Future Directions in Acute Myeloid Leukemia and Acute Lymphoblastic Leukemia

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Disclosures
- Speaker’s Bureau: Jazz Pharmaceuticals, BTG
- External Reviewer for LexiComp

Objectives
- Describe current remission/cure rates for Acute Lymphoblastic Leukemia (ALL) and Acute Myeloid Leukemia (AML)
- Identify patients at high risk for relapse
- Examine opportunities to improve cure rates in high risk patients with ALL and AML
- Analyze novel agents with potential to improve cure rates in high risk patients with ALL and AML
Background

<table>
<thead>
<tr>
<th>Year</th>
<th>Therapeutic Advance</th>
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<tbody>
<tr>
<td>1948</td>
<td>“Transient remissions” induced by aminopterin</td>
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<tr>
<td>1967</td>
<td>Combination chemotherapy and effective CNS-directed therapy cure ~50% of patients</td>
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<tr>
<td>1981</td>
<td>Reinduction treatment improves outcomes</td>
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<td>1982</td>
<td>Triple intrathecal therapy with methotrexate (MTX), hydrocortisone (HC), and cytarabine may be substituted for prophylactic cranial irradiation in some patients</td>
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<td>1983</td>
<td>Prophylaxis weekly high-dose asparaginase improves outcomes</td>
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<tr>
<td>1991</td>
<td>Interim-dose MTX with leucovorin rescue decreases systemic and testicular relapses</td>
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<tr>
<td>1995</td>
<td>Inherited genetic polymorphism in gene encoding thiopurine methyltransferase influence mercaptopurine toxicity</td>
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<tr>
<td>1996</td>
<td>Individualized methotrexate dose improves outcomes</td>
</tr>
<tr>
<td>2000</td>
<td>Effective systemic and intrathecal chemotherapy can eliminate the need for prophylactic cranial irradiation in all patients</td>
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“Current” Survival Rates

5-Year Survival Rate, Age 0–19


Survivors of childhood cancer are at risk for long-term health complications. Many survivors are living healthy lives, but they may experience late effects related to their treatments. Some of these effects are physical, such as hearing loss or growth issues. Others can be psychological, such as anxiety or depression. Understanding the long-term effects of childhood cancer treatments is important for survivors and their families. It is also important for healthcare providers to monitor survivors and provide support as needed.

Effective systemic and intrathecal chemotherapy can eliminate the need for prophylactic cranial irradiation in all patients. Imatinib improves early treatment outcome in Philadelphia chromosome-positive ALL.


Current and future research is focused on developing new therapies that can improve outcomes and reduce complications associated with childhood cancer treatments. Researchers are also exploring ways to better understand the long-term effects of childhood cancer treatments on survivors.

Survivors of childhood cancer are a diverse group with different needs and experiences. It is important for healthcare providers to be culturally competent and provide personalized care to each survivor.

Survivors of childhood cancer are an inspiration to many. They demonstrate resilience and strength in the face of adversity. Their stories of survival and recovery can be inspiring for others and help to raise awareness about the importance of research and early detection.

Effective systemic and intrathecal chemotherapy can eliminate the need for prophylactic cranial irradiation in all patients. Imatinib improves early treatment outcome in Philadelphia chromosome-positive ALL.


Recent Advances

- Genetic Sequencing/Technology
- Risk Stratification
- Novel Therapeutic Approaches

- Decrease toxicity
- Improve outcomes

Identification of prognostic factors
Identify tumor specific targets
ARS Question 1

JT is a 4 year old girl diagnosed with standard risk ALL. What is JT’s 5 year event-free survival rate likely to be?

A. 90%
B. 60%-70%
C. 40%-50%
D. Less than 40%

Acute Lymphoblastic Leukemia (ALL)

- Overall cure rate close to 90% (the good news)
- Room for improvement (…the bad news)
  - 20% will relapse (OS rates between 25 and 40%)
  - Infants ~50% survival
  - 80% MLL gene rearrangement
  - T cell leukemia
  - Decrease treatment related toxicities
Advances in ALL

Prognostic Factors \rightarrow Risk Stratification \rightarrow Intensity Therapy \rightarrow Deescalate Therapy

Improve outcomes

Maintain outcomes

Decrease toxicity
ARS Question 2

JT’s cytogenetics have come back showing her leukemic blasts are positive for the Philadelphia chromosome (Ph+). How does this affect her risk stratification?

A. Does not change her risk status or treatment regimen
B. Increases her to high risk requiring intensified treatment and the inclusion of targeted agents
C. Decreases her to low risk limiting the exposure to chemotherapy decreasing the incidence of toxicity and long term side effects

Previously Known Prognostic Factors-ALL

- Diagnosis: WBC & Age
  - WBC >50K
  - Age <1y or >10y
- Immunophenotyping
  - T-Cell vs B Cell
- Induction response
  - Early vs late
- Cytogenetics
  - Mixed lineage leukemia (MLL) (11q23)
  - Philadelphia chromosome
  - Hyperdiploidy (>50 chromosomes) vs hypodiploidy (<44 chromosomes)

Advances in Prognostic Factors- ALL

- Immunophenotyping
  - Early Precursor T-Cell (EPT)
- Cytogenetics (Exploded)
- Response to Therapy
  - Minimal residual disease (MRD)
  - One of the most significant predictors of relapse/refractory disease
- Adherence
  - 6-mercaptopurine
Early T Cell Precursor (ETP) ALL

- Biologically distinctive subgroup of T ALL
  - 15% of pediatric T ALL
  - Immunophenotype: CD1a-, CD8-, CD5 weak, co-expression of stem cell or myeloid markers
  - Initially thought to have poorer overall outcomes
  - UKALL 2003 demonstrated 5 yr EFS 77% (not significantly lower than non-ETP T ALL).
  - AIEOP group looked at 49 patients with ETP
    - High rates of poor response to prednisone and high rates of induction failure
    - Treated with BFM risk-stratified therapy
    - 78% maintained a complete sustained remission


World Health Organization (WHO)

2008 WHO classification of B-ALL

- B lymphoblastic leukemia/lymphoma, NOS
- B lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
- B lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2); BCR-ABL1
- B lymphoblastic leukemia/lymphoma with t(v;11q23.3); KMT2A rearranged
- B lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1); ETV6-AML1
- B lymphoblastic leukemia/lymphoma with hyperdiploidy
- B lymphoblastic leukemia/lymphoma with hypodiploidy
- B lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.3); IL3-IGH
- B lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3); TCF3-PBX1
- Provisional entity: B lymphoblastic leukemia/lymphoma, BCR-ABL1–like
- Provisional entity: B lymphoblastic leukemia/lymphoma with iAMP21

2016 WHO classification of B-ALL

- B lymphoblastic leukemia/lymphoma, NOS
  - B lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
    - B lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2); BCR-ABL1
    - B lymphoblastic leukemia/lymphoma with t(v;11q23.3); KMT2A rearranged
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- Provisional entity: B lymphoblastic leukemia/lymphoma with iAMP21

ARS Question 3

The MLL rearrangement genetic mutation has been reclassified as what acronym?

A. KMT2A
B. CRBLF
C. TCR
D. WAP1
Examples of Molecularly Targeted Trials

<table>
<thead>
<tr>
<th>Therapeutic target</th>
<th>Potentially sensitive genotypes</th>
<th>Inhibitor</th>
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<tbody>
<tr>
<td>HDOT1L*</td>
<td>MLL rearranged</td>
<td>EPZ-6474</td>
</tr>
<tr>
<td>IDH2</td>
<td>IDH2 mutated</td>
<td>Ag-221</td>
</tr>
<tr>
<td>CDK6</td>
<td>MLL rearranged</td>
<td>Palbociclib</td>
</tr>
<tr>
<td>BET proteins**</td>
<td>MLL rearranged, NPM1*</td>
<td>CTX015, GSK520162</td>
</tr>
<tr>
<td>XPDL1/CRM1-1</td>
<td>NPM1*</td>
<td>Broadly Specific</td>
</tr>
<tr>
<td>BCL-2*</td>
<td>BCL2 mutated</td>
<td>Venetoclax</td>
</tr>
<tr>
<td>FLT3*</td>
<td>FLT3 mutated</td>
<td>Casitasibs, Quizartinib, Midostinib</td>
</tr>
<tr>
<td>C-RIT*</td>
<td>C-KIT mutated</td>
<td>Risk Adapted</td>
</tr>
<tr>
<td>CDK13</td>
<td>CBF leukemia</td>
<td>Gamursamab conjugation (Mylotarg)</td>
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ALL Cytogenetic Explosion

<table>
<thead>
<tr>
<th>Favorable</th>
<th>Unfavorable</th>
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<tbody>
<tr>
<td>High-hyperdiploidy (51-65 chromosomes)</td>
<td>Low-hypodiploidy (32-39 chromosomes)</td>
</tr>
<tr>
<td>Trisomies of 4 and 10</td>
<td>MLL rearrangements (KMT2A, 11q23)</td>
</tr>
<tr>
<td>ETv6-Runx1 (TEL-AML1)</td>
<td>Ph+ t(9,22)</td>
</tr>
<tr>
<td></td>
<td>TP53 mutations</td>
</tr>
<tr>
<td></td>
<td>iKZF1 deletions</td>
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<tr>
<td></td>
<td>iAMP21</td>
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iAMP21- A Cytogenetic Success Story

- Internal amplification of the AML1 gene on chromosome 21 (iAMP21)
- Occurs in 2% childhood ALL
- Associated with older age at diagnosis (median age 10y)
- Lower presenting WBC (<50K) at diagnosis (NCI standard risk)
  - UKALL 5 yr EFS 29%, BFM group EFS 37%
- UKALL 2003 trial: treated as high risk (intensified therapy)
  - 78% EFS
- COG reported no statistical difference in EFS when stratified as high risk

Risk-Directed Therapy for Ph-Like

- Ph-Like (15% pediatric B-ALL)
  - Subset of B-ALL but without the BCR-ABL1 fusion
  - High incidence of IKZF1 deletions
  - More common in older children and adolescents
  - Genomic analysis of 154 patients with Ph-Like ALL
    - 90% contained kinase activating alterations involving ABL1, ABL2, CRLF2, EPOR, JAK2, PDGFRB and others
    - ABL1, ABL2, CSFIR and PDGFRB: sensitive in vitro to dasatinib
    - EPOR and JAK2 rearrangements: sensitive in vitro to ruxolitinib
  - Study of 40 pts treated with risk-directed therapy based on MRD
    - Demonstrated poor prognostic value of cytogenetics could be overcome

MRD as a Prognostic Factor in ALL

- Measured by flow cytometric detection of aberrant immunophenotypes and allele-specific oligonucleotide polymerase chain reaction (ASO-PCR) amplification of immunoglobulin and T-cell receptor genes.
  - Can get false-negative due to clonal evolution
  - Deep sequencing methods
    - Identify evolved clonal populations
    - More precise
    - Can detect very low levels of leukemia (<0.01%)

ARS Question 4

JT has finished induction therapy. What does her end of induction MRD need to be to be considered “MRD negative”?

A. >1%
B. ≥ 0.1% - <1%
C. >0.01%
D. <0.01%
MRD as a Prognostic Factor in ALL

- Risk of relapse strongly correlates with MRD level at end of induction and end of consolidation
  - Stratify intensity of regimens based on these time points
  - UKALL 2003 study (randomized)
    - Showed intensified treatment for pts with high end of induction MRD (>0.01%) resulted in a superior EFS compared to those receiving standard chemotherapy
    - Also de-intensified therapy for non-high risk patients with low/favorable MRD
  - No significant difference in EFS

Advances in Prognostic Factors - MRD

End of induction MRD as a predictor of relapse

EFS on 9900 series COG studies by end of induction MRD

Advances in ALL Therapy

- Decrease Treatment Related Toxicity
  - Substitution of CNS-directed therapies in place of radiation
    - High dose methotrexate
    - Intrathecal chemotherapy
  - Prevention of anthracycline-associated cardiotoxicity
    - Dexrazoxane
  - Response based de-escalation of therapy
ARS Question 5
Which area of improvement seems to have the best chance of improving outcomes for JT?
A. Deintensification of chemotherapy which reduces toxicity and long term sequelae
B. Genetic testing to find polymorphisms that impact how JT processes medications
C. Improved radiation techniques decreasing potential tissue damage
D. The addition of targeted agents such as dasatinib to an intensified chemotherapy regimen

Impact of TKIs on Ph+ ALL
- Approximately 3-5% of childhood ALL
- Historically poor outcomes requiring HSCT in first remission
- European intergroup study of safety and efficacy of post-induction imatinib evaluated patients from 2004 to 2009
  - Risk directed therapy
  - 178 patients enrolled
  - 4yr DFS of imatinib patients 75.2% vs 55.9% control (p=0.06)

Impact of TKIs on Ph+ ALL
- Dasatinib started day 15 of induction
Philadelphia Chromosome-Like ALL-TKIs

![Table]

Novel Approaches to Therapy - New Agents

- Immunotherapy
  - Blinatumomab
  - Inotuzumab ozogamicin (CMC-544)
- Cellular Therapy
  - Chimeric antigen receptor (CAR) T Cells
- Tyrosine kinase inhibitors
  - Philadelphia chromosome-like ALL: Imatinib, dasatinib, ruxolitinib
  - T-Cell: nelarabine, bortezomib, clofarabine
  - Infant ALL: azacitidine

Immunotherapy

- Utilizing / enhancing the anti-tumor effect of the immune system
- Limits systemic toxicities due to specific cell kill
- Targets a specific leukemic cell antigen
- Blinatumomab (CD19/CD3)
  - Due to short ½ life, drug is given as a continuous infusion over 4 weeks
- Cytokine release syndrome (CRS)
  - Premedicate with corticosteroids
  - Tocilizumab (anti-IL-6) for treatment
- Neurotoxicities
**Blinatumomab – Bispecific T cell-engaging antibody**

- **Blinatumomab**
  - *Bi-specific T cell Engager (BiTE)*
  - Binds CD19 (on the B Cell) AND CD3 on the T Cell
    - Present on the surface of >90% of B Cell leukemias
    - Promotes upregulation of T cell activation markers and perforin-mediated cytotoxicity
    - Increases T Cell proliferation
- Phase III studies in children (n=70)
  - 39% Achieved CR within the first 2 cycles
  - 52% achieved MRD negative status
  - Response rate was better with lower tumor burden at initiation
    - >50% bone marrow blasts: CR 56%
    - <50% bone marrow blasts: CR 33%


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**Inotuzumab Ozogamicin (INO)**

- >90% B Cell ALL express CD22
- Monoclonal antibody (humanized) targeting CD22 bound to a cytotoxic agent (calicheamicin)
  - Binding to CD22 causes internalization of the molecule, DNA damage and cell death
  - Capable of targeting quiescent cells
- Retrospective analysis of 43 patients receiving compassionate use
  - 62% achieved CR
  - Common adverse effects: infection, hepatotoxicity
- 9 of 15 patients that went on to HSCT developed VOD (1 died)

Cellular Therapy

- Chimeric Antigen Receptor (CAR) T Cells
  - Adoptive immunotherapy
    - Use patient’s own effector T Cells that have been re-engineered ex vivo to induce an immune response
    - Demonstrated long-lasting in vivo survival
    - Diffuse into bone marrow, tissues and CNS
      - Furthest along - CD19

Development of CAR T-Cells

- CTL019 study (CHOP and University of Pennsylvania)
  - 25 children and 5 adults relapsed/refractory B ALL
  - 90% CR, 67% EFS, 78% OS at 6 months
  - All patients experienced CRS
    - 27% considered severe
    - All responded to tocilizumab

- Follow-up study 59 children and adolescents
  - 93% CR 1 month post-infusion
  - 88% MRD negative by flow cytometry
  - 12 month follow-up
    - 58% remained in remission
    - 79% OS (34% eventually relapsed over half with CD19 - clones)

Chemotherapy for Infant ALL

- P9407 – 5 year EFS of 36%
- Interfant-99 – 4 year EFS of 37%
- AALL0631
  - Added FLT3 inhibition with lestaurtinib with no significant improvement in EFS
- Relapse occurs early, often during therapy
- Second remission is very difficult to achieve

Epigenetic Modification

- Novel approach involving changing the cellular environment of the malignant cells
- KMT2A-R ALL cells have characteristic gene expression profiles and epigenetic alterations
  - DNA promoter hypermethylation can lead to silencing of tumor suppressor genes
  - Methylation changes can increase chemo-resistance and relapse

Azacitidine

- DNA methyltransferase inhibitor (DNMTi)
- Exposure of KMT2A-R cells in vitro to DNMTi can reverse the methylation pattern of silenced genes and induce selective cytotoxicity
- Some experience with DNMTi + chemotherapy in children but not in infants
- COG AALL15P1 Trial
  - Adding azacitidine post induction for infants with KMT2A rearrangement
Adherence Impact on Outcomes

- Adherence with 6-mercaptopurine during maintenance
  - Patients with an adherence rate of <90% have 3.9 fold increased risk of relapse
  - Risk factors for non-compliance
    - Age >12y
    - Low annual household income/Low parental education
    - Non-white race/ethnicity
    - Household structure
    - Lack of established pill taking routine

Acute Myeloid Leukemia (AML)

- Approximately 25% of all leukemia diagnosis
- Survival rates between 60% and 70%
  - Intensified chemotherapy/ risk stratification
  - Supportive care strategies
  - Hematopoietic stem cell transplant
- Therapeutic regimens based on subtype
  - APML: all-trans retinoic acid (ATRA) + chemotherapy
    - Arsenic trioxide (AAML1331)
  - Unacceptable relapse rate (~1/3)

Acute Myeloid Leukemia (AML)

- Advances in Molecular Genetics
  - Identification of new genetic abnormalities
    - Clinical significance still undefined
    - Improve risk stratification
    - Identify targeted therapy
  - Identification and validation of new prognostic factors
    - Minimum residual disease (MRD)
Acute Myeloid Leukemia (AML)

**Favorable**
- t(8;21)/RUNX1
- t(15;17)/PML-RARA
- t(9;22)/Bcr-Abl
- t(1;19)/PML-RARA
- t(1;17)/PML-RARA
- t(16;16)/CBF1-MYH11
- Mutated NPM1 without FLT3-ITD
- Biallelic mutations of CEBPA
- t(1;11)/MLLT11
- t(11;19)/MLLT1
- t(9;22)/Bcr-Abl
- t(1;22)/RBM15

**Unfavorable**
- t(6;11)/MLLT4
- t(10;11)/MLLT10
- t(10;11)/ABI1
- t(6;9)/DEK
- t(8;16)/KAT6A
- t(16;21)/RUNX1-CBFA2T3
- t(5;11)/NUP98
- inv(16)/CBFA2T3-GLIS2
- t(11;15)/NUP98
- t(3;5)/NPM1
- FLT3-ITD

**Intermediate/Unknown**
- t(9;11)/MLLT3
- Other KMT2A fusions

MRD as a predictor of outcomes in AML

- St. Jude AML02 MRD measured by flow cytometry after induction
  - MRD positive 39% 3 yr cumulative incidence of relapse vs. 17% for MRD negative
  - Relapse rate was higher in those with >1% after one course of therapy and >0.1% after two courses
- Nordic Society of Pediatric Hematology Oncology (NOPHO) study group
  - MRD Negative (1 course): EFS 65%, OS 77%
  - MRD Positive (1 course): EFS 22%, OS 51%
  - MRD Positive (start consolidation): EFS 11%, OS 28%

Impact of minimal residual disease (MRD) after induction therapy on outcomes in patients with acute myeloid leukemia.
Juvenile Myelomonocytic Leukemia (JMML)

- Approximately 90% have mutations in the RAS pathway
  - PTPN11, NRAS, Kras, NF1 and CBL
- Azacitidine (epigenetic alteration)
  - Case reports/case series
- Tipifarnib
  - Farnesyltransferase inhibitor
  - Phase 1 trial in peds
  - 52% farnesyltransferase inhibition in leukemic blasts

Novel Therapeutic Approaches in AML

- Antigen-targeted therapies
  - Immunotherapy
    - Bi-specific T-cell Engaging (BiTE) antibodies against CD33
    - Chimeric antigen receptor (CAR) T-Cells (CD33, CD123)
- Intensification of current regimens
  - Clofarabine, sorafenib, dasatinib
- Relapse/refractory AML: Liposomal cytarabine-daunorubicin (Vyxeos®) (AAML1421)

Liposomal Cytarabine-Daunorubicin

- Fixed combination of liposomal cytarabine and daunorubicin (5:1 molar ratio) optimal for synergistic activity
- Each unit contains 1 mg cytarabine and 0.44 mg daunorubicin
- Accumulates in bone marrow yielding higher concentrations
- Selectively taken up into leukemia cells with intracytoplasmic release of the drugs
Cellular Therapy for AML

- Bi-Specific T cell Engager (BiTE) antibody (AMG330)
  - CD33/CD3
- Epigenetic modification to enhance CD33 expression
  - Histone deacetylase (HDAC) inhibitors
    - panobinostat
  - DNA methyltransferase (DNMT) I inhibitor
    - azacitidine


Questions