ACUTE LYMPHOBLASTIC LEUKEMIA (ALL): DIAGNOSIS, TREATMENT AND SIDE EFFECTS MANAGEMENT
LEARNING OBJECTIVES

▪ Describe the various types and subtypes of acute lymphoblastic leukemia (ALL)
▪ Identify tests used to diagnose disease and monitor treatment of ALL
▪ Explain the overarching goals of treatment for the subtypes of ALL
▪ Explain approved and emerging treatment options for ALL, including stem cell transplantation, and the role of clinical trials
▪ Describe strategies to manage treatment side effects as well as potential long-term and late effects of treatments for ALL
FACULTY

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ALL Morphology

Clonal expansion of immature lymphoblasts
EPIDEMIOLOGY
## Estimated Incidence of ALL in 2018

<table>
<thead>
<tr>
<th></th>
<th>New Cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>3290</td>
<td>830</td>
</tr>
<tr>
<td>Females</td>
<td>2670</td>
<td>640</td>
</tr>
<tr>
<td>Total</td>
<td>5,960</td>
<td>1,470</td>
</tr>
</tbody>
</table>

## ALL Statistics

<table>
<thead>
<tr>
<th></th>
<th>Incidence per 1,000,000 person-years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Peak age of 1-4 years</strong></td>
<td>78.7</td>
</tr>
<tr>
<td><strong>Nadir age of 40 – 59 years</strong></td>
<td>8.1</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>24.9</td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>16.6</td>
</tr>
<tr>
<td>Asian and Pacific Islanders</td>
<td>14.8</td>
</tr>
<tr>
<td>Black</td>
<td>10.2</td>
</tr>
</tbody>
</table>

Age-related Incidence of ALL

![Graph showing age-related incidence of ALL and AML.](image-url)

Age
15-19
20-29
30-44
45-59
60+
WHO Classification 2008 Revisions

- **B lymphoblastic leukemia/lymphoma (L/L)**
  - B lymphoblastic L/L, NOS
  - B lymphoblastic L/L, recurrent genetic abnormalities

- **T lymphoblastic leukemia/lymphoma**
Diagnostic Work-Up

• Bone marrow biopsy with:
  – Cytogenetics
  – Flow Cytometry
  – FISH for major recurrent abnormalities
  – PCR testing for BCR-ABL if t(9;22) is suspected

• Lumbar puncture to assess CSF
  – Usually not done while circulating blasts are present

• Testicular exam
  – Especially in T-cell ALL
Diagnosis

• Morphology
  – Wright-Giemsa-stained BM aspirate smears
  – H&E-stained core biopsy and clot sections

• Immunophenotype
  – Comprehensive flow cytometric immunophenotyping

• Cytogenetics
  – Karyotyping of G-banded metaphase chromosomes

• Molecular Characteristics
  – FISH for major recurrent genetic abnormalities
  – RT-PCR for fusion genes (ie, \textit{BCR-ABL1})
Cytogenetic Abnormalities Adult ALL

- **Hyperdiploidy and Hypodiploidy**: 9%
- **t(9;22)(q34;q11)**: BCR-ABL1 25%
- **t(12;21)(p13;q22)**: ETV6-RUNX1 (TEL-AML1) 2%
- **t(v;11q23), t(11;19)**: KMT2A (MLL) 10%
- **t(1;19)(q23;p13)**: TCF3-PBX1 (E2A-PBX1) 3%
- **t(5;14)(q31;q32)**: IL3-IGH <1%
- **t(8;14), t(2;8), t(8;22)**: c-MYC 4%

**Ikaros**
- IKZF1 25%-35%

**ETP**
- 2%

**BCR-ABL1-like**
- 10%-30%

**t(11;14)(q11)**
- TCRα and TCRδ 20%-25%

**t(5;14)(q35;q32)**
- HOX11L2 1%

**t(10;14)(q24;q11)**
- HOX11 (TLX1) 8%

**t(1;14)(p32;q11)**
- TAL-1 12%

# Key Genetic Alterations in ALL

<table>
<thead>
<tr>
<th>ALL subtype</th>
<th>Alterations/Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-lineage</td>
<td>PHF6, CNOT3, RPL5, RPL10, Notch/FBXW7</td>
</tr>
<tr>
<td>ETP</td>
<td>Loss of function (GATA3, IKZF1, RUNX1, ETV6)</td>
</tr>
<tr>
<td></td>
<td>Gain of function (Ras, FLT-3, IL7R)</td>
</tr>
<tr>
<td></td>
<td>Inactivating (EZH2, SUZ12, EED, SETD2, DNMT3A)</td>
</tr>
<tr>
<td>BCR-ABL1-like</td>
<td>Rearrangement CRLF2 in 50%; activating JAK mutations in 50% CRLF2r</td>
</tr>
<tr>
<td></td>
<td>Rearrangement kinase genes ABL1, ABL2, EPOR, PDGFRB</td>
</tr>
<tr>
<td>Hypodiploid</td>
<td>Ras (NF1, PTPN11, NRAS, KRAS)</td>
</tr>
<tr>
<td></td>
<td>IKZF2/IKZF2</td>
</tr>
<tr>
<td></td>
<td>TP53, commonly germline</td>
</tr>
<tr>
<td>Burkitt</td>
<td>TCF3/ID3, CCND</td>
</tr>
<tr>
<td>Relapsed</td>
<td>CREBBP, NT5C2 enriched</td>
</tr>
<tr>
<td>Familial</td>
<td>TP53 low hypodiploid; PAX5 pGly193Ser in autosomal dominant</td>
</tr>
<tr>
<td>Ph+</td>
<td>IKZF1 deletion</td>
</tr>
</tbody>
</table>

Cytogenetic Risk Groups

• Good risk (rare in adults)
  – Hyperdiploidy
    • 51-65 chromosomes
    • Trisomy of chromosomes 4, 10, 17
  – t(12;21)(p13;q22): *ETV6-RUNX1* (*TEL-AML1*)

• Poor risk
  – Hypodiploidy
    • <44 chromosomes
  – *KMT2A* rearranged (t[4;11] or others)
  – t(v;14q23)/IgH
  – t(9;22)(q34;q11.2): *BCR-ABL1* (defined as high risk in the pre-TKI era)
  – Complex karyotype (≥5 chromosomal abnormalities)
  – Ph-like ALL
  – Intrachromosomal amplification of chromosome 21 (iAMP21)

**BCR-ABL1- Like ALL**

- 10% –30% cases B-lymphoblastic leukemia
  - Associated with poor prognosis
  - Responsive to TKIs
- **IKZF1** alterations
  - IKAROS for lymphoid lineage development
- **CRLF2** rearrangements
  - Receptor for thymic stromal lymphopoietin
- JAK/STAT pathway
- Other alterations
  - **ABL1, ABL2, EPOR, JAK2, IL7R, PDGFRβ, EBF1, FLT2, NTRK3** and **SH2B3**
Actionable Genetic Lesions in Philadelphia Chromosome–like (Ph-like) Precursor B-Cell Acute Lymphoblastic Leukemia (ALL)

A

Children (1–15 years of age)

Adolescents (16–20 years of age)

Young Adults (21–39 years of age)

B

Kinase | Inhibitor
--- | ---
JAK2 | Ruxolitinib
EPOR | CRLF2
ABL1 | Dasatinib
ABL2 | CSF1R
PDGFRB | Crizotinib
NTRK3 |
Two methods of MRD detection

1) Flow cytometry
   • Looks for ALL-specific immunophenotype or abnormal antigen expression

2) PCR
   • Looks for clonal rearrangement of immunoglobulin and T-cell receptor genes unique to the leukemic clone

RISK STRATIFICATION AND PROGNOSTIC FACTORS
## Adult ALL

### Risk Categories

<table>
<thead>
<tr>
<th>Prognostic factors</th>
<th>Standard Risk</th>
<th>Adverse Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>≤ 35 years old</td>
<td>&gt;60 years old</td>
</tr>
<tr>
<td>WBC at diagnosis</td>
<td>&lt;30K</td>
<td>&gt;100K</td>
</tr>
<tr>
<td>Immunophenotype</td>
<td>Precursor B-cell</td>
<td>Early/mature T-cell</td>
</tr>
<tr>
<td>Cytogenetics</td>
<td>---</td>
<td>t(9;22)/BCR-ABL1, t(4;11), Hypodiploid &lt;44, t(1;19) Complex (≥ 3 abnormalities)</td>
</tr>
<tr>
<td>Mutations</td>
<td>---</td>
<td>IKZF1</td>
</tr>
<tr>
<td>Minimal residual disease after induction</td>
<td>&lt;0.01%</td>
<td>≥ 1%</td>
</tr>
<tr>
<td>Time to CR1</td>
<td>≤ 4 weeks</td>
<td>&gt; 4 weeks</td>
</tr>
<tr>
<td>Cycles to obtain CR</td>
<td>1 cycle</td>
<td>&gt; 1 cycle</td>
</tr>
</tbody>
</table>
Overall Survival by Risk Class

OS

Cumulative Survival

Months

SR (n = 96)  
HR (n = 91)  
VHR (n = 88)

Standard risk
High risk
Very high risk

P = .0005

Disease-free Survival According to MRD Status

DFS

MRD$^{\text{neg}}$ (n = 58)

MRD$^{u/k}$ (n = 30)

MRD$^{\text{pos}}$ (n = 54)

$P = .001$

Factors Affecting Treatment Decisions

• Comorbidities
  – Hepatitis
  – High bilirubin
  – Neuropathy
  – Congestive heart failure

• Age

• BCR-ABL

• Time point and cutoff for minimal residual disease (MRD) will be dependent on the induction regimen used
PRINCIPLES IN ADULT ALL THERAPY: FRONT-LINE THERAPY
Principles of ALL Therapy

**Induction**
- Vincristine/Pred
- Anthracyclines
- Asparaginase
- Cyclophosphamide
- Cytarabine

**Consolidation Intensification**
- HD Cytarabine
- HDMTX
- Etoposide/teniposide
- Allo/auto SCT

**Maintenance**
- 6-mercaptopurine
- Methotrexate
- Vincristine
- Steroids

**CNS prophylaxis:** XRT, IT chemo

Pharmacological Considerations

- **Vinca alkaloids**
  - Vincristine
  - Liposomal vincristine

- **Anthracyclines**
  - Doxorubicin
  - Daunorubicin

- **Tyrosine kinase inhibitors**
  - Imatinib
  - Dasatinib
  - Nilotinib
  - Ponatinib

- **Antimetabolites**
  - Cytarabine
  - Mercaptopurine

- **Enzyme**
  - Asparaginase

- **Corticosteroids**
  - Dexamethasone
  - Prednisone

- **Monoclonal antibody**
  - Rituximab

- **Alkylation agents**
  - Cyclophosphamide
Methotrexate

• Mechanism:
  – Methotrexate binds to dihydrofolate reductase which results in the inhibition of reduced folates and thymidylate synthetase. Purine and thymidylic acid formation is inhibited, interfering with DNA synthesis.

• Metabolism:
  – Methotrexate is metabolized via numerous routes, which include hepatic oxidation, intracellular glutamation, and intestinal flora metabolism (oral administration only)

• Toxicities:
  – Myelosuppression
  – Neurotoxicity
  – Nephrotoxicity
  – Hepatotoxicity
  – Dermatological reactions
  – Gastrointestinal (nausea/vomiting, anorexia, diarrhea, stomatitis)

Methotrexate

- High-dose methotrexate (≥1,000 mg/m²) is associated with a number of toxicities including acute nephrotoxicity, hepatotoxicity, and neurotoxicity.

- To reduce the toxicity of high-dose methotrexate, efforts should be made to expedite the clearance of the drug:
  - Hydration should be administered to maintain a urine output >100 mL/hour.
  - Urine alkalization reduces the formation of methotrexate crystal in the renal tubules:
    - Hydration with D5W + sodium bicarbonate, oral sodium bicarbonate, acetazolamide.
  - Leucovorin should be administered until methotrexate clearance:
    - Dosing should start at 15-25 mg orally every 6 hours, with doses greater than 25 mg given as IV.
  - Screen for drug-drug interactions:
    - Sulfa analogs, penicillins, tetracyclines, NSAIDs, salicylates, PPIs.
Anthracyclines

- **Agents:**
  - Daunorubicin, doxorubicin

- **Mechanism:**
  - Anthracyclines to inhibit DNA replication and induce DNA strand breakage through several mechanisms including intercalation of DNA strands, inhibition of DNA polymerase, and topoisomerase II inhibition

- **Metabolism:**
  - Hepatically metabolized to active and inactive compounds

- **Toxicities:**
  - Myelosuppression
  - Gastrointestinal
  - Extravasation
  - Cardiotoxicity
Anthracyclines

- All patients should have an echocardiogram prior to anthracycline administration
  - Caution in patients with LVEF ≤45% or those with ≥10-15% drop from baseline

- Several cardiotoxicity prevention/treatment strategies have been studied, including:
  - Continuous infusion, extended infusion, dose fractionation
  - ACE-I and ARB administration
  - Dexrazoxane administration

<table>
<thead>
<tr>
<th>Drug</th>
<th>Maximum Lifetime Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daunorubicin</td>
<td>600 mg/m²</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>450 mg/m²</td>
</tr>
<tr>
<td>Epirubicin</td>
<td>900 mg/m²</td>
</tr>
<tr>
<td>Idarubicin</td>
<td>150 mg/m²</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>160 mg/m²</td>
</tr>
</tbody>
</table>

Anthracyclines

• Extravasation can occur with any anthracycline agent
  – Risk is reduced with shorter infusions or IV push
    • Ensure appropriate line and access prior to administration
  – Treatment:
    • Cold compresses should be applied
    • Dexrazoxane may be used when indicated

• Patients should be advised that their urine may turn red or dark yellow
  – This is a common side effect that continues for 1 – 2 days following administration
Cytarabine

• Mechanism:
  – Cytarabine is a pyrimidine analog that is incorporated into DNA chains, as well as inhibition of DNA polymerase, resulting in decreased DNA synthesis and repair

• Metabolism:
  – Metabolized primarily through hepatic pathways, with deoxycytidine kinase and other nucleotide kinases converting cytarabine to aracytidine triphosphate (active) and uracil arabinoside (inactive)

• Toxicities:
  • Neurotoxicity
  • Gastrointestinal toxicity
  • Hand-foot syndrome
  • Corneal toxicity
  • Hepatic toxicity
Cytarabine

- High dose cytarabine ($\geq 1,000 \text{ mg/m}^2$) is associated with a number of toxicities that require unique prophylaxis and monitoring
  - Conjunctivitis
    - High cytarabine concentrations in the aqueous humor can result in conjunctivitis
    - Patients should receive prophylaxis with dexamethasone 0.1% eye drops
      - Administer as two drops in each eye every 6 hours, starting 24 hours prior to cytarabine infusion and continued until 48 hours after last cytarabine dose
  - Neurotoxicity
    - High-dose cytarabine readily crosses the blood-brain barrier, and can result in cerebellar toxicity which presents as difficulty with speech, confusion, tremors, instability, and seizures
    - Risk factors for the development of cerebellar toxicity include: age $>50$ years, renal impairment, and higher cytarabine doses
    - Patients should be assessed for cerebellar toxicity prior to every dose
Vincristine

• Mechanism:
  – Vincristine binds to tubulin and inhibits microtubule formation, arresting the cell in the M and S phases by inhibiting mitotic spindle formation

• Metabolism:
  – Metabolized hepatically via cytochrome P450 enzymes, specifically CYP450 3A4

• Toxicities:
  – Extravasation
  – Gastrointestinal (constipation, paralytic ileus, intestinal perforation)
  – Neuropathy
  – Alopecia
  – Loss of appetite/weight loss

Vincristine

- Neurological toxicities are a common occurrence with vinca-alkaloid therapy
  - Neurotoxicity is dose-dependent and dose-limiting with vincristine
  - Presents as paresthesia, loss of deep tendon reflex, peripheral neuropathy, constipation, paralytic ileus, and urinary retention
    - All patients should be administered sufficient bowel regimens
    - Doses should generally be dosed at 2 mg, depending on protocols
    - Doses should generally be held for severe peripheral neuropathies, severe constipation, or ileus
    - Doses should never be administered in an IV syringe to reduce confusion regarding administration route (NEVER given intrathecally)

- All patients should be screened for drug-drug interactions prior to dosing
  - All moderate/strong CYP450 3A4 inhibitors should be held during administration
CNS Prophylaxis in Adult ALL

- All ALL treatment regimens include CNS prophylaxis
- Regimens without cranial irradiation effective
- High-dose systemic therapy for low-risk disease
- Intrathecal MTX alone or alternating with ara-C effective
- Early IT therapy + high-dose systemic therapy effective for high-risk disease
- Risk-oriented approach optimal
## ALL Therapy “Personalized Therapy”

<table>
<thead>
<tr>
<th>Entity</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burkitt</td>
<td>HCVAD-R x 8; ITx16; Rituximab+brief high-intensity chemo with filgrastim</td>
</tr>
<tr>
<td>Ph-positive ALL</td>
<td>HCVAD + TKI; TKI maintenance; allo SCT in CR1</td>
</tr>
<tr>
<td>T-ALL</td>
<td>HD CTX, HD ara-C, Asp; nelarabine?</td>
</tr>
<tr>
<td>CD20 – positive ALL</td>
<td>ALL chemo Rx+ rituximab</td>
</tr>
<tr>
<td>AYA</td>
<td>Pediatric-inspired therapy; HCVAD-R</td>
</tr>
<tr>
<td>MRD by FCM</td>
<td>Prognosis; need for allo SCT in CR1</td>
</tr>
</tbody>
</table>

NCCN Guidelines. Acute Lymphoblastic Leukemia. V1.2018
Adult ALL
No Clear Standard of Care

• Multiple chemotherapy regimens and no comparable trials
  – NCCN guidelines: clinical trial or pick your favorite

• Very wide age range
  – Younger Adults 40-60/65yrs.
  – Older adults 60/64+

• Uncertainty about the role of alloHSCT

• Relapse/ refractory – ??? (bridge to alloHSCT)
Adult Ph- ALL
NCCN Guidelines

< 65 years
No substantial comorbidities

Clinical trial or Multiagent chemotherapy

CR

Blinatumomab (B-ALL) or Consider allogeneic HSCT (MRD+)

Allogeneic HSCT

Maintenance

No CR

Continue multiagent chemotherapy or Consider allogeneic HSCT (MRD-)

Chemotherapy

Maintenance

≥ 65 years
-or-
substantial comorbidities

Clinical trial or Multiagent chemotherapy or Corticosteroids

CR

Relapsed/refractory regimen

≥ 65 years
-or-
substantial comorbidities

Clinical trial or Multiagent chemotherapy or Corticosteroids

No CR

Relapsed/refractory regimen

## Comparison of Standard Adult Ph- ALL Regimens

### Table 3. Acute Lymphoblastic Leukemia Induction Regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Induction</th>
<th>Consolidation</th>
<th>Maintenance</th>
<th>CR Rate, %</th>
<th>5-Year DFS Rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>LALA-94; Thomas &amp; Fiere 2006</td>
<td>P, V, C, D, or Ida</td>
<td>Ara-C, MTZ, or C, Ara-C, 6-MP based on risk</td>
<td>HSCT or MTX/6-MP or additional chemotherapy based on risk</td>
<td>84</td>
<td>30</td>
</tr>
<tr>
<td>Hyper-CVAD; Kantarjan 2004</td>
<td>Hyper C, V, A, and D alternating with MD MTX and Ara-C × 8 cycles</td>
<td>See induction</td>
<td>Allo HSCT or 6-MP, V, MTX, P</td>
<td>92</td>
<td>38</td>
</tr>
<tr>
<td>UCSF 8707; Linker 2002</td>
<td>P, V, D, and L-Asp</td>
<td>V, P, D, A, Ara-C, VM-26, MTX</td>
<td>6-MP, MTX</td>
<td>93</td>
<td>52</td>
</tr>
<tr>
<td>CALGB 8811; Larson 1995</td>
<td>P, V, C, D, L-Asp</td>
<td>C, subq Ara-C, 6-MP, V, L-Asp</td>
<td>6-MP, MTX</td>
<td>85</td>
<td>39 (Ages 30-59 y); 69% (aged &lt;30 y)</td>
</tr>
</tbody>
</table>

Faderl et al, Cancer 2010.
Remission Duration and Overall Survival
CD20 pos. Standard Risk < 55 yrs

GMALL 07/2003

Remission Duration

Overall Survival

+ Rituximab: 80% (N=130)
- Rituximab: 47% (N=53)

+ Rituximab: 71% (N=128)
- Rituximab: 51% (N=56)

Hoelzer. 2010.
ASH Plenary 2015

• Addition of Rituximab Improves the Outcome of Adult Patients with CD20-Positive, Ph-Negative, B-Cell Precursor Acute Lymphoblastic Leukemia (BCP-ALL): Results of the Randomized Graall-R 2005 Study. Maury et al.
Role for Allogeneic Stem Cell Transplantation in ALL

- Myeloablative SCT in young pts <35 yo
- Reduced intensity SCT in older pts > 35 yo
- High risk disease determined by
  - Poor prognosis cytogenetics (Ph+, MLL, complex karyotype)
  - High WBC at diagnosis (>100K)
  - Central nervous system disease
  - Delayed CR achievement with induction
  - Disease refractory to induction
  - Any relapsed disease
  - MRD positive disease after induction chemotherapy
## Allogeneic Stem Cell Transplantation

**MRC/ECOG UKALLXII/E2993 Trial**

**Ph- Negative ALL**

<table>
<thead>
<tr>
<th></th>
<th>Overall survival</th>
<th>Relapse</th>
<th>Non relapse death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Donor</td>
<td>No donor</td>
<td>Donor</td>
</tr>
<tr>
<td><strong>High risk</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donor</td>
<td>41%</td>
<td>35%</td>
<td>37%</td>
</tr>
<tr>
<td>No donor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Standard risk</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donor</td>
<td>62%</td>
<td>52%</td>
<td>24%</td>
</tr>
<tr>
<td>No donor</td>
<td></td>
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<tr>
<td>No donor</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

High risk any of:
- Age $\geq$ 35 years
- WBC $> 30,000/\mu L$ (B Lineage)
- WBC $> 100,000/\mu L$ (T Lineage)
- Time to CR $> 4$ weeks

*Goldstone Blood. 2008;111:1827.*
AYA Ph- ALL
NCCN Guidelines

AYA Ph- ALL (15-39 years)

Clinical trial or Pediatric-inspired regimens or multiagent chemotherapy

CR

Blinatumomab (B-ALL) or Consider allogeneic HSCT (MRD+)

Continue multiagent chemotherapy or Consider allogeneic HSCT (MRD-)

Less than CR

Relapsed/refractory regimen

Maintenance

Allogeneic HSCT

Adolescents & Young Adults with ALL

<table>
<thead>
<tr>
<th>Country</th>
<th>Regimen</th>
<th>Age</th>
<th>No.</th>
<th>%CR</th>
<th>% 5-yr EFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>U.S.</td>
<td>CCG CALGB</td>
<td>16–21</td>
<td>196</td>
<td>96</td>
<td>64</td>
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<tr>
<td></td>
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<td></td>
<td>103</td>
<td>93</td>
<td>38</td>
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<tr>
<td>France</td>
<td>FRALLE 93 LALA94</td>
<td>15–20</td>
<td>77</td>
<td>94</td>
<td>67</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>100</td>
<td>83</td>
<td>41</td>
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<tr>
<td>Holland</td>
<td>DGOG HVON</td>
<td>15–18</td>
<td>47</td>
<td>98</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>44</td>
<td>91</td>
<td>34</td>
</tr>
<tr>
<td>UK</td>
<td>ALL97 UKALLXII</td>
<td>15–17</td>
<td>61</td>
<td>98</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>67</td>
<td>94</td>
<td>49</td>
</tr>
<tr>
<td>Italy</td>
<td>AIEOP Gimema</td>
<td>14–18</td>
<td>150</td>
<td>94</td>
<td>80*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>95</td>
<td>89</td>
<td>71*</td>
</tr>
</tbody>
</table>

*2-yr event-free survival (EFS)

Comparison of EFS and OS
CALGB or CCG

EFS
Peds at 7 yrs: 63%
Adult at 7 yrs: 34%

OS
Peds at 7 yrs: 67%
Adult at 7 yrs: 46%

Why Do AYA Have a Better Outcome on Pediatric Protocols?

• Patients?

• Treatment team?

• Clinical trials?

• Treatment?
# Childhood vs Adult ALL: Disease Biology

<table>
<thead>
<tr>
<th></th>
<th>Children</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak incidence</td>
<td>5 years of age</td>
<td>50 years of age</td>
</tr>
<tr>
<td>% of all leukemias</td>
<td>80-85%</td>
<td>5%</td>
</tr>
<tr>
<td>T cell</td>
<td>10-15%</td>
<td>20-25%</td>
</tr>
<tr>
<td>Mature B cell</td>
<td>1-2%</td>
<td>3-5%</td>
</tr>
<tr>
<td>Ph positive ALL</td>
<td>3%</td>
<td>20-30%</td>
</tr>
</tbody>
</table>

## Dose Intensity of Induction
### Pediatric versus Adult ALL Regimens

<table>
<thead>
<tr>
<th>Drug</th>
<th>CCG</th>
<th>CALGB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone</td>
<td>1680 mg/m²</td>
<td>1260 mg/m²</td>
</tr>
<tr>
<td>Vincristine</td>
<td>8 mg</td>
<td>8 mg</td>
</tr>
<tr>
<td>L-asparaginase</td>
<td>54,000 U/m²</td>
<td>36,000 U/m²</td>
</tr>
<tr>
<td>Daunorubicin</td>
<td>100 mg/m²</td>
<td>135 mg/m²</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>—</td>
<td>1200 mg/m²</td>
</tr>
<tr>
<td>IT-methotrexate</td>
<td>Day 14</td>
<td>—</td>
</tr>
<tr>
<td>IT-cytarabine</td>
<td>Day 0</td>
<td>—</td>
</tr>
</tbody>
</table>

# Asparaginase Intensification

## Pediatric and Pediatric-”Inspired” Regimens

<table>
<thead>
<tr>
<th>Asparaginase Intensification</th>
<th>Upper age</th>
<th>OS @ 3-7 yrs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>True Pediatric</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DFCI</td>
<td>E. Coli</td>
<td>50</td>
</tr>
<tr>
<td>CALGB 10403</td>
<td>Pegasparagase 2,5000</td>
<td>39</td>
</tr>
<tr>
<td>Pediatric “Inspired”</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PETHEMA</td>
<td>E. Coli</td>
<td>30</td>
</tr>
<tr>
<td>GRAALL-2003</td>
<td>E. Coli</td>
<td>45/60</td>
</tr>
<tr>
<td>USC</td>
<td>Pegasparagase 2,000</td>
<td>57</td>
</tr>
<tr>
<td>Princess Margaret</td>
<td>E. Coli (retrospective)</td>
<td>60</td>
</tr>
<tr>
<td>Asparaginase Intensification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GMALL 7/03</td>
<td>PEG 500/1000 $\rightarrow$ 2,000</td>
<td>55</td>
</tr>
</tbody>
</table>

Asparaginase

• Mechanism:
  – Acts by hydrolyzing serum asparagine, inhibiting protein synthesis through amino acid depletion. Normal cells can synthesize their own asparagine, and therefore are spared the cytotoxic effects.

• Metabolism:
  – Undergoes systemic degradation

• Toxicity:
  – Myelosupression
  – Gastrointestinal
  – Hepatotoxicity
  – Pancreatitis
  – Fevers, malaise, fatigue, somnolence
  – Anaphylactic reactions

Erwinaze (asparaginase) [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals; March 2016.
Asparaginase

- Anaphylaxis
  - Various forms of asparaginase are available, including E. coli derived, Erwinia derived, and pegylated E. coli derived
  - Patients receiving asparaginase products are at an increased risk of anaphylactic reactions
  - Epinephrine, diphenhydramine, and hydrocortisone should be readily available during the drug administration, and patient should be observed for at least 1 hour following administration
  - Patients should generally not receive pre-medications prior to asparaginase administration, as it can mask a true hypersensitivity reaction

- Laboratory abnormalities
  - Patients receiving asparaginase products are at an increased risk of hepatotoxicity and pancreatitis, and pharmacists should closely review baseline labs prior to each administration

Augmented Berlin-Frankfurt-Münster Therapy in Adolescents and Young Adults With Acute Lymphoblastic Leukemia

- **Objective**: Compare ABFM and hyper-CVAD treatment in AYA patients

  - 85 patients (ages 12-40) with Ph-negative ALL received ABFM regimen
  - 71 historic AYA patients with ALL who received hyper-CVAD regimen

- Patient and disease characteristics, as well as MRD status, were analyzed for their impact on outcomes
Augmented Berlin-Frankfurt-Münster Therapy in Adolescents and Young Adults With Acute Lymphoblastic Leukemia
Augmented Berlin-Frankfurt-Münster Therapy in Adolescents and Young Adults With Acute Lymphoblastic Leukemia

- ABFM tolerable in AYA patients with ALL, but not associated with significant improvements in CRD or OS
- Shift to pediatric-based therapy for AYA patients with ALL (notably those ≥ 21 years) may need further assessment
- The toxicity profiles between the two groups differed significantly
- High WBC count at baseline remained an independent predictor of OS in multivariate analysis
Maintenance
NCCN Guidelines

• Ph+ ALL
  – Maintenance regimen + TKIs (imatinib, dasatinib, nilotinib or ponatinib)
  – Monthly vincristine/prednisone pulses (2-3 years)
  – Optional: weekly methotrexate + daily 6-MP as tolerated

• Ph- ALL
  • Weekly methotrexate + daily 6-MP + monthly vincristine/prednisone pulses (duration based on regimen)
PRINCIPLES OF ADULT ALL THERAPY: RELAPSED OR REFRACTORY ALL
Adult ALL

• Primary refractory (resistant) disease
  – Patients who fail to obtain a complete response (CR) with induction therapy
    • failure to eradicate all detectable leukemia cells (>5% blasts) from the bone marrow and blood with subsequent restoration of normal hematopoiesis

• Relapsed disease
  – Reappearance of blasts in the bone marrow or peripheral blood (>5%) after the attainment of a complete remission
Relapsed ALL Facts

• CR rates with initial induction are 85-90%
• The 5y-OS is now 40-50%
• However, 1/3rd of standard risk and 2/3rd of high risk ALL patients will eventually relapse
  – CR rates after 1st salvage are 31-44%
  – CR rates after 2nd salvage are 18-20%

Relapsed ALL

• **Ascertain the type of relapse**
  – Flow cytometry for immunophenotype: is it similar to the original disease or has there been a lineage switch?
  – Is this secondary leukemia, especially if late relapse?

• **Ascertain site of relapse**
  – Isolated BM relapse
  – CNS relapse
  – Isolated extramedullary (EM) relapse
  – Combination

• **Ascertain timing of relapse**
  – Early (<18m from diagnosis) or Late (>36m) relapse

NCCN Guidelines. Acute Lymphoblastic Leukemia. V1.2018
Outcomes Are Poor For Adults with Relapsed ALL Following Frontline Therapy (MRC UKALL/ECOG 2993)

- Median OS after relapse was 4.6 months; 1-year OS was 22%
- With nearly 4.5 years of follow-up, only 42/609 (7%) patients are alive and disease free; 5% of patients died during induction therapy
- Patient age, sex, time to relapse (below), site of relapse, and type of therapy in CR1 were associated with OS

![Graph showing survival rates over time](chart)

- At risk:
  - <6 months: 153
  - 6 m – 1 yr: 177
  - 1-2 yrs: 163
  - > 2 yrs: 116
- Percent (%)
- Time (years)

Relapsed/Refractory ALL

NCCN Guidelines

Ph+ ALL
Adult and AYA

Relapsed/refractory

Ph- ALL
Adult and AYA

ABL1 kinase domain mutation testing

Clinical Trial or
TKI ± Chemotherapy or
TKI ± Corticosteroids or
Blinatumomab (TKI intolerant/refractory) or
Inotuzumab ozogamicin (TKI intolerant/refractory) or
Tisagenlecleucel (patients < 26 y with refractory disease or ≥ 2 relapses)

Consider HSCT

Clinical trial or
Blinatumomab or
Inotuzumab ozogamicin or
Tisagenlecleucel (patients < 26 y with refractory disease or ≥ 2 relapses) or
Chemotherapy

Consider HSCT

Relapsed/Refractory ALL Treatment

- Treatment decisions affected by:
  - Initial treatment
  - Duration of complete response (CR)
  - Ph- and Ph+ status

- Treatment is challenging because these patients have very poor prognosis

- There are no established standards of care for conventional therapies, but many promising clinical trials

Relapsed/Refractory ALL Treatment Options

- Depends on duration of 1st complete remission
- Approved drugs: nelarabine (T-ALL), clofarabine, liposomal vincristine

<table>
<thead>
<tr>
<th>Regimen</th>
<th>%CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoclonals (inotuzumab ozogamicin, blinatumomab)</td>
<td>50-70%</td>
</tr>
<tr>
<td>Hyper-CVAD* (± augmented); augmented BFM</td>
<td>30-70%</td>
</tr>
<tr>
<td>FLAG-IDA*, BID FA ± asparaginase</td>
<td>30-40%</td>
</tr>
<tr>
<td>MOpAD*</td>
<td>30%</td>
</tr>
<tr>
<td>Tisagenlecleucel</td>
<td>83%</td>
</tr>
</tbody>
</table>

- If T-cell ALL: nelarabine
- If Ph+ ALL: add tyrosine kinase inhibitor

*Augmented hyper-CVAD*: hyperfractionated cyclophosphamide, intensified vincristine, doxorubicin, intensified dexamethasone, pegaspargase; alternating with high-dose methotrexate and cytarabine; **FLAG-IDA**: fludarabine, cytarabine, granulocyte colony-stimulating factor ± idarubicin; **MOpAD**: methotrexate, vincristine, pegaspargase, dexamethasone
Relapsed/Refractory Ph- ALL Treatment Options

• The ideal salvage regimen is not known; consider trials

• In general, therapy depends upon the timing of relapse:
  
  – If relapse ≥ 36 months from initial diagnosis, retreatment with the same induction regimen is a reasonable option
  
  – Primary resistant disease/relapse during induction, consolidation, or maintenance therapy: reinduction with novel therapies

• After CR2 with a salvage regimen, allogeneic HCT should be considered as soon as possible

Relapsed/Refractory Ph- ALL Treatment Options

• FDA-approved treatment options:
  
  – Clofarabine
    • A nucleoside analog
    • Approved for pediatric patients (ages 1 to 21 years) with relapsed/refractory ALL with treatment failure after at least 2 prior regimens; Limited data in adults

  – Vincristine sulfate liposome injection
    • Liposome encapsulation prolongs the exposure of active drug in the circulation and may allow for delivery of increased doses of vincristine without increasing toxicities

  Approved for the treatment of adults with Ph- ALL in 2nd or greater relapse or whose disease has progressed following two or more antileukemia therapies
Vincristine Sulfate Liposomes (VSL)

- Sphingoliposomal encapsulation of free vincristine
- Liposomal formulation optimized to provide extended tumor exposure time
- Efficacy of vincristine dose and time-dependent

VSLI in Relapsed ALL
Phase 2: Relapsed ALL Study (rALLy)

- **Schedule**
  - VSLI 2.25 mg/m² weekly x 4
  - No dose cap, highest dose received in study was 5.5 mg
  - Outpatient regimen

- **Patient Eligibility**
  - age ≥ 18, no Ph+ positivity or Burkitt
  - one CR duration ≥ 3 months
  - peripheral neuropathy ≤ Grade 2
  - PS 0-3
  - Second relapse or progression after two or more lines of therapy

VSLI in Relapsed ALL

Phase 2: Relapsed ALL Study (rALLy)

- Significant response rate of 35% in heavily pretreated patients with ALL
  - Poor PS 23%
  - 46% ≥ 4th line therapy
  - All had prior VCR

- CR/CRi rate of 20%
  - Compares to 4% CR with single agents @ MD Anderson

- No unexpected toxicities
  - Neurotoxicity primary side effect
  - 82% had prior neurotoxicity

Liposomal Vincristine

- The sphingosome encapsulation of vincristine allows for extended half-life, and enhanced cytotoxicity in cells

- Comparatively better-tolerated than conventional vincristine, and frequently allows clinicians to avoid dose-capping
  - Usual dosing is 2.25 mg/m² once every 7 days
    - Warning that doses are NOT interchangeable

- Similar overall toxicity profile:
  - Peripheral neuropathy
  - Constipation (ensure adequate bowel movement frequency)
  - Thrombocytopenia
  - Febrile neutropenia
  - Increase serum AST
Relapsed/Refractory Ph- ALL Treatment Options

—FDA Approved Antibody Therapy

—Blinatumomab

• Bispecific anti-CD3/CD19 monoclonal antibody
• High CR rates (69%; including rapid MRD-negative responses) in patients with relapsed/refractory B-precursor ALL
Relapsed/Refractory Ph+ ALL Treatment Options

• Mutation testing for the *ABL1* kinase domain is recommended
• TKIs (imatinib, dasatinib, nilotinib, bosutinib, or ponatinib) are options if not administered during initial induction
• For second- and third-generation TKIs, relevant *BCR-ABL1* mutations should be considered
Relapsed/Refractory Ph+ ALL Treatment Options

• Participation in a clinical trial is preferred

• In the absence of an appropriate clinical trial,
  – An alternative TKI (ie, different from the TKI used in induction therapy)
  – TKI combined with multiagent chemotherapy
  – TKI combined with corticosteroids

• Treatment options should be combined with allogeneic HCT in eligible patients if a donor is available
Relapsed/Refractory Ph+ ALL Treatment Options

- For patients who are refractory to TKIs, treatment options include
  - Blinatumomab
  - Inotuzumab ozogamicin

- Tisagenlecleucel is an option for patients up to age 25 years and with refractory disease or ≥2 relapses and failure of 2 TKIs.

- For patients that relapse after an initial allogeneic HCT, other options may include a second allogeneic HCT and/or donor lymphocyte infusion.

Blinatumomab (MT103) is a bispecific T-cell engager antibody designed to direct cytotoxic T-cells to CD19 expressing cancer cells.

Blinatumomab
ALL Salvage

• Open-label, multicenter, exploratory phase 2 study (Simon 2-stage)
• Primary endpoint: complete remission CR and CRi* rate within 2 cycles

Dose–finding Run-in Phase

Screening and Enrollment

Cohort 1
15 μg/m²/d

Cohort 2a
5-15 μg/m²/d

Cohort 2b
5-15-30 μg/m²/d

Safety Evaluation

Cohort 3
Extension Phase
5-15 μg/m²/d

• Blinatumomab continuous IV infusion, 4 weeks on/2 weeks off, for up to 5 cycles
• Consolidation after CR/CRi* within the first 2 cycles, 3 more cycles or allogeneic HSCT

Blinatumomab
ALL Salvage

Responses (n=36)

<table>
<thead>
<tr>
<th>CR/CRi, n (%)</th>
<th>25 (69)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>15 (42)</td>
</tr>
<tr>
<td>CRi</td>
<td>10 (28)</td>
</tr>
<tr>
<td>LFBM, n (%)</td>
<td>3 (8)</td>
</tr>
</tbody>
</table>

- 13 patients were transplanted after achieving CR/CRi

Blinatumomab
Refractory Minimal Residual Disease

- Most Common adverse events (any grade)
  - Pyrexia 100%
  - Immunoglobulins decrease 71%
  - Headache 43%

- Most Common adverse events ≥ 10% (Grade 3-4)
  - Lymphopenia 33.3%
  - Blood immunoglobulins 23.8%

- Discontinuation due to adverse event
  - One patient: grade 3 seizure after 2 days of Rx
  - One patient: syncope (convulsive) on d7 of 3rd cycle
  - Events were reversible

Topp et al. JCO. 2011;29:2493-2498.
BLAST: Blinatumomab in MRD+ Patients With ALL in Hematologic CR

- Open-label phase II study (N = 113)

**Cycle 1**
- Blinatumomab 15 μg/m²/day
- Primary endpoint assessment

**Patients ineligible for allo-HSCT**
- Up to 3 additional cycles

**Patients eligible for allo-HSCT**
- Up to 3 additional cycles
- Allo-HSCT when donor is available

- Blinatumomab was given by continuous IV infusion, 15 μg/m²/day x 28 days per cycle, for 4 wks on/2 wks off (one cycle) for a maximum of up to 4 cycles
  - All eligible patients received HSCT after the first cycle
  - Primary endpoint: complete MRD after 1 cycle (MRD- with no PCR amp)

2-yr follow-up for efficacy

100-day HSCT-related mortality assessment

Survival follow-up

Conclusions

• Blinatumomab induced complete MRD response in 80% of patients with ALL who achieved hematologic CR but had persistent or recurrent MRD
  – Complete MRD response rate after 1 cycle: 78%

• Treatment interruptions due to treatment-related AEs in 28% of pts

• Primarily neurologic events, influenzalike symptoms
  – Most neurologic AEs grade 2 or less

Blinatumomab approved 3/29/2018 to treat pts with ALL MRD+ with hematologic CR

Blinatumomab

• Dosing:
  – Patients 45 ≥ kg: 9 mcg CIVI on days 1-7, 28 mcg CIVI on days 8 to 28 of a 6-week cycle (2 weeks treatment free)
  – Pre-medicate with dexamethasone 20 mg one hour prior to the first dose of each cycle (and day 8 of cycle 1 only)
  – Bags may contain overfill, do NOT flush the infusion line when changing bags or finishing an infusion
  – Should be given via a dedicated line with no other medications

• Logistics:
  – May be prepared as a 24-hour, 48-hour infusion, or 7-day infusion (preservatives)
  – Pharmacists can help coordinate outpatient infusions and ensure appropriate dosage calculations

Blinatumomab

- Cytokine release syndrome (boxed warning)
  - Flu-like symptoms, fevers, chills, capillary leak, hypotension, pulmonary edema
  - Treatment: tocilizumab +/- corticosteroids

- Neurotoxicity (boxed warning)
  - Seizure, syncope, headache, tremor, confusion, slurred speech, balance disorders

- In the event of serious adverse events, treatment should be withheld

- Treatments held for ≥ 7 days should restart cycle
ANTI CD 22 ANTIBODY

INOTUZUMAB OZOGAMICIN
Inotuzumab Ozogamicin (IO) Mechanisms of Action

- Antibody-antigen complex rapidly internalized upon binding to CD22
- Calicheamicin released inside the tumor cell; more potent than other cytotoxic chemoRx agents
- Calicheamicin binds to DNA, inducing double-stranded DNA breaks
- Development of DNA breaks followed by apoptosis of tumor cell

Intotuzumab Ozogamacin vs. Standard Salvage Chemo in Relapsed B-ALL

- 326 patients randomized to receive intotuzumab vs standard induction chemo
- 218 included in intention to treat analysis
- CR IO 80.7% vs SCT 29.4% p<.001
- MRD negative in 78.4% vs 28.1% p<.001
- Major complication of IO, VOD in 11% vs 1% in SCT group

Kantarjian et al, NEJM 2016, 375 (8).
Intotuzumab Ozogamycin vs. Standard Therapy for Relapsepd CD22 Postive B-Cell ALL

IO in Relapsed/Refractory ALL

Dosing Schedule

**Monthly:**

Cycle 1
1.8mg/m²

Cycle 2
1.8mg/m²

D1      D8      D15      D22
D29      D8      D15      D22

**Weekly:**

Cycle 1
0.8mg/m²

0.5mg/m²  0.5mg/m²

Cycle 2
0.8mg/m²

0.5mg/m²  0.5mg/m²

D1      D8      D15      D22
D29      D8      D15      D22

up to 8 cycles

## IO

### Relapsed/Refractory ALL Response

<table>
<thead>
<tr>
<th>Response</th>
<th>Monthly, N=49</th>
<th>Weekly, N=40</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>CR</td>
<td>9 (18)</td>
<td>7 (18)</td>
</tr>
<tr>
<td>CRp</td>
<td>14 (29)</td>
<td>12 (30)</td>
</tr>
<tr>
<td>CRi (marrow CR)</td>
<td>5 (10)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Resistant</td>
<td>19 (39)</td>
<td>15 (38)</td>
</tr>
<tr>
<td>Death &lt; 4 wks</td>
<td>2 (4)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>OR</td>
<td>28 (57)</td>
<td>23 (58)</td>
</tr>
</tbody>
</table>

# IO in Relapsed/Refractory ALL Minimal Residual Disease

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Monthly, N=27</th>
<th>Weekly, N=20</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>8/9 (89)</td>
<td>6/7 (86)</td>
</tr>
<tr>
<td>CRp</td>
<td>9/14 (64)</td>
<td>7/10 (70)</td>
</tr>
<tr>
<td>CRi (marrow CR)</td>
<td>0/4 (0)</td>
<td>1/3 (33)</td>
</tr>
<tr>
<td>MRD negative</td>
<td>17/27 (63)</td>
<td>14/20 (70)</td>
</tr>
</tbody>
</table>

Inotuzumab Ozogamicin

• Toxicities:
  – Nausea, headache, fever, febrile neutropenia, cytopenias

• Hepatotoxicity (boxed warning)
  – Severe, life-threatening, and sometimes fatal sinusoidal obstructive syndrome has been seen
  – Greatest risk was in patients who received a hematopoietic stem cell transplant (HSCT) following inotuzumab ozogamicin treatment
  – Risk also high in patients getting 2 alkylating agents and a bilirubin higher than the upper limit of normal prior to HSCT
  – Median time to onset is 15 days after treatment, but may be delayed up to 57 days
    • Patients proceeding to HSCT should be limited to 2 cycles of inotuzumab ozogamicin
Chimeric Antigen Receptors MOA

- Chimeric antigen receptors\(^1\)
  - Genetically engineered receptors that combine anti-CD19 single chain variable fragment of an antibody with intracellular signaling domains of T cells
  - With the use of lentiviral-vector technology, CTL019 T cells express a CAR with CD3 zeta and 4-1BB (CD137) signaling domains\(^2\)

Chimeric Antigen Receptor–Modified T Cells

- Patient specific T-cells engineered to attack cells that express CD19
- In vivo expansion and robust antileukemic effects of CTL019 (formerly CART19) cells was previously demonstrated in 3 CLL patients
CAR T-cells (CTL019) Lead to Sustained Remissions in ALL Patients

30 pts with relapsed/refractory ALL with 2 years of follow-up

Characteristics
- Ages 5-60 yrs old
- 18 (60%) had prior alloHSCT
- 3 (10%) had refractory ALL
- 22 (73%) had ≥ 2 relapses

Responses
- 27 pts (90%) achieved CR one month after T-cell infusion
- 2 of 3 prior blinatumomab Rxed pts responded

Maude et al NEJM 2014; 371: 1507-1517.
# Biological Effects Associated with CAR T-cell Therapy

<table>
<thead>
<tr>
<th>Effects</th>
<th>Pts (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokine Release Syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>30 pts (100%)</td>
<td>Rx Tocilizumab (anti-IL-6R antibody) Needed for efficacy</td>
</tr>
<tr>
<td></td>
<td>Mild-mod: 22 pts (73%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe: 8 pts (27%)</td>
<td></td>
</tr>
<tr>
<td>Neurologic Events</td>
<td>13 (43%)</td>
<td>Self-limiting</td>
</tr>
<tr>
<td>Delayed Encephalopathy</td>
<td>5 (10%)</td>
<td>Self-limiting</td>
</tr>
<tr>
<td>Persistent B cell Aplasia</td>
<td>All responding pts</td>
<td>? Predicts risk of relapse</td>
</tr>
</tbody>
</table>

Maude et al NEJM 2014; 371: 1507-1517.
Novartis receives first ever FDA approval for a CAR-T cell therapy, Kymriah™ (tisagenlecleucel, CTL019), for children and young adults with B-cell ALL that is refractory or has relapsed at least twice

AUG 30, 2017

First-in-class therapy showed an 83% (52/63) overall remission rate in this patient population with limited treatment options and historically poor outcomes1,2

Novel approach to cancer treatment is the result of pioneering CAR-T cell therapy collaboration with University of Pennsylvania

Reproducible, flexible and validated manufacturing process builds on years of global clinical trial experience at our facility in New Jersey, US

Novartis also announces innovative collaboration with the US Centers for Medicare and Medicaid Services

Conclusions

• Jury still out on efficacy and safety of pediatric style regimens in AYA and Adult ALL patients
• Clinical trials underway to incorporate antibody therapy in initial induction ALL treatment
• Elderly AML trials show efficacy of incorporation of inotuzumab in mini-hyperCVAD patients and are under investigation as a standard of care
Conclusions

• New agents such as venetoclax and navitoclax also show efficacy in ALL pts and are under investigation in the relapsed/refractory setting

• CAR-T is expensive and difficult to offer to broad population of patients. Many challenges remain in cost of therapy and insurance coverage

• Cellectis “off the shelf” CD 19 CAR-T may show promise in making this therapy more available
Acute Lymphoblastic Leukemia (ALL)

The RN’s and NP’s Role in Managing the Side Effects of ALL Treatment

Lauren Ziskind, APN, NP-C, OCN
Nurse Practitioner
Adult Leukemia Program
The University of Chicago
Chicago, IL
The RN’s & NP’s Role in ALL Management

• Point of care, continuity of care

• Recognize type of ALL

• Side Effects/Toxicities

• Side Effect Management

• Education
B-Cell, T-Cell ALL

• Common induction chemotherapy regimens

• CNS Prophylaxis

• Subsequent cycles of consolidation chemotherapy

• Antimicrobial prophylaxis
Side Effects

- Constitutional
- Tumor lysis syndrome (TLS)
- Myelosuppression
- Cardio/pulmonary
- Gastrointestinal
- Endocrine
- Neurological
Side Effect/Toxicity Management

- Constitutional
- Tumor lysis syndrome (TLS)
- Myelosuppression
- Cardio/pulmonary
- Gastrointestinal
- Endocrine
- Neurological
Ph-Positive ALL Therapy

- Induction regimen: TKI + corticosteroids or TKI + chemotherapy
- Subsequent courses
Side Effects

- Constitutional
- Tumor lysis syndrome (TLS)
- Myelosuppression
- Cardio/pulmonary
- Gastrointestinal
- Endocrine
- Neurological
Side Effect/Toxicity Management

- Constitutional
- Tumor lysis syndrome (TLS)
- Myelosuppression
- Cardio/pulmonary
- Gastrointestinal
- Endocrine
- Neurological
Immunotherapy

• CD-3 and CD-19 Blinatumomab

• CD-22 Inotuzumab Ozogamicin
Side Effects/Toxicities

- Blinatumomab - CRS, neurotoxicity
- Inotuzumab Ozogamicin - Cytopenia, hepatotoxicity, VOD
Side Effects/Toxicity Management

- Blinatumomab - CRS, neurotoxicity
- Inotuzumab Ozogamicin - Cytopenia, hepatotoxicity, VOD
Treatment Outcomes

• Molecular testing and MRD based on treatment protocol or regimen

• Bone marrow biopsy (first pull of aspirate) or peripheral blood sampling

• Flow cytometry, molecular studies, NGS
Follow-Up Care

• The RN’s and NP’s Role

• Understanding the disease state

• Treatment regimen side effects

• Education
ACUTE LYMPHOBLASTIC LEUKEMIA: DIAGNOSIS, TREATMENT, AND SIDE EFFECTS MANAGEMENT

For You – Continuing Education

- Online & In-person free CME & CE courses – www.LLS.org/CE
- New Podcast series for healthcare professionals – www.LLS.org/CE

Listen as we speak with experts about diagnosis, treatment and survivorship to educate HCPs treating with blood cancer.

Clinical Trials and Research

- Learn more about clinical trials – www.LLS.org/ClinicalTrials
- Research: finding cures and bridging the gap between academic discovery & drug development – www.LLS.org/Research
ACUTE LYMPHOBLASTIC LEUKEMIA: DIAGNOSIS, TREATMENT, AND SIDE EFFECTS MANAGEMENT

Resources for Patients

- Additional support resources: www.LLS.org/support
- ALL Specific Resources – www.LLS.org/AML
- Free Information Booklets – www.LLS.org/Booklets
- Telephone/Web Education Programs – www.LLS.org/Programs
- Videos – www.LLS.org/Educationvideos
- Podcasts – www.LLS.org/LLS-podcast
ACUTE LYMPHOBLASTIC LEUKEMIA: DIAGNOSIS, TREATMENT, AND SIDE EFFECTS MANAGEMENT

Resources for Patients

Information Resource Specialists – www.LLS.org/IRC

Assist through treatment, financial & social challenges, and give accurate treatment and support information. HCPs can also order free materials to distribute to patients.

Clinical Trial Support Center – www.LLS.org/CTSC

Patients & caregivers work one-on-one with clinical trial specialists who are registered nurses with expertise in blood cancers. RNs will personally assist through the clinical trial process, providing an additional resource to your HCP team.

- Phone: (800) 955-4572, M-F, 9 am to 9 pm ET
- Email: infocenter@LLS.org
- Live chat: www.LLS.org/InformationSpecialists
ACUTE LYMPHOBLASTIC LEUKEMIA: DIAGNOSIS, TREATMENT, AND SIDE EFFECTS MANAGEMENT

- One-On-One Nutrition Consultations (PearlPoint)
- LLS Community (social media platform)
- Patti Robinson Kaufman First Connection Program (peer-to-peer)
Resources For Patients and Caregivers

- **Information Specialists** – Provide patients and caregivers with personalized assistance for managing treatment decisions, side effects, and dealing with financial and psychosocial challenges.
  - They can also send you free materials to distribute to your patients.

- **Clinical Trial Specialists** – RNs nurses navigate patients to find an appropriate clinical trial and sift through the information.

- **Expert Nutrition Consultations** – One-on-one patient consultations from a certified dietician.

These specialists can serve as an additional resource for your HCP team.

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- Live chat: [www.LLS.org/InformationSpecialists](http://www.LLS.org/InformationSpecialists)
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THANK YOU