Acute Myeloid Leukemia in Down Syndrome

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Simultaneous Occurrence of Mongolism and Leukemia

Report of a Nationwide Survey

WILLIAM KRIVIT, M.D., and ROBERT A. GOOD, Ph.D., M.D., Minneapolis

New Orleans Medical and Surgical Journal

Vol. 82
JUNE, 1950
No. 12

CASE REPORTS AND CLINICAL SUGGESTIONS

ACUTE LYMPHATIC LEUKEMIA: REPORT OF CASE IN ELEVENTH MONTH MONGOLIAN IDIOT.

HYDER P. BRYANT, M.D., and HERBAN E. CANNON, M.D.

NEW ORLEANS

In 1938, von Friedrich first described a case of acute leukemia. In 1939, E. Frankel described the pathologic changes of the blood in such cases and stated that acute leukemias were all lymphatic in which the increase in the white cells was almost, if not entirely, in the lymphocytes. Following this lead, many contributions to the literature on acute leukemia appeared. As late as 1934 nearly all cases were diagnosed as acute lymphatic leukemia and, in fact, nearly all writers denied the existence of acute myelogenous leukemia. However, more recently, careful studies without, but especially with, special differential staining methods, have shown that not only is acute myelogenous leukemia, far more frequent than was formerly thought, but that actually acute lymphatic leukemia is the rarer disease.

Several factors have entered into the gradual elucidation of the problem of acute leukemias and their proper differentiation. Perhaps the greatest single factor has been the application of the oxydase staining method.

REPORT OF CASE

Our search of the literature failed to reveal the report of any other case of acute leukemia in a Mongolian idiot. This patient, a predominantly white colored male, eleven months of age, was admitted to Charity Hospital, New Orleans, December 10, 1939, with the complaint of fever, weakness, and restlessness. The baby was the sixth full term child and appeared normal to the parents until about the sixth or eighth month when inability to support her head or to sit alone against support of nurse was noted. The entire life history was uneventful except for a few colds, weakness, and the terminal illness. The child rarely cried, unless from hunger or pain. The state of weakness persisted; sitting alone or crawling were never observed. Teeth failed to appear at the proper time. Five or six days previous to admission, restlessness and fever developed; these symptoms increased as greater weakness, anorexia, and air hunger made their appearance and progressed steadily.

The five older children in the family were all well, intelligent, and making normal progress. The parents were well and rather surprisingly intelligent; the father was forty-six and the mother thirty-seven years of age.

Physically, the patient was well nourished, weighing twenty-five pounds, and the body proportions were all practically normal. Restlessness was apparent; the head being thrown back at times and attempts made at deep breathing. The Mongoloid factor was, however, readily apparent. The eyes were far apart, separated by a broad, flat nose, and the typical depressed and inward slant of the relatively narrow palpebral fissures existed. The mouth was open most of the time, and a thick heavy tongue was in evidence. The enterprising manner of the hands was increased. The limbs were of normal length and proportions, but the muscles and ligaments about the joints were extremely lax and flabby; great over-play and contortions could be easily produced about any of the joints. The fingers were of normal length but rather thick at the bases; the distal phalanges of the little fingers possessed slight inward deflections.

More minute examination revealed a normal scalp with straight, black hair, coiling rather far down on the forehead. The anterior fontanelle was 1 1/2 by 1 cm. The convolutions were extremely acute. There were no teeth, but the sockets of the gum, as well as the floor of the oral cavity, presented small, shallow, irregular ulcers. The lips were almost white in that of a white child and presented anemic and a few widely scattered punctate spots. Small glands were palpated in the neck, as well as in the axillae. The area of cardiac dullness was increased. Specific movements of swallowing were heard at all vascular areas; heart sounds were modified. Resonance and voice were heard throughout most of both lungs, but no dullness could be detected. A small subcutaneous tumor was present. The spleen was readily palpated as a moderately firm mass, about 6 by 8 cm, located rather finely movable and almost entirely below the costal margin. It extended medially to the umbilicus and downward half the distance to the symphysis pubis. The liver was smooth, firm, and extended to the umbilicus.

The blood Wassermann was negative. Urinalysis revealed a trace of albumin and a moderate number of white blood cells; barium meal and upper gastro-intestinal examination were negative; reticulocytes were normal; blood picture was normal; slight listlessness; slight leukopenia; blood urea nitrogen was normal; blood sugar was normal; a trace of albumin in the stool; blood hemoglobin was 60 per cent; bone marrow was hyperactive; no abnormal cells; no circulating parasites; blood and stool were negative for amebae; hemoglobin was 60 per cent; blood urea nitrogen was normal; blood sugar was normal; a trace of albumin in the stool; bone marrow was hyperactive; no abnormal cells; no circulating parasites; blood and stool were negative for amebae. Laboratory examination of the blood showed:

- White blood cells: 3,000
- Red blood cells: 5,000,000
- Hemoglobin: 60 per cent
Case Study

• A newborn baby has dysmorphic facial features, transverse palmar creases, systolic ejection murmur.

• A CBC reveals:
  WBC:  59,000/µl
  Hemoglobin: 17 gm/dL
  Platelets: 80,000/µl
  Peripheral smear: 50% blasts
What is the most likely diagnosis?

1. Infection
2. Leukemoid reaction
3. Infant ALL
4. Transient Myeloproliferative Disorder of DS
Transient Myeloproliferative Disorder
Transient Myeloproliferative Disorder (TMD)/Transient Abnormal Myelopoiesis

- Estimated that 5-10% of DS newborns have a precursor of acute megakaryocytic leukemia (AML-M7; AMkL), TMD, in which blasts in the peripheral blood and/or bone marrow have the same morphology and antigen expression as AMkL.
- TMD has also been diagnosed in DS mosaics and in infants with isolated trisomy 21 in blast cells with no other evidence of mosaicism.
- Majority of TMD cases can spontaneously regress with supportive care alone, though ~20-30% of patients will subsequently develop AML.
- A subset of patients present with high risk features (e.g. high WBC counts, liver dysfunction with hepatic fibrosis) which are associated with high mortality rates. These patients may benefit from early chemotherapy intervention with low dose cytarabine (ara-C).
Case Study

• A 14 month old male baby with Down syndrome has a past history of TMD [maximum WBC 45,000/µL) which resolved with supportive care alone without the use of chemotherapy treatment.

• Ongoing monitoring of the baby’s CBC revealed a slow decrease in the platelet count though he remained clinically asymptomatic. Mild hepatomegaly was present on exam as well as a heart murmur. A CBC revealed:
  WBC: 18,000/µl
  Hemoglobin: 10.2 gm/dL; MCV: 83 fl
  Platelets: 33,000/µl
  Approximately 5-10% atypical blast-like cells on the peripheral smear.
Acute Megakaryocytic Leukemia-AMKL M7
Myeloid Leukemia of Down Syndrome (ML-DS)

- 2008 WHO classification of ML-DS encompasses the group of both MDS patients (blasts <30%) as well as AML patients who predominantly have the AMKL phenotype.
- Approximately 95% of ML-DS cases diagnosed before the age of 4 years.
- Median age of diagnosis 1.8 years vs 7.5 years for non-DS AML (Children’s Cancer Group 2891 study). [Gamis et al., J Clin Oncol 2003]
- Down syndrome represent ~15% of total pediatric AML patients. [Nordic Society of Pediatric Hematology and Oncology Zeller et al. Br J Haemat 2005; CCG 2891]
Down Syndrome and AML

- For AML, most cases in DS children occur under the age of 4 years and a high proportion (>75%) are the acute megakaryocytic leukemia phenotype (M7; AMkL) while AMkL represents ~5-10% of AML cases in non-DS children.
- Estimated that DS children have a 500-fold increased risk of developing AMkL compared to non-DS children. [Zipursky et al., Leukemia Research 1994]
Characterization of Blast Cells

- Immunophenotype: CD41/61 (platelet antigens glycoprotein IIb/IIIa), CD7 (aberrant T-cell antigen expression), CD36 (thrombospondin receptor).

- Common cytogenetics abnormalities include trisomies +8, +21, +11 and structural abnormalities dup(1q), del(6q), del(7p), dup(7q), del(16q). [Forestier et al., Blood 2008]

- Classic cytogenetic abnormalities detected in pediatric AML cases are extremely rare in DS-AML including t(8;21), inv(16), t(15;17), MLL (11q23) rearrangements or t(1;22) seen in non-DS AMKL cases.
• The intensity of AML chemotherapy is adjusted according to the risk of relapse (risk stratification) for all children including those with DS.

True or false?
AAML0431 PROTOCOL

Recommended criteria for proceeding to each cycle of therapy: ANC ≥ 1,000/µL and platelets ≥ 100,000/µL.

Cumulative Doses for Induction I and II:
AraC: 24,800 mg/m² 
Daunorubicin 160 mg/m²
Prognostic value of MRD in DS-AML

AAML0431

DFS

OS

Taub, Berman, Hitzler et al., ASH 2014
Challenges in Treating Children with Down Syndrome and Leukemia
<table>
<thead>
<tr>
<th>Cycle</th>
<th>Median number of days on cycle (range)</th>
<th>Time to ANC recovery (median, days)</th>
<th>ICU admission (% of patients)</th>
<th>Febrile neutropenia Grade ≥3 (% patients)</th>
<th>Sterile site bacterial infection Grade &gt; 3 (% patients)</th>
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<tbody>
<tr>
<td>Induction I</td>
<td>34 (15-66)</td>
<td>30</td>
<td>7</td>
<td>27</td>
<td>19.2</td>
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<tr>
<td>TAD</td>
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<tr>
<td>Induction II</td>
<td>42 (27-69)</td>
<td>37</td>
<td>7</td>
<td>29.7</td>
<td>22.6</td>
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<tr>
<td>HD Ara-C</td>
<td></td>
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<tr>
<td>Induction III</td>
<td>32 (20-59)</td>
<td>28</td>
<td>2</td>
<td>6.2</td>
<td>11.3</td>
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<td>TAD</td>
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</tr>
<tr>
<td>Induction IV</td>
<td>34 (22-63)</td>
<td>28</td>
<td>2</td>
<td>5.6</td>
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<td>TAD</td>
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</tr>
<tr>
<td>Intensification I</td>
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<td>Ara-C/Etoposide</td>
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<td>35 (22-124)</td>
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<td>1</td>
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<td>Ara-C/Etoposide</td>
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</tbody>
</table>
Study Design
AAML1531

Down syndrome
< 4 years of age at diagnosis

BMA at diagnosis

Induction I (all patients)
TAD + IT Ara-C

MRD Risk Group Assessment
BMA

High Risk
(Arm B)
MRD >0.05%

Induction II
Mitoxantrone/Ara-C

BMA and MRD

Intensification I
HR Ara-C/Etoposide

Intensification II
Capizzi II

Follow up

Standard Risk
(Arm A)
MRD <0.05%

Induction II TAD

Induction III - TAD

Intensification I
Ara-C/Etoposide

Intensification II
Ara-C/Etoposide

Follow up

BMA, bone marrow Aapirate; MRD, minimal residual disease

Induction I (all patients)
AD: continuos infusion ytarabine; short infusion Daunorubicin; oral 6-Thioguanine; intrathecal Cytarabine

STANDARD ARM (Arm A)
Induction II and III ; TAD, continuos infusion Cytarabine (Ara-C) ; short infusion Daunorubicin; oral 6-Thioguanine
Intensifications I and II : Cytarabine (Ara-C)/Etoposide

HIGH RISK ARM (Arm B)
Induction II: Mitoxantrone/ Cytarabine (Ara-C)
Intensification I: High dose Cytarabine (Ara-C)/Etoposide
Intensification II: Capizzi II, High Dose Cytarabine (Ara-C)/L-Asparaginase
Why does DS-AML have very high cure rates?

1. Due to a gene(s) on chromosome 21
2. Extraordinary adherence to chemotherapy
3. Very low toxicity
4. Due to a gene not located on chr. 21
## Ex Vivo Chemotherapy Sensitivity of DS-AML Blasts

<table>
<thead>
<tr>
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<th>Down Syndrome AMKL (n=22)</th>
<th>Non-Down Syndrome AML (n=362)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ara-C IC&lt;sub&gt;50&lt;/sub&gt; (nM)</td>
<td>77.5</td>
<td>350.9</td>
</tr>
<tr>
<td>Daunorubicin IC&lt;sub&gt;50&lt;/sub&gt; (nM)</td>
<td>5.8</td>
<td>71.2</td>
</tr>
<tr>
<td>Ara-CTP (pmol/mg prot) (n=11)</td>
<td>737.3</td>
<td>166.9 (n=20)</td>
</tr>
</tbody>
</table>
Identification of Somatic GATA1 Mutations in DS-AML

Acquired mutations in GATA1 in the megakaryoblastic leukemia of Down syndrome

Joshua Wechsler¹, Marianne Greene¹, Michael A. McDevitt², John Anastasi³, Judith E. Karp⁴, Michelle M. Le Beau⁵ & John D. Crispino¹

Published online: 12 August 2002, doi:10.1038/ng955

[Diagram showing the normal and mutated GATA1 proteins and their effects on megakaryocyte and erythroid cell development, and acute megakaryocytic leukemia transformation.]
Cytidine Deaminase Expression and AML

• CDA transcripts were a median 5.1-fold lower in DS AML blasts compared to non-Down syndrome AML blasts.
• CDA transcript is transcribed from a CDA “long form” promoter (CDAlf) while a “short form” promoter (CDAsf) acts as an enhancer for the promoter.
• GATA1s protein in DS AML cases, results in reduced CDA enhancer activity and decreased CDA expression compared to non-DS AML cases. [Ge et al., Cancer Research 2004]
• Is there linkage between chromosome 21 and GATA1 mutations?
• True or false.
Model: Trisomy 21 accelerates CBS activity and drives mutagenesis of \textit{GATA1} toward TMD/AMKL

[Cabelof D et al., Blood 2009]
Can children with Down syndrome develop leukemia more than once?

- A) Yes
- B) No
Down Syndrome AML/ALL Cases

- Patient diagnosed at birth with the transient myeloproliferative disorder (TMD)/transient abnormal myelopoiesis (TAM) which resolved spontaneously with supportive care.
- Diagnosed at the age of 18 months with myeloid leukemia of Down syndrome (AMKL phenotype). Treated with chemotherapy on the COG AAML0431 protocol. She received 4 of 6 planned cycles of therapy due to fungal sepsis/pneumonia.
- Routine follow-up visit 3.5 years off therapy
  WBC: 7100/µL; ANC: 700; Hemoglobin: 11 g/dL;
  Platelets: 112,000/µL and blasts on the peripheral smear
- Diagnosed with ETV6-RUNX1 ALL and currently on therapy.
- 2/204 patients enrolled on AAML0431 have subsequently developed ALL.
Expression of chromosome 21-localized genes

\[ \uparrow \text{expression of chromosome 21-localized genes} \]

GATA1 exon 2 mutations develop prenatally

\[ \text{GATA1 exon 2 mutations develop prenatally} \]

Uncontrolled proliferation of immature megakaryocytes/
Additional unknown genetic hits

\[ \text{Uncontrolled proliferation of immature megakaryocytes/}
\text{Additional unknown genetic hits} \]

Expression of GATA1-target genes/Chromosome 21-localized gene result in altered activity and increased sensitivity to ara-C/anthracyclines

\[ \text{Expression of GATA1-target genes/Chromosome 21-localized gene result in altered activity and increased sensitivity to ara-C/anthracyclines} \]

Ara-C/anthracycline therapy

\[ \text{Ara-C/anthracycline therapy} \]

DS AMkL patients with EFS rates of 80-100% vs. 50% for non-DS AML patients and <35% for non-DS AMkL patients

\[ \text{DS AMkL patients with EFS rates of 80-100% vs. 50% for non-DS AML patients and 35% for non-DS AMkL patients} \]

Diagnosis of AMkL

\[ \text{Diagnosis of AMkL} \]

LINKAGE OF LEUKEMOGENESIS AND TREATMENT RESPONSE IN DS AML

\[ \text{LINKAGE OF LEUKEMOGENESIS AND TREATMENT RESPONSE IN DS AML} \]
Future Directions

• Can the intensity of AML therapy be reduced for children with ML-DS, while maintaining high EFS rates?
• Are there biomarkers which may be used to select treatment intensity for ML-DS?
• What is the basis for refractory/relapsed ML-DS cases which are outliers from a group who are overall very chemotherapy-responsive?
• Identify new therapeutic agents for refractory/relapsed ML-DS cases.
Acute Lymphoblastic Leukemia and Down syndrome

Johann (Hans) Hitzler, M.D.
The Hospital for Sick Children
Division of Hematology/Oncology
Developmental and Stem Cell Biology
Toronto, ON

POGO 2016 Multi-Disciplinary Symposium on Childhood Cancer, Nov 4-5
Distribution of Cancers in DS

Hasle H 2000 Lancet
Increased Risk for Leukemia in DS - Hypotheses

- **Genes on HSA21**
  - **Gene dosage** imbalance, Down syndrome critical region candidate genes (e.g. *ETS*, *RUNX1*, *ERG*, other)
  - **Epigenetic regulation**: differential gene expression organized in domains (GEDD) correlated with histone mark profile (H3K4me3)

- **Developmental features of hematopoiesis in DS**
  - ↑ megakaryocyte-erythroid progenitors, hematopoietic stem cells in DS fetal liver

Antonorakis 2004 Nat Rev Genet
Letourneau 2014 Nature
Tunstall-Pedoe O 2008 Blood
Chou S 2008 Blood
• **Cellular Pathways in DS**
  
  – Folate, homocysteine, one-carbon metabolism (*CBS, SOD*): functional intracellular folate deficiency
  
  – **NFAT signaling** (*DSCR1, DYRK1A*): ↑megakaryocyte proliferation ↓tumour angiogenesis
  
  – **miRNA125b**: repressed TGFβ (↑megakaryopoiesis) increased WNT signaling (↑HSC self-renewal)

• **Environmental**
  
  – Abnormal immune function
  
  – Carcinogen exposure (e.g. paternal smoking; negative association with infection in first 2 years of life)
Clinical Characteristics of ALL in Children with DS

- Age distribution: similar to non-DS ALL (5.0 vs. 4.7 yrs) infant ALL absent (< 1 year)
- **B precursor** immunophenotype predominant T-ALL rare (5 vs. 653 B precursor ALL)
- CNS involvement: not different
### Cytogenetic and molecular markers in DS-ALL

<table>
<thead>
<tr>
<th></th>
<th>DS-ALL</th>
<th>Non-DS-ALL</th>
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</tr>
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<tbody>
<tr>
<td></td>
<td>n=653</td>
<td>n=4445</td>
<td></td>
</tr>
<tr>
<td><strong>Cytogenetics (%)</strong></td>
<td></td>
<td></td>
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<tr>
<td>normal karyotype</td>
<td>40.3</td>
<td>6.9</td>
<td></td>
</tr>
<tr>
<td><em>ETV6-RUNX1</em> t(12;21)</td>
<td>8.3</td>
<td>25.8</td>
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<tr>
<td><em>BCR-ABL1</em> t(9;22)</td>
<td>0.7</td>
<td>2.4</td>
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<tr>
<td><em>MLL</em> rearrangement 11q23</td>
<td>0.5</td>
<td>1.2</td>
<td>n.s</td>
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<tr>
<td>high hyperdiploidy</td>
<td>9</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td><em>CRLF2</em> rearrangement</td>
<td>69</td>
<td>07-May</td>
<td></td>
</tr>
<tr>
<td><em>JAK2</em> mutation (R683)</td>
<td>21</td>
<td>10 (HR ALL)</td>
<td></td>
</tr>
<tr>
<td><em>IKZF1</em> deletion</td>
<td>35</td>
<td>29 (HR-ALL)</td>
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</tr>
<tr>
<td>RAS mutations *</td>
<td>36</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Buitenkamo T 2014 Blood, 2012 Leukemia  Hertzberg L 2010 Blood,  
Russell L 2009 Blood  Mullighan C 2009 Nat Genet  
*Nikolaev 2014 Nat Commu*
CRLF2 (Cytokine Receptor-Like Factor 2)

- Thymic stromal-derived lymphopoietin (TSLP) receptor
- overexpressed in 50-60% of DS-ALL
- activation of JAK2/STAT5 and PI3K/mTOR pathways
- *not prognostic in DS-ALL*

Mullighan C 2009 Nat Genet
Russell L 2009 Blood
Hertzberg L 2010 Blood
Tasian 2012 Blood
**JAK2 Mutations**

- Activating mutations
  19-27% of DS-ALL (R683)
  (10 % HR non-DS ALL)
- constitutive JAK/STAT activation
- *not prognostic in DS-ALL*

Bercovich B 2008 Lancet
Gaikwad A 2009 BJH
Mullighan C 2009 Nat Genet
Hertzberg L 2010 Blood
Epigenetic Aberrations in DS-ALL

- **HMGN1** – nucleosome remodeling protein
  21q22 suppresses global H3K27me3 overexpression of H3K27me3 marked genes can distinguish DS from non-DS
  Lane 2014 Nat Genet

- **Mutations in epigenetic regulators**
  CREBBP, SETD2, EZH2, SUZ12, NCOR1
  Nikolaev 2014 Nat Comm
Pathways and genes involved in DS-ALL

Acute lymphoblastic leukaemia

JAK2
24%

KRAS/NRAS
36%

CRLF2 (36%)
Chromatin remodelling (61%)
Haematologic lineage TFs (37%)
Tumour suppressors (27%)
Cohesin complex (5%)

B-cell precursor lymphocyte with trisomy 21

Nikolaev 2014 Nat Comm
Treatment of ALL in children with DS

- Increased susceptibility to infection
- Increased sensitivity to methotrexate (stomatitis, mucositis)
- Hyperglycemia during steroid and asparaginase therapy
striking contrast to the 14% incidence of TT and 20% incidence of TEL-AML1 rearrangements among the ALL-NDS cohort in CCG-1952. These results confirm, in a larger cohort, a previous study reporting the absence of the TEL-AML1 rearrangement among 11 samples of leukemic blasts from children with DS [26].

A similar low frequency of high hyperdiploidy (>51 chromosomes) was previously reported among patients with ALL-DS treated on CCG-1952.

### Table III. Toxicity Data

<table>
<thead>
<tr>
<th>Phase</th>
<th>Bacteremia (%)</th>
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<th>Stomatitis (%)</th>
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<th>Hyperglycemia (%)</th>
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<tbody>
<tr>
<td></td>
<td>DS</td>
<td>NDS</td>
<td>P-value</td>
<td>DS</td>
<td>NDS</td>
<td>P-value</td>
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<tr>
<td>Induction</td>
<td>14</td>
<td>9</td>
<td>0.29</td>
<td>2</td>
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<td>0.37</td>
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<tr>
<td>C/IM #1</td>
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<td>8</td>
<td>0.004</td>
<td>9</td>
<td>1</td>
<td>0.0003</td>
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<td>DI #1</td>
<td>17</td>
<td>9</td>
<td>0.05</td>
<td>28</td>
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<td>0.0001</td>
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<td>IM #2</td>
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<td>10</td>
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<td>Maint #1</td>
<td>10</td>
<td>4</td>
<td>0.03</td>
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</table>
High-dose Methotrexate in DS patients

- MTX pharmacokinetics not different in DS
- higher frequency of grade 3-4 gastrointestinal AE
  25.5% DS-ALL
  3.9% non-DS (P=0.001)
- not related to plasma MTX AUC, plasma levels at 24, 48h

Current use in DS-ALL
- 2g/m2 initially earlier LCV rescue (COG)
- gradually increasing dose 0.5, 1, 2, 4 g/m2 according to tolerance (BFM)

Buitenkamp T 2011 Haematologica
Outcomes of Treatment ALL in children with DS

<table>
<thead>
<tr>
<th></th>
<th>DS-ALL</th>
<th>non-DS-ALL</th>
<th>P</th>
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<tr>
<td>8-year OS</td>
<td>74</td>
<td>89</td>
<td>&lt;0.001</td>
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<tr>
<td>8-year EFS</td>
<td>64</td>
<td>81</td>
<td>&lt;0.001</td>
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<tr>
<td>8-year CI relapse</td>
<td>26</td>
<td>15</td>
<td>0.001</td>
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<tr>
<td>2 year TRM</td>
<td>7</td>
<td>2</td>
<td>&lt;0.001</td>
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</table>
High Infection-related Mortality During Treatment of DS-ALL

UK ALL2003

- DS-ALL 18.6% (1.9% non-DS ALL)
- all treatment phases
- one third in maintenance

86 patients: 17 TRM 16 sepsis

O’Connor D 2014 Blood
# Treatment-related mortality - DS ALL

Children’s Oncology Group Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>DS</th>
<th>non-DS</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SR ALL AALL0932</td>
<td>Induction: 2/203 (1.0%)</td>
<td>17/5528 (0.3%)</td>
<td>p=0.14*</td>
</tr>
<tr>
<td></td>
<td>Post-induction: 3/146 (2.05%)</td>
<td>12/3119 (0.4%)</td>
<td>p=0.03</td>
</tr>
<tr>
<td>HR ALL AALL1131</td>
<td>Induction: 4/88 (4.5%)</td>
<td>34/2116 (1.6%)</td>
<td>p=0.06</td>
</tr>
<tr>
<td></td>
<td>Post-induction: 5/106 (4.7%)</td>
<td>13/1258 (1.0%)</td>
<td>p=0.01</td>
</tr>
</tbody>
</table>

*Fisher exact test

Rabin K 2015 ASH
Increased risk of infection in DS

Abnormal innate and adaptive immunity in DS

- reduced T and B cell number
- Dysgammaglobulinemia
- lower titers of immunization-specific antibodies
- decreasing IgM in adolescence
decreased IgA in saliva

Ram G, Chinen J, 2011

Bloemers 2010 J Ped
Intensified Supportive Care for Patients with ALL and DS on COG Trials

- **HR-ALL**: Induction, Consolidation, Delayed Intensification
- **SR-ALL**: Induction, Delayed Intensification

- **Monitor in hospital** until signs of marrow recovery
- **Antibiotic prophylaxis** against gram-positive and -negative organisms (e.g., levofloxacin).
- **Antifungal prophylaxis** (echinocandin e.g. caspofungin or micafungin; azoles). Avoid concomitant administration ofazole and vincristine.
- correction of hypogammaglobulinemia
- vigilance for infections (may present with subtle signs)
The Challenge of Treatment for DS-ALL

Reduce treatment-related mortality

without increasing the risk of relapse
Frequency and Impact of Treatment Modifications
DS-ALL

- Lower doses of MTX, 6MP higher WBC (in maintenance)
- Modification of treatment in 43%
- EFS in DS-ALL comparable to non-DS group if treated without major modification (65% vs. 70% p0.66)

Bonstedt C 2013 Leukemia,
Doerdelmann M 1998 Leukemia
Goto H 2011 Int J Hem
Survival after ALL Relapse Therapy

DS-ALL

Meyr F 2013 BJH

pOS = .48 ± .06
pOS = .39 ± .01
pOS = .17 ± .08
# Survival after Stem Cell Transplantation

**DS-ALL**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Number events/evaluable</th>
<th>Probability (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophil recovery</td>
<td>24/27</td>
<td>81% (65–93)</td>
</tr>
<tr>
<td>28 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet recovery</td>
<td>22/26</td>
<td>85% (64–94)</td>
</tr>
<tr>
<td>100 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2–4 acute graft vs. host disease</td>
<td>8/26</td>
<td>31% (15–49)</td>
</tr>
<tr>
<td>100 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>180 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic graft vs. host disease</td>
<td>7/26</td>
<td>27% (12–45)</td>
</tr>
<tr>
<td>3 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transplant-related mortality</td>
<td>6/27</td>
<td>19% (6–35)</td>
</tr>
<tr>
<td>100 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapse</td>
<td>12/27</td>
<td>54% (33–74)</td>
</tr>
<tr>
<td>3 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease-free survival</td>
<td>18/27</td>
<td>24% (8–45)</td>
</tr>
<tr>
<td>3 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall survival</td>
<td>17/27</td>
<td>29% (12–50)</td>
</tr>
<tr>
<td>3 years</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CIBMTR n=27 2000-2009
CR2 52%
Myeloablative 78%
3-yr DFS 24%

Hitzler 2014 PBC
Strong Rationale for a New Approach to Treatment of DS-ALL

- particularly vulnerable population
  low tolerance for conventional ALL chemotherapy
- urgent and unmet need
  less toxic
  more efficacious treatment

Pathway inhibitors

Immunotherapy
Summary DS-ALL

- Increased incidence of ALL in DS (10- to 20-fold)
- Specific blast features (*CRLF2* rearrangement, activating *JAK2* mutations) and host factors
- Toxicity of ALL treatment (treatment-related mortality from infection) a significant problem
- Need for vigilance to subtle signs of infection, for aggressive management and enhanced supportive care
- Need for new agents with lower toxicity and better efficacy in DS-ALL (e.g. blinatumomab, CAR T cells, JAK inhibitors)
Leukemia and the Down Syndrome population

Considering the Psychosocial implications

Presented By: Dr. Kim S. Daniel & Dr. Maru Barrera
The Hospital for Sick Children
Overarching Aim

- To explore psychosocial interventions and assessments that can better support patients with Down Syndrome (DS)/Leukemia and their families
Pre-existing Risk Factors in Children with Down Syndrome

Present with differing clinical phenotypes:

- **Cognitive Deficits**
  - poor working memory
  - language delays (e.g. poor expressive language skills)
  - motor skills deficits
  - low adaptive skills

- **Medical Problems**
  - Cardiac (e.g. atrioventricular canal defects)
  - Gastrointestinal (e.g. GERD)
  - Ears, Nose and Throat issues
  - Endocrine Problems (e.g. thyroid disease)
  - Ophthalmology issues
Pre-existing Risk Factors in Children with Down Syndrome (Con’t)

- **Behavioural Issues:**
  - low motivation *(e.g. avoids opportunity for new learning)*
  - temperamental
  - stubborn or strong willed
  - distractible
  - sensitive to change in their social environments *(e.g. transition from home to medical appts)*
Increased Risk Factors for Patients with DS and Leukemia

May include:

- Psychological distress (e.g. sadness, fear)
- Higher rate of mental health disorders (e.g. anxiety disorder, depression, OCD, oppositional disorder, sleep related disorders, PTSD)
- Decline in overall cognitive skills related to treatment
- More intense parental-caregiver involvement; may lead to increased social, and adaptive competence declines
- Higher risk for mental health issues for caregivers and siblings (e.g., trauma, anxiety, depression)
- Financial issues (e.g. caregivers taking long periods of time off work)
- Increased isolation and social withdrawal
What can we do as Health Care Professionals (HCP)?

- **Psycho-Education is KEY:** Gain a better understanding of the strengths and weaknesses and overall functioning of the DS population.
- Gain a better understanding of the mental health related concerns for children/adolescents with DS/Leukemia and how their psychosocial distress and discomfort may heighten during their cancer treatments are presented.
- Gain a better understanding of the mental health concerns for the caregivers of kids with DS/Leukemia and how they present during cancer treatment.
- **Psycho-education can inform HCP to provide time-sensitive early interventions.**
<table>
<thead>
<tr>
<th>Age</th>
<th>Developmental Characteristics</th>
<th>Mental Health Concerns</th>
</tr>
</thead>
</table>
| Older school aged children, adolescence, and young adults | Present with better language and communication and cognitive skills e.g. relative strengths in symbolic representation, Complex reasoning, self regulation, and modeling of behaviours and languages | - Depression, social withdrawal, diminished interests and coping skills  
- Generalized anxiety  
- Obsessive compulsive behaviors  
- Chronic sleep difficulties, daytime sleepiness, fatigue, and mood related problems |
<table>
<thead>
<tr>
<th>Age</th>
<th>Developmental Characteristics</th>
<th>Mental Health Concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young school aged children</td>
<td>-limitations in language and communication skills (e.g. expressive &amp; receptive skills)</td>
<td>-Disruptive, impulsive, inattentive, hyperactive &amp; oppositional behaviors</td>
</tr>
<tr>
<td></td>
<td>-overall decrease in cognitive ability (e.g. working memory)</td>
<td>-Anxious, stuck, ruminative, inflexible behaviors</td>
</tr>
<tr>
<td></td>
<td>-non-verbal problem solving abilities</td>
<td>-Deficits in social relatedness, self-immersed, repetitive stereotypical behaviors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-Chronic sleep difficulties, daytime sleepiness, fatigue, and mood related problems</td>
</tr>
<tr>
<td>Age</td>
<td>Developmental Characteristics</td>
<td>Mental Health Concerns</td>
</tr>
<tr>
<td>---------------</td>
<td>-------------------------------</td>
<td>---------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Older adults</td>
<td>N/A</td>
<td>- Generalized anxiety</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Depression, social withdrawal, loss of interest, and diminished self-care</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Decline in cognitive and social skills</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Dementia</td>
</tr>
</tbody>
</table>
Psychosocial Distress in the DS population

- Differs from typical population, instead of seeing sadness, irritability or express distress/discomfort verbally, the DS population may express their distress with a more complex presentation for example:

  - Decline in cognitive functioning (e.g. loss of language)
  - Decline in toilet control
  - Sleep disturbances
What can we do as HCPs?

- Early and time sensitive screening (e.g. Cognitive, Adaptive, Social Emotional assessment) is crucial (at dx and throughout the patients and their family’s cancer journey)
  - E.g. Psychological Assessment Tool (PAT)

Note: Early screening and continuous assessment can help guide and implement appropriate interventions
<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Involved</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Universal</strong> low</td>
<td>psycho-education and family centred support - Ongoing monitoring</td>
</tr>
<tr>
<td><strong>Targeted</strong> low-moderate</td>
<td>monitor patient and family distress/ risk factors, provide interventions specific to needs/symptoms</td>
</tr>
<tr>
<td><strong>Clinical</strong> moderate-high</td>
<td>Increase psychosocial services, address impact on medical tx, trauma specific intervention</td>
</tr>
</tbody>
</table>
What can we do as HCPs?

- Integrate psychosocial support as a part of the circle of care
- Use multifaceted interventions (e.g. using medical and psychosocial model etc.)
- Work collaboratively (institution, other professionals (e.g. SLP, OT, BT) families, community)
- Circulate resources/knowledge (e.g. funding/supports for DSO and ODSP) to fellow staff and families
- Con’t professional development
What can we do as HCPs?

- Provide developmentally appropriate psycho-education/interventions
- Help caregivers to de-escalate distressful situations
- Learn about child’s developmental strengths and weaknesses
- Conduct psychosocial assessment to identify areas of risk and intervene before they become areas of pronounced difficulties
- Utilize the family as active agents in treatment
What can we do as HCPs?

- **Stay calm and model coping** (e.g. HCP models behaviour to parents and parents model behaviour to child)
- **Manage antecedents** (e.g. minimize or accommodate things in the environment, if possible, that tend to “set off” an incident or negative feeling or behaviour)
- **Expand on relative strengths** (e.g. visual imitation and visual memory, forming meaningful relationships, non-verbal interactions (e.g. play, turn taking))
Exploring visual psychological tools
Visual Feelings Card

- Excited
- Sad
- Angry
- Sick
- Surprised
- Happy
- Unhappy
- Bored
Size or Intensity of Emotion

- Small
- Medium
- BIG
Pain Management Scale

(Patel et al., 2014, Zadeh, 2015)
Guided breathing

breathe in through nose

blow out of mouth

Lazy 8 Breathing
Positive Thoughts

- I can get through this"
- “I am brave”
- “I can do calm breathing”
- “I am not alone”
Distraction Techniques
Empower the patient and their family
VIDEO: Living with Down Syndrome and battling cancer, a family's struggle


The father of Cade Wegener on coping with down syndrome and battling cancer

SOURCE: TULSA WORLD
Thank-you

Questions?
References:


References:


