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>Relapse treatment improves outcomes</td>
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<tr>
<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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<tr>
<td>1983</td>
<td>Primrose weekly high-dose asparaginase improves outcomes</td>
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<tr>
<td>1991</td>
<td>Interim-dose MTX with leucovin 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>
</tr>
<tr>
<td>1996</td>
<td>Methotrexate methotrexate dose improves outcome</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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10/10/17

"Current" Survival Rates

<table>
<thead>
<tr>
<th>5-Year Survival Rate, Age 0–19</th>
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<tbody>
<tr>
<td>Overall</td>
</tr>
<tr>
<td>Acute Lymphoblastic Leukemia</td>
</tr>
<tr>
<td>Acute Myeloid Leukemia</td>
</tr>
<tr>
<td>Hodgkin Lymphoma</td>
</tr>
<tr>
<td>Non-Hodgkin Lymphoma</td>
</tr>
<tr>
<td>Brain and Spinal</td>
</tr>
<tr>
<td>Brain and CNS</td>
</tr>
<tr>
<td>Bone and Joint</td>
</tr>
<tr>
<td>Soft Tissue</td>
</tr>
<tr>
<td>Metastatic Tumor</td>
</tr>
</tbody>
</table>

Source: Surveillance, Epidemiology, and End Results (SEER) Program (seer.cancer.gov) SEER 9 area. Based on follow-up of patients into 2012.
Recent Advances

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

- Decrease toxicity
- Improve outcomes

- Identification of prognostic factors
- Identify tumor specific targets
Recent Advances

- Genetic Sequencing/Technology
- Novel Therapeutic Approaches
- Risk Stratification
- Immunotherapy
- Cellular therapy
- New agents

Risk Stratification
- Decrease toxicity
- Improve outcomes

Identification of prognostic factors
- Identify tumor specific targets

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
- Risk Stratification
- Intensity Therapy
- Deescalate Therapy

Advances in ALL

**Prognostic Factors**
- Risk Stratification
- Intensify Therapy → Improve outcomes
- Deescalate Therapy

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 11q23 rearrangements
- B lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3) TCF3-PBX1
- B lymphoblastic leukemia/lymphoma with hyperdiploidy
- B lymphoblastic leukemia/lymphoma with hyperdiploidy
- B lymphoblastic leukemia/lymphoma with hypodiploidy
- B lymphoblastic leukemia/lymphoma with t(5;14)(q31;q32) IL3-IGH

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
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- B lymphoblastic leukemia/lymphoma with hypodiploidy
- B lymphoblastic leukemia/lymphoma with t(5;14)(q31;q32) IL3-IGH
- Provisional entity: B lymphoblastic leukemia/lymphoma, BCR-ABL1-like
- Provisional entity: B lymphoblastic leukemia/lymphoma with iAMP21

Examples of Molecularly Targeted Trials

<table>
<thead>
<tr>
<th>Therapeutic target</th>
<th>Potentially sensitive genotypes</th>
<th>Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCDT1*</td>
<td>MLL rearranged</td>
<td>EPZ-5676</td>
</tr>
<tr>
<td>IDH1</td>
<td>IDH1 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,</td>
<td>CTX015, GSK20742</td>
</tr>
<tr>
<td>XPO1/C2RM1-1†</td>
<td>NPM1 mutated</td>
<td>KPT-330 (Selinexor)</td>
</tr>
<tr>
<td>BCL-2*</td>
<td>CYC2 mutated</td>
<td>Venetoclax</td>
</tr>
<tr>
<td>FLT3*</td>
<td>FLT3 mutated</td>
<td>Casitasib, Quizartinib, Midostaurin</td>
</tr>
<tr>
<td>C-KIT†</td>
<td>C-KIT mutated</td>
<td>Dasatinib</td>
</tr>
<tr>
<td>CD33</td>
<td>CBF leukemia</td>
<td>Gemtuzumab conjugate (Mylotarg)</td>
</tr>
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Therapeutic target

Potentially sensitive genotypes

Inhibitor

ALL Cytogenetic Explosion

Favorable
- High-hyperdiploidy (51-65 chromosomes)
- Trisomies of 4 and 10
- ETV6-Runx1 (TEL-AML1)

Unfavorable
- Low-hypodiploidy (32-39 chromosomes)
- MLL rearrangements (KMT2A, 11q23)
- Ph+ t(9,22)
- TP53 mutations
- IKZF1 deletions
- iAMP21

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%)
  - 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

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
  - 4 yr 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>
<thead>
<tr>
<th>Gene</th>
<th>Philadelphia-like</th>
<th>Philadelphia-like</th>
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<tbody>
<tr>
<td>BCR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABL1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ETV</td>
<td></td>
<td></td>
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<tr>
<td>PML-NCO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MLL</td>
<td></td>
<td></td>
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<tr>
<td>MLL-AF9</td>
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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
- 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 II/III studies in children (n=70)
  - 39% Achieved CR within the first 2 cycles
  - 50% 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%

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 inforce an immune response
    - Demonstrated long-lasting in vivo survival
    - Diffuse into bone marrow, tissues and CNS
      - Furthest along- CD19

Development of CAR T-Cells
### CAR T Cell Experience in Children

- **CTL019 study (CHOP and University of Pennsylvania)**
  - 25 children and 5 adults relapsed/refractory B ALL
  - 80% CR, 67% EFS, 76% 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 (AAML1311)
- 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)

Favorable
- t(8;21)(q22;q22)/RUNX1
- inv(16)(p13.1;q22)/CBFb-MYH11
- t(16;16)(p13.1;q22)/CBFb-MYH11
- Mutated NPM1 without FLT3-ITD
- Biallelic mutations of CEBPA
- t(1;11)(q21;q23)/MLLT11-KMT2A

Unfavorable
- t(6;11)(q27;q23)/MLLT4-KMT2A
- t(10;11)(p12;q23)/MLLT10-KMT2A
- t(10;11)(p11.2;q23)/ABI1-KMT2A
- t(6;9)(p23;q34)/DEK-NUP214
- t(8;16)(p11;p13)/KAT6A-CREBBP
- t(16;21)(q24;q22)/RUNX1-CBFA2T3
- t(5;11)(q35;p15.5)/NUP98-NSD1
- inv(16)(p13.3q24.3)/CBFA2T3-GLIS2
- t(11;15)(p15;q35)/NUP98-KDM5A
- t(3;5)(q25;q34)/NPM1-MLF1
- FLT3-ITD

Intermediate/Unknown
- t(9;11)(p12;q23)/MLLT3-KMT2A
- Other KMT2A fusions
- t(1;22)(p13;q13)/RBM15-MKL1

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
  - 82% farnesyltransferase inhibition in leukemic blasts

Novel Therapeutic Approaches in AML
- Antigen-targeted therapies
  - Immunotherapy
    - Bispecific 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

Future Directions in Acute Myeloid Leukemia and Acute Lymphoblastic Leukemia

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