **(Creutzig et al., 1996 and Lange et al., 1998),** and several collaborative groups adapted their AML protocols for DS-AML by reducing the dose of chemotherapeutic agents **(Creutzig et al., 2005 and Zeller et al., 2005)**

Transient myeloproliferative disorder (TMD), or transient leukemia (TL), is a form of self-limited leukemia that occurs almost exclusively in neonates with Down syndrome (DS). The first case was reported by Schunk and Lehman in 1954 **(Schunk and Lehman, 1954)**. Most neonates with TMD do not need chemotherapy as the clinical and laboratory abnormalities spontaneously resolve within 3–6 months after birth. The treatment for DS patients with TMD is generally supportive. Children with TMD can die as a result of hydrops fetalis, organ infiltration, renal failure, hepatic failure, respiratory failure, DIC (disseminated intravascular coagulation), and progression to AML or ALL. It is generally estimated that TMD has a mortality rate of 10% to 20%. **(Hayashi et al., 1988 and Zipursky et al., 1996)**.