Practical Management Pearls for Immunotherapy for the Treatment of Acute Leukemia

October 14, 2021
11:30 a.m. – 12:30 p.m. ET
Webinar faculty

Mark R. Litzow, MD – Mayo Clinic Cancer Center

Daniel A. Arber, MD – University of Chicago
Learning objectives

• Outline practical considerations for diagnostic testing and classification in acute leukemia and the implications for immunotherapy treatment planning
• Appropriately manage challenging and/or uncommon toxicities/irAEs associated with immunotherapy in acute leukemia
• Determine optimal sequencing of immunotherapies in all stages of acute leukemia treatment, including treatment for persistent or relapsed/refractory disease after initial therapy
Outline

• Guideline development
• Diagnostic testing in AL
  • New data in acute leukemia (new classifications)
• Toxicities associated with immunotherapy for acute leukemia
• Sequencing therapies in acute leukemia
The Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immunotherapy for the treatment of acute leukemia

Michael M Boyiadzis,1 Ivan Aksentijevich,2 Daniel A Arber,3 John Barrett,4 Renier J Brentjens,5 Jill Brufsky,1 Jorge Cortes,6 Marcos De Lima,7 Stephen J Forman,8 Ephraim J Fuchs,9 Linda J Fukas,10 Steven D Gore,11 Mark R Litzow,12 Jeffrey S Miller,13 John M Pagei,14 Edmund K Waller,15 Martin S Tallman6
Guideline development

• *The Institute of Medicine’s Standards for Developing Trustworthy Practice Guidelines* used to develop these recommendations

• Panel consisted of 17 participants, including medical oncologists, hematologists, a hematopathologist, a leukemia research nurse, and a patient advocate

• Recommendations come from literature evidence, supplemented with clinical experience of the panel members where necessary

• Consensus defined as $\geq 75\%$ agreement
Outline

• Guideline development

• Diagnostic testing in AL
  • New data in acute leukemia (new classifications)

• Toxicities associated with immunotherapy for acute leukemia

• Sequencing therapies in acute leukemia
Initial Diagnostic Workup of Acute Leukemia

Guideline From the College of American Pathologists and the American Society of Hematology

Daniel A. Arber, MD; Michael J. Borowitz, MD, PhD; Melissa Cesna, MD; Joan Ettell, MD; Kathryn Foucar, MD; Robert P. Hassettian, MD; J. Douglas Rizzo, MD; Karl Theil, MD; Sa A. Wang, MD; Anthony T. Smith, MLS; R. Bryan Rumble, MSc; Nicole L. Thomas, MPH. CT(ASCP)"; James W. Vardiman, MD

Context.—A complete diagnosis of acute leukemia requires knowledge of clinical information combined with morphologic evaluation, immunophenotyping and karyotype analysis, and often, molecular genetic testing. Although many aspects of the workup for acute leukemia are well accepted, few guidelines have addressed the different aspects of the diagnostic evaluation of samples from patients suspected to have acute leukemia.

Objective.—To develop a guideline for treating physicians and pathologists involved in the diagnostic and prognostic evaluation of new acute leukemia samples, including acute lymphoblastic leukemia, acute myeloid leukemia, and acute leukemias of ambiguous lineage.

Design.—The College of American Pathologists and the American Society of Hematology convened a panel of experts in hematology and hematopathology to develop recommendations. A systematic evidence review was conducted to address 6 key questions. Recommendations were derived from strength of evidence, feedback received during the public comment period, and expert panel consensus.

Results.—Twenty-seven guideline statements were established, which ranged from recommendations on what clinical and laboratory information should be available as part of the diagnostic and prognostic evaluation of acute leukemia samples to what types of testing should be performed routinely, with recommendations on where such testing should be performed and how the results should be reported.

Conclusion.—The guideline provides a framework for the multiple steps, including laboratory testing, in the evaluation of acute leukemia samples. Some aspects of the guideline, especially molecular genetic testing in acute leukemia, are rapidly changing with new supportive literature, which will require on-going updates for the guideline to remain relevant.


Initial Diagnostic Work-Up of Acute Leukemia: ASCO Clinical Practice Guideline Endorsement of the College of American Pathologists and American Society of Hematology Guideline

Valerie de Haas, PhD; Nosrat Ismaila, MD; Anjali Advani, MD; Daniel A. Arber, MD; Rutasha S. Dabney, MD; Dipit Patel-Donnelly, MD; Elizabeth Kitlas, LMSW; Rob Pietten, MD, PhD; Ching-Hon Pui, MD; Kendra Sweet, MD; and Ling Zhang, MD

PURPOSE The College of American Pathologists (CAP) and the American Society of Hematology (ASH) developed an evidence-based guideline on the initial diagnostic work-up of acute leukemia (AL). Because of the relevance of this topic to the ASCO membership, ASCO reviewed the guideline and applied a set of procedures and policies for endorsing clinical practice guidelines that have been developed by other professional organizations.

METHODS The CAP-ASH guideline on initial diagnostic work-up of AL was reviewed for developmental rigor by methodologists. Then, an ASCO Endorsement Expert Panel updated the literature search and reviewed the content and recommendations.

RESULTS The ASCO Expert Panel determined that the recommendations from the guideline, published in 2016, are clear, thorough, and based on the most relevant scientific evidence. ASCO fully endorsed the CAP-ASH guideline on initial diagnostic work-up of AL and included some discussion points according to clinical practice and updated literature.

CONCLUSION Twenty seven guideline statements were reviewed. Some discussion points were included to better assess CNS involvement in leukemia and to provide novel insights into molecular diagnosis and potential markers for risk stratification and target therapy. These discussions are categorized into four sections: (1) initial diagnosis focusing on basic diagnostics and determination of risk parameters, (2) molecular makers and minimal residual disease detection, (3) context of referral to another institution with expertise in the management of AL, and (4) reporting and record keeping for better outlining and follow-up discussion. Additional information is available at: www.asco.org/hematologic-malignancies-guidelines.
# CAP/ASH Guideline

<table>
<thead>
<tr>
<th>Expert Panel</th>
<th>Advisory Panel</th>
<th>CAP/ASH Staff</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daniel Arber, MD, Co-Chair, CAP</td>
<td>Frederick R. Appelbaum, MD</td>
<td>Nicole Thomas, MPH, CT(ASCP), CAP</td>
</tr>
<tr>
<td>James Vardiman, MD, Co-Chair, ASH</td>
<td>Clara Bloomfield, MD</td>
<td>Robert Plovnick, MD, ASH</td>
</tr>
<tr>
<td>Michael Borowitz, MD, PhD, ASH</td>
<td>William L. Carroll, MD</td>
<td>Robert Kunkle, ASH</td>
</tr>
<tr>
<td>Melissa Cessna, MD, CAP</td>
<td>Laura Housley, Patient Advocate</td>
<td>Kendall Alexander, MPH, ASH</td>
</tr>
<tr>
<td>Joan Etzell, MD, CAP</td>
<td>Jerry Hussong, MD</td>
<td>R. Bryan Rumble, MSc, methodologist</td>
</tr>
<tr>
<td>Kathryn Foucar, MD, ASH</td>
<td>Steven H. Kroft, MD, FASCP</td>
<td>Christina Lacchetti, MHSc, methodologist</td>
</tr>
<tr>
<td>Robert Hasserjian, MD, ASH</td>
<td>Michelle Le Beau, PhD</td>
<td>Tony Smith, MLS, CAP, Medical Librarian</td>
</tr>
<tr>
<td>J. Douglas Rizzo, MD, ASH</td>
<td>Martin S. Tallman, MD</td>
<td></td>
</tr>
<tr>
<td>Karl Theil, MD, CAP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sa Wang, MD, CAP</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
• Developed key questions
• Performed baseline survey of pathologists and hematologists (Arch Pathol Lab Med (2017) 141(8):1101-1106)
• Performed meta-analysis
• Public comment period
• Resulted in 27 guideline statements regarding the initial workup of acute leukemia (Arch Pathol Lab Med (2017) 141(10):1342–1393)
CAP/ASH Guideline

• Wide variety of recommendations, including
  • Immunophenotyping
  • Genetic and molecular genetic testing
  • Classification
Immunophenotyping

<table>
<thead>
<tr>
<th>Disease type</th>
<th>Marker</th>
<th>Agents for consideration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute lymphoblastic leukemia</td>
<td>CD19</td>
<td>Blinatumomab</td>
</tr>
<tr>
<td></td>
<td>CD19</td>
<td>Tisagenlecleucel (patients aged ≤25 years)</td>
</tr>
<tr>
<td></td>
<td>CD22</td>
<td>Inotuzumab ozogamicin</td>
</tr>
<tr>
<td></td>
<td>CD20</td>
<td>Rituximab</td>
</tr>
<tr>
<td>Acute myeloid leukemia</td>
<td>CD33</td>
<td>Gemtuzumab ozogamicin</td>
</tr>
</tbody>
</table>
Immunophenotyping – Baseline Survey

<table>
<thead>
<tr>
<th>Method</th>
<th>AML Response Percent</th>
<th>AML Response Count</th>
<th>ALL Response Percent</th>
<th>ALL Response Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphologic assessment</td>
<td>100.0%</td>
<td>234</td>
<td>99.1%</td>
<td>232</td>
</tr>
<tr>
<td>Flow cytometric analysis</td>
<td>99.1%</td>
<td>232</td>
<td>98.3%</td>
<td>229</td>
</tr>
<tr>
<td>Conventional cytogenetics (karyotype)</td>
<td>96.2%</td>
<td>225</td>
<td>96.6%</td>
<td>225</td>
</tr>
<tr>
<td>Molecular testing</td>
<td>78.2%</td>
<td>183</td>
<td>54.9%</td>
<td>128</td>
</tr>
</tbody>
</table>
## Genetic and Molecular Genetic Testing (Karyotype; Mutational studies)

<table>
<thead>
<tr>
<th>Method</th>
<th>AML Response Percent</th>
<th>AML Response Count</th>
<th>ALL Response Percent</th>
<th>ALL Response Count</th>
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<td>128</td>
</tr>
</tbody>
</table>
Genetic and Molecular Genetic Testing (Karyotype; Mutational studies)

Statement 15 Other ALL Testing

• B-ALL
  • Mutations panels that may include, but are not limited to
    • $PAX5$, $JAK1$, $JAK2$, and/or $IKZF1$ R
    • Expression of CRLF2 R

• T-ALL
  • Mutations panels that may include, but are not limited to
    • $NOTCH1$ and/or $FBXW7$ R

R, recommendation
Genetic and Molecular Genetic Testing (Karyotype; Mutational studies)

Statements 16, 17, 19 Adult and Pediatric AML

• FLT3-ITD SR – all types
• NPM1, CEBPA, RUNX1 SR – most types
• KIT SR (adult), R (peds) – Core binding factor AML
• Mutations panels that may include, but are not limited to
  • IDH1, IDH2, TET2, WT1, DNMT3A, and/or TP53 R
  • (ASXL1)

SR, strong recommendation; R, recommendation
# Diagnostic tests for ALL/AML

<table>
<thead>
<tr>
<th>ASCO/CAP/ASH recommended genetic tests (Adopted by SITC Guideline)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute lymphoblastic leukemia</strong></td>
</tr>
<tr>
<td><em>t</em>(9;22)(q34.1;q11.2); <em>BCR-ABL1</em></td>
</tr>
<tr>
<td><em>PAX5</em>; <em>CRLF2</em>; <em>JAK1</em>; <em>JAK2</em></td>
</tr>
<tr>
<td><em>CRLF2</em> overexpression (for B-ALL)</td>
</tr>
<tr>
<td><em>KMT2A</em> (MLL); <em>IKZF1</em> (for B-ALL)</td>
</tr>
<tr>
<td><em>NOTCH1</em> and/or <em>FBXW7</em> (for T-ALL)</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

Classification

**Current Recommendation**
- Use the current WHO classification diagnostic terminology

**Future Direction**
- 5th edition WHO classification in the works with IARC
  - Expected publication date of late 2022
  - Have changed their process to not incorporate a clinical advisory committee, to exclude prior editors and to refuse input from hematopathology societies
Classification

• Current Recommendation
  • Use the current WHO classification terminology diagnostic terminology

• Future Direction
  • 5th edition WHO classification in the works with IARC
    • Expected publication date of late 2022
    • Have changed their process to not incorporate a clinical advisory committee, to exclude prior editors and to refuse input from hematopathology societies
  • Separate International Consensus Classification of Myeloid and Lymphoid Neoplasms
    • Clinical Advisory Committee meeting held in September 2021
    • Expected publication in 2022
  • Update of CAP/ASH guidelines
    • Planned to occur after new classifications are published
Outline

• Diagnostic testing in AL
• Toxicities associated with immunotherapy for acute leukemia
• Sequencing therapies in acute leukemia
T cell engagers vs. CAR T therapy
# T cell engagers vs. CAR T therapy

<table>
<thead>
<tr>
<th>CAR T cells</th>
<th>T cell engagers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Structure</strong></td>
<td>Recombinant protein with two specificities: one for tumor antigen and one for T cell antigen (usually CD3)</td>
</tr>
<tr>
<td>Synthetic gene construct encoding an scFv against tumor antigen linked to activation/costimulatory motifs</td>
<td></td>
</tr>
<tr>
<td><strong>Effector cell types</strong></td>
<td></td>
</tr>
<tr>
<td>Engineered CD8+ and CD4+ T cells</td>
<td>Endogenous CD8+ and CD4+ T cells</td>
</tr>
<tr>
<td><strong>Immune synapse</strong></td>
<td></td>
</tr>
<tr>
<td>Atypical</td>
<td>Typical</td>
</tr>
<tr>
<td><strong>Serial killing</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Killing mechanisms</strong></td>
<td></td>
</tr>
<tr>
<td>Perforin and granzyme B, Fas-Fas-L, or TNF/TNF-R</td>
<td>Perforin and granzyme B</td>
</tr>
<tr>
<td><strong>Trafficking</strong></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>Passive</td>
</tr>
<tr>
<td><strong>Clinical applications</strong></td>
<td></td>
</tr>
<tr>
<td>Pre-treatment lymphodepletion followed by a single infusion</td>
<td>No lymphodepletion; repeat administration and continuous infusions</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td></td>
</tr>
<tr>
<td>Manufactured for each patient</td>
<td>“Off-the-shelf”</td>
</tr>
<tr>
<td><strong>Availability</strong></td>
<td></td>
</tr>
<tr>
<td>Limited to REMS program facilities</td>
<td>Most cancer centers</td>
</tr>
</tbody>
</table>
Common toxicities with tisagenlecleucel and blinatumomab

- Cytokine release syndrome
- Neurotoxicity
- B cell aplasia
Cytokine release syndrome

**Constitutional**
- Fever +/- rigors
- Malaise/fatigue
- Myalgias
- Arthralgias
- Headache

**Gastrointestinal**
- Nausea/vomiting
- Diarrhea
- Anorexia

**Skin**
- Rash

**Respiratory**
- Tachypnea
- Hypoxia
- Pulmonary edema

**Cardiovascular**
- Tachycardia
- Hypotension
- Capillary leak
- Widened pulse pressure
- Increased cardiac output (early)
- Potentially diminished cardiac output (late)

**Hepatic dysfunction**
- Transaminitis
- Hyperbilirubinemia

**Coagulation**
- Elevated D-dimer
- Hypofibrinogenemia +/- bleeding

**Renal function**
- Azotemia
## ASTCT CRS grading

<table>
<thead>
<tr>
<th>CRS parameter</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>&gt; 38°C</td>
<td>&gt; 38°C</td>
<td>&gt; 38°C</td>
<td>&gt; 38°C</td>
</tr>
<tr>
<td>Hypotension</td>
<td>None</td>
<td>Not requiring vasopressors</td>
<td>Requiring a vasopressor with or without vasopressin</td>
<td>Requiring multiple vasopressors (excluding vasopressin)</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>None</td>
<td>Requiring low-flow nasal cannula or blow-by</td>
<td>Requiring high-flow nasal cannula, face mask, non-rebreather mask or venturi mask</td>
<td>Requiring positive pressure (e.g. CPAP, BiPAP, intubation and mechanical ventilation)</td>
</tr>
</tbody>
</table>

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Monitoring for CRS

- Events requiring physician notification include:
  - Deviations from baseline systolic blood pressure
  - Heart rate >120 or <60 bpm
  - Arrhythmia
  - Respiratory rate >25 or <12 breaths/minute
  - Arterial oxygen saturation <92% on room air
  - Upward trend in blood creatinine or liver function tests
  - Tremors or jerky movements in extremities
  - Altered mental status
  - Temperature ≥ 38°C
Management of CRS with CAR T

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Tocilizumab-unresponsive</th>
<th>Tocilizumab + steroids-unresponsive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Close monitoring and supportive care</td>
<td>Consider tocilizumab</td>
<td>Tocilizumab</td>
<td>Tocilizumab + steroids</td>
<td>If CRS does not respond to 1 dose of tocilizumab, combine steroids + tocilizumab</td>
<td>Options include: Anakinra, siltuximab, HD methylprednisone</td>
</tr>
</tbody>
</table>

- For elderly patients or those with significant co-morbidities, tocilizumab should be considered earlier in the treatment course.
- If CRS does not improve after tocilizumab + steroids, infections should be considered and managed appropriately.
- If steroids are used, a rapid taper should be employed once symptoms begin to improve.
## Management of CRS with blinatumomab

<table>
<thead>
<tr>
<th>CRS grade</th>
<th>Patients weighing 45 kg or more</th>
<th>Patients weighing less than 45 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>• Interrupt blinatumomab.</td>
<td>• Interrupt blinatumomab.</td>
</tr>
<tr>
<td></td>
<td>• Administer dexamethasone 8 mg Q8h intravenously or orally for up to 3 days and taper thereafter over 4 days</td>
<td>• Administer dexamethasone 5 mg/m² Q8h intravenously or orally for up to 3 days and taper thereafter over 4 days</td>
</tr>
<tr>
<td></td>
<td>• When CRS is resolved, restart blinatumomab at 9 mcg/d, and escalate to 28 mcg/d after 7 days if CRS does not recur.</td>
<td>• When CRS is resolved, restart blinatumomab at 5 mcg/m²/d, and escalate to 15 mcg/m²/d after 7 days if CRS does not recur.</td>
</tr>
<tr>
<td>4</td>
<td>Discontinue blinatumomab permanently. Administer dexamethasone as instructed for Grade 3 CRS.</td>
<td></td>
</tr>
</tbody>
</table>
# ASTCT ICANS grading - adults

**ICANS:** Immune cell associated neurotoxicity syndrome

<table>
<thead>
<tr>
<th>Neurotoxicity domain</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICE score</td>
<td>7–9</td>
<td>3–6</td>
<td>0–2</td>
<td>0 (patient is unarousable)</td>
</tr>
<tr>
<td>Depressed level of consciousness</td>
<td>Awakens spontaneously</td>
<td>Awakens to voice</td>
<td>Awakens only to tactile stimulus</td>
<td>Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse; stupor or coma</td>
</tr>
<tr>
<td>Seizure</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>Any clinical seizure focal or generalized that resolves rapidly or non-convulsive seizures on EEG that resolve with intervention</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Life-threatening prolonged seizure (&gt;5 min), repetitive clinical or electrical seizures without return to baseline in between</td>
</tr>
<tr>
<td>Motor findings</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Deep focal motor weakness such as hemiparesis or paraparesis</td>
</tr>
<tr>
<td>Elevated ICP/cerebral edema</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>Focal/local edema on neuroimaging</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Diffuse cerebral edema on neuroimaging, decerebrate or decorticate posturing, cranial nerve VI palsy, papilledema, or Cushing’s triad</td>
</tr>
</tbody>
</table>

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### ASTCT ICANS grading - pediatric

<table>
<thead>
<tr>
<th>Neurotoxicity domain</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ICE score (age ≥12 years)</strong></td>
<td>7–9</td>
<td>3–6</td>
<td>0–2</td>
<td>0 (patient is unarousable)</td>
</tr>
<tr>
<td><strong>CAPD score (age &lt;12 years)</strong></td>
<td>1–8</td>
<td>1–8</td>
<td>≥9</td>
<td>Unable to perform CAPD</td>
</tr>
<tr>
<td><strong>Depressed level of consciousness</strong></td>
<td>Awakens spontaneously</td>
<td>Awakens to voice</td>
<td>Awakens only to tactile stimulus</td>
<td>Unarousable or requires vigorous or repetitive tactile stimuli to arouse</td>
</tr>
<tr>
<td><strong>Seizure (any age)</strong></td>
<td>N/A</td>
<td>N/A</td>
<td>Any clinical seizure focal or generalized that resolves rapidly or non-convulsive seizures on EEG that resolve with intervention</td>
<td>Life-threatening prolonged seizure (&gt;5 min), repetitive clinical or electrical seizures without return to baseline in between</td>
</tr>
<tr>
<td><strong>Motor weakness (any age)</strong></td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Deep focal motor weakness such as hemiparesis or paraparesis</td>
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<tr>
<td><strong>Elevated ICP/cerebral edema (any age)</strong></td>
<td>N/A</td>
<td>N/A</td>
<td>Focal/local edema on neuroimaging</td>
<td>Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing, cranial nerve VI palsy, papilledema, or Cushing’s triad</td>
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Immune effector cell-associated encephalopathy (ICE) score

- **Orientation**: Orientation to year, month, city, hospital: 4 points (1 point each)
- **Naming**: Name 3 objects (e.g., clock, pen, button): 3 points (1 point each)
- **Following commands**: (e.g., Show me 2 fingers or close your eyes and stick out your tongue): 1 point
- **Writing**: Ability to write a standard sentence (e.g., Our national bird is the bald eagle): 1 point
- **Attention**: Count backwards from 100 by 10: 1 point
- **Total scale**: 0-10
Monitoring for ICANS

• Altered mental status defines the onset of ICANS
• Work-up should include:
  • CRP
  • CBC
  • CMP
  • Fibrinogen
  • Prothrombin time test
  • PT/INR
• Head CT, EEG, and brain MRI may be considered
Management of ICANS with CAR T

• **4-1BB** CAR T agents: consider steroids at grade 2 ICANS; administer steroids for grades 3-4 ICANS

• Management of neurotoxicity **may take precedence** over low-grade CRS, due to possibility of tocilizumab worsening ICANS
  
  • For example: in the case of a patient with concomitant grade 1 CRS (fever) and grade 2 ICANS, steroids should be given. This does not apply to higher-grade CRS.

• If **steroids** are used, administer at least two doses and employ a fast taper

• **Levetiracetam** is recommended for management of seizures
Management of ICANS with blinatumomab

<table>
<thead>
<tr>
<th>ICANS grade</th>
<th>Patients weighing more than 45 kg</th>
<th>Patients weighing less than 45 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Withhold blinatumomab until no more than Grade 1 and for at least 3 days, then restart blinatumomab at 9 mcg/d. Escalate to 28 mcg/d after 7 days if symptoms do not recur. If ICANS occurred at 9 mcg/d or takes more than 7 days to resolve, discontinue permanently.</td>
<td>Withhold blinatumomab until no more than Grade 1 and for at least 3 days, then restart blinatumomab at 5 mcg/m²/d. Escalate to 15 mcg/m²/d after 7 days if symptoms do not recur. If ICANS occurred at 5 mcg/m²/d or takes more than 7 days to resolve, discontinue permanently.</td>
</tr>
<tr>
<td>4</td>
<td>Discontinue blinatumomab permanently.</td>
<td></td>
</tr>
</tbody>
</table>
B cell aplasia

• Due to current clinical agents targeting CD19, which is expressed by both normal and neoplastic B cells
• Short- or long-term
• May result in hypogammaglobulinemia
• Increased risk of infection – prophylaxis required
• Managed through administration of intravenous immunoglobulin
• Might indicate persistence of CAR T cells
Outline

• Diagnostic testing in AL
• Toxicities associated with immunotherapy for acute leukemia
• Sequencing therapies in acute leukemia
First Results of an Open Label Phase II Study to Evaluate the Efficacy and Safety of Inotuzumab Ozogamicin for Induction Therapy followed by a Conventional Chemotherapy Based Consolidation and Maintenance Therapy in Patients Aged 56 Years and Older with Acute Lymphoblastic Leukemia (INITIAL-1 trial)

Matthias Stelljes
University of Muenster / Germany
for the GMALL study group
INITIAL-1 Trial: Treatment Schedule

An open label phase II study to evaluate the efficacy and safety of Inotuzumab Ozogamicin for Induction Therapy followed by a conventional chemotherapy-based consolidation and maintenance therapy in patients aged 55 years and older with Acute Lymphoblastic leukemia (ALL)

Stelljes, ASH 2020
INITIAL-1 Trial: Results

**Evaluable for hematological remission, n=31**

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR / CRi after at least 1 induction</td>
<td>31 pts (100%)</td>
</tr>
<tr>
<td>Patients receiving 3 cycles inotuzumab</td>
<td>29 pts (94%)</td>
</tr>
<tr>
<td>Early deaths within the first 3 months</td>
<td>0</td>
</tr>
</tbody>
</table>

**Evaluable for MRD (by PCR), n=27**

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRD negative remission as best response</td>
<td>21 pts (78%)</td>
</tr>
<tr>
<td>Hematological / molecular relapse</td>
<td>2 / 1 pts</td>
</tr>
<tr>
<td>Allogeneic HSCT in remission / after relapse</td>
<td>3 / 1 pts</td>
</tr>
</tbody>
</table>

Stelljes, ASH 2020

Median FU: 249 (70-842) days
Hyper-CVAD + blinatumomab in newly-diagnosed B-ALL

Intensive phase

1 2 3 4

Blinatumomab phase

1 2 3 4

*After 2 cycles of chemo for MRD+, Ho-Tr, Ph-like, TP53, t(4;11)

4 wk 2 wk

Maintenance phase

1-3 4 5-7 8 9-11 12 13-15

Hyper-CVAD Ofatumumab or rituximab Blinatumomab
MTX + Ara-C IT MTX / Ara-C x 8 POMP

Short, ASH 2020
Hyper-CVAD + blinatumomab in newly-diagnosed B-ALL

<table>
<thead>
<tr>
<th>Response</th>
<th>n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR after induction</td>
<td>26/32 (81)</td>
</tr>
<tr>
<td>CR at any time</td>
<td>32/32 (100)</td>
</tr>
<tr>
<td>MRD negativity after induction</td>
<td>24/34 (71)</td>
</tr>
<tr>
<td>MRD negativity at anytime</td>
<td>33/34 (97)</td>
</tr>
<tr>
<td>30-day mortality</td>
<td>0</td>
</tr>
</tbody>
</table>

*6 pts in CR at start; 4 pts MRD negative at start

Fraction survival

Total Events 1yr OS 2yr OS

Hyper-CVAD + blinatumomab 38 6 85% 80%
Hyper-CVAD + blinatumomab in B-ALL: Historical comparison

![Graph showing survival rates and event counts for HCVAD + blinatumomab + ofatumumab/rituximab and HCVAD + ofatumumab treatments.]

- **HCVAD + blinatumomab + ofatumumab/rituximab**
  - Total Events: 38
  - 2yr. OS: 80%

- **HCVAD + ofatumumab**
  - Total Events: 69
  - 2yr. OS: 81%
E1910: Randomized Ph III Adult Frontline ALL

Study Design
- U.S. Intergroup study
- n=488 patients
- U.S., Canada, Israel
- 1:1 Randomization
- **Completed accrual October, 2019**

*MRD positive patients at time of randomization assigned to blinatumomab
# Approved immunotherapies for ALL

<table>
<thead>
<tr>
<th>Drug</th>
<th>Type</th>
<th>Mechanism</th>
<th>Approval</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blinatumomab</td>
<td>Bispecific T cell engager (BiTE)</td>
<td>CD3 x CD19 bispecific</td>
<td>March 2018</td>
<td>Adult and pediatric patients with B-cell precursor ALL in first or second complete remission with MRD ≥0.1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>July 2017 Relapsed or refractory B-cell precursor ALL in adults and children</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>December 2014</td>
<td>Relapsed or refractory B-cell precursor ALL</td>
</tr>
<tr>
<td>Inotuzumab ozogamicin</td>
<td>Anti-CD22 antibody–drug conjugate</td>
<td>Antibody-drug conjugate, CD22 antibody + calicheamicin</td>
<td>August 2017</td>
<td>Adults with relapsed or refractory B-cell precursor ALL</td>
</tr>
<tr>
<td>Tisagenlecleucel</td>
<td>CAR T cell therapy</td>
<td>CD19 CAR T cells</td>
<td>August 2017</td>
<td>Patients up to 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse</td>
</tr>
</tbody>
</table>
New CAR-T cell therapy just approved

- Brexucabtagene autoleucel (BA) approved on October 1 for adult patients with relapsed/refractory B cell precursor ALL
- Similar structure to axicabtagene ciloleucel, the approved CAR-T product for NHL (somewhat different manufacturing)
- Retroviral vector vs lentiviral vector for tisagenlecleucel (T)
- Signaling domain CD28z for BA, 41BBz for (T)
- In Zuma-3 phase 2 trial CR rate by 3 months 28/54 (52%); 97% MRD negative
- ≥grade 3 CRS and neurotoxicity 24 and 25%, respectively
Role of HCT and immunotherapy

• There is some concern of increased GVHD with combination of checkpoint inhibitors and HCT

• ELIANA and TOWER trials treated patients with prior allo-HCT, apparently safely

• In one study of CD19 CAR T treatment:
  • 17 patients with CR after CAR T proceeded to transplantation
  • 5 were alive with a complete remission
  • 6 had a relapse
  • 6 died from transplant-related toxic effects

Park, N Engl J Med 2018
Role of immunotherapy post-CAR T

• Patients may relapse after CAR T treatment due to lack or loss of target antigen, or other reasons.
• Potential treatment options include CAR T therapy targeting different antigens, blinatumomab, allo-HCT or salvage chemotherapy.
• Clinical trial enrollment should be strongly considered.
Thank you!
Case Studies in Immunotherapy for the Treatment of Acute Leukemia

November 15, 2021, 11:30 a.m. – 12:30 p.m. ET

Immunotherapy for the Treatment of Breast Cancer

October 29, 2021, 1 – 2 p.m. ET

Case Studies in Immunotherapy for the Treatment of Urothelial Cancer

November 5, 2021, 5:30 – 6:30 p.m. ET

Learn more and register at: https://www.sitcancer.org/CPG-webinars
Targets for Cancer Immunotherapy: A Deep Dive Seminar Series

Eight online seminars will address key questions in the field of cancer immunotherapy drug development

SEMINAR 6: THE 4-1BB PATHWAY – October 21, 2021, 3:30 - 5:30 p.m. ET

SEMINAR 7: T CELL FUNCTIONAL STATES –
November 18, 2021, 4:30 – 6:30 p.m. ET

Learn more and register at: https://www.sitcancer.org/education/deepdive
A Focus on Genitourinary Cancers

October 27, 2021, 12 – 4 p.m. ET

*CME-, CPE-, CNE-, MOC-certified*

Learn more and register at:
[https://www.sitcancer.org/education/aci](https://www.sitcancer.org/education/aci)
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Cancer Immunotherapy Clinical Practice Guidelines Mobile App

sitcancer.org/CPG-app
Thank you for attending the webinar!

Questions or comments: connectED@sitcancer.org