Objectives

- Review newest therapies in pediatric oncology
- Discuss the use of Blinatumomab in pediatric patients
- Review CAR T-Cell immunotherapy in pediatric patients
- Discuss the latest therapy approved for use in neuroblastoma

Disclosure

- I have no financial conflicts to disclose

Pediatric Leukemia

- Acute lymphoblastic leukemia (ALL) is the most common cancer in children
  - Accounts for ~30% of all cancers
  - 3000 new cases in US each year
    - (Birth – 21 years old)
      - ~ 80% are ALL and ~20% are AML
  - Incidence of 3.4 cases per 100,000
  - Most common between 2 and 5 years old
  - Boys > girls
  - Higher incidence in Caucasians and Hispanics vs. African American Children

Classification

- Over 85% of childhood ALL is B-cell ALL
  - Most commonly precursor-B cell ALL
  - 2% mature B-cell ALL
  - 15% T-cell ALL
  - Investigating use of nelarabine and/or high dose methotrexate

- Risk Criteria
  - Initial WBC count
  - Age
  - Cytogenetics
  - Immunologic subtype
Risk Stratification

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Age (years)</th>
<th>WBC (cells/mm³)</th>
<th>Cytogenetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>1-9.99</td>
<td>&lt;50,000</td>
<td>Hypodiploidy, trisomy 4 &amp; 10, ETHERS-10 (t(8;14), t(4;11), hypodiploidy, aminor), hyperdiploidy negative</td>
</tr>
<tr>
<td>Standard risk</td>
<td>1-9.99</td>
<td>&lt;50,000</td>
<td>normal</td>
</tr>
<tr>
<td>High risk</td>
<td>1-9.99 ≥10</td>
<td>≥50,000</td>
<td>Any</td>
</tr>
<tr>
<td><em>Very High Risk</em></td>
<td></td>
<td></td>
<td>CNS 3 (t(9;22), t(4;11), hypodiploidy, aminor), MIB = at end of induction</td>
</tr>
</tbody>
</table>

Outcomes

- ~85% overall 5-year event-free survival
  - 90 – 95 % in low- or standard-risk pre-B ALL with good response to induction chemotherapy
  - 75 – 85 % in high-risk with good early response
  - <75% in very high-risk (Ph+, hypodiploidy, CNS3) or slow response to chemo
- T-cell ALL survival lower at 70 – 75 %
- Infant ALL
  - Poor prognosis with 10-30% event-free survival

Relapsed/Recurrent ALL

- 20 - 25% relapse or fail initial treatment
  - Bone marrow, CNS, testes, lymph nodes
  - Aggressive re-induction, consolidation, ± SCT
  - 5 - 60% survival
- 60-75% of recurrences occur within first year after completion of therapy
- Rates decrease years 2 - 4 and are rare after 5 years post-treatment

Relapsed/Recurrent B-ALL

- Backbone Chemotherapy for relapse B-ALL

<table>
<thead>
<tr>
<th>Block 1</th>
<th>Block 2</th>
<th>Block 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRED 40 mg/m²/day, Days 1-29</td>
<td>CPM Days 1-5</td>
<td>HD ARAC Days 1, 2, 8, 9</td>
</tr>
<tr>
<td>VCR 1.5 mg/m², Days 1, 7, 15, 21</td>
<td>HDMTX Day 22 with lenalidomide</td>
<td>L-ASP Days 2, 9</td>
</tr>
<tr>
<td>PEG 2500 IU/m², Days 2, 9, 15, 23</td>
<td>ETOP Days 1-5</td>
<td>IT MTX or ITT Days 1, 22</td>
</tr>
<tr>
<td>DOXO 60 mg/m², on Day 1</td>
<td>ITT if CNS positive</td>
<td></td>
</tr>
</tbody>
</table>

Blinatumomab (Blincyto®)

- Novel agent for B-lineage malignancies
- Fusion protein
  - Bispecific T-cell engager (BiTE®) antibody, dual specificity for CD19 and CD3
  - Through CD3 binding, it recruits and engages T-cells for lysis of CD19 positive B-cells
- Accelerated approval from FDA for relapsed/refractory B-cell ALL
  - Phase II trial showed CR in 43% of patients after 2 cycles (Topp et al. Lancet Oncol. 2015a)

- AALL1121- Phase I/II trial
  - Early data shows efficacy in relapse patients
- AALL1331- Phase III trial, currently enrolling patients
  - Risk stratification after Block 1
  - Randomized to Block 2 or blinatumomab
  - Also may receive salvage blinatumomab if relapse/refractory on standard therapy
  - Dose of blinatumomab 15 µg/m²/24 hours x 4 weeks then one week off

Blinatumomab (Blincyto®).

Blinatumomab (Blincyto®)

- **Adverse reactions**
  - Cytokine release syndrome (CRS)
  - Chills, fever, flushing, bronchospasm, hypotension
  - Give dexamethasone prior to starting infusion
  - Neurologic
    - Headache, tremor, dizziness, confusion, memory impairment, aphasia, seizures
  - Stop infusion and give steroids. Should be reversible
  - Coagulopathy
  - Prolong activated PTT, fibrinogen decreased, INR increased
  - Hepatic abnormalities
  - ALT and AST increased, bilirubin increase, GGT increase

Chimeric antigen receptor (CAR) T-cell therapy

- **Adoptive cell therapy (ACT)**
- **Pediatrics trials in B-Cell ALL pediatric patients at NCI and CHOP**
- **Using CTL019, an antigen that targets CD19**
  - CD19 is a B-cell surface protein
  - Universal expression in B-cell ALL

CAR T-Cell Therapy

- **Preliminary results**
  - 90% CR in 30 adult and pediatric patients (CHOP Phase I)¹
  - Probability of persistence of CAR T-cells at 6 months being 68%
  - 88% CR in 16 adult patients with relapsed B-cell ALL at Memorial Sloan-Kettering²
  - Persistent of CAR T-cells of 1-3 months
  - 70% CR in 20 children and adults at NCI³
  - Average persistence is 68 days

CAR T-Cell Adverse Reactions

- **CRS- most common and potentially severe**
  - Potentially correlation to presence of CRS and response to CAR T-cells
  - Severity might correlate to tumor burden
  - Inflammatory response related to exponential T-cell proliferation and increased cytokines
    - Marked increases in IL-2, IL-6, IL-10 and interferon
    - Wide range of severity, from flu-like symptoms to multi-organ failure
  - Tocilizumab- IL-6 inhibitor
  - Used to treat CRS
  - Other IL-6 inhibitors might be effective
  - Steroids- controversial- maybe useful for 2-4 day burst

CAR T-Cell Therapy: The Process

- T-cells collected from patient
- T-cells re-engineered in laboratory to produce chimeric antigen receptor (CARs) on their surface (CTL019)
- Expand the CAR T-cells in the lab until there are millions
- Patient given chemotherapy preparatory regimen (cytosinephosphoramide-based) before infusion
- CAR T-cells infused into patient
- Hopefully, CAR T-cells guard against recurrence
Neuroblastoma

Incidence and Epidemiology
• Solid tumor that originates from primordial neural crest cells that normally give rise to adrenal medulla and sympathetic ganglia
• Most common extracranial solid tumor in children, accounting for 8–10% of childhood malignancies
  ▫ Accounts for 15% of childhood mortality
• 800 cases annually in the US
  ▫ Median age of diagnosis is 19 months and ~90% diagnosed by age 5
• Occurs more often in males than females (1.2:1)

Pathogenesis
• Exact cause is unknown
  ▫ Most common cytogenetic abnormalities are deletions or rearrangements of the short arm of chromosome 1 or chromosome 17
• N-MYC is an oncogene on chromosome 2
  ▫ ~25% of patients with neuroblastoma have N-MYC amplification
  ▫ Associated with advanced stage disease and poor prognosis

Pathophysiology
• Originates in adrenal medulla or paraspinal site in sympathetic nervous system
  ▫ Can present along a spectrum of differentiation from benign ganglioneuroma to ganglioneuroblastoma, or malignant neuroblastoma
• "Small blue round cell" neoplasm
  ▫ Differentiate from Ewings, NHL, PNET, rhabdomyosarcoma
  ▫ 65% are abdominal and 20% are thoracic

Signs and symptoms
• Thoracic/pelvic tumor
  ▫ Abdominal fullness/discomfort
  ▫ Bowel or bladder symptoms
  ▫ Hypertension (renal vasculature)
  ▫ Cord compression (emergency)
  ▫ Horner’s Syndrome
  ▫ Secretory diarrhea secondary to increased vasoactive intestinal peptide
• Orbital tumor
  ▫ Opopodochus—myosotis (Dancing eye syndrome)
  ▫ Proptosis or peri orbital ecchymoses
  ▫ Bone lesions
  ▫ Focal pain, limp, refusal to walk
  ▫ Skin nodules (infants)
  ▫ Nonspecific
  ▫ Fever, weight loss, generalized pain

Diagnosis and Staging
• Urine catecholamines (VMA and HVA) are elevated in 85–90% of patients
  ▫ Normal VMA < 8 μg/mL and HVA < 17 μg/mL
  ▫ VMA/HVA ratio also important
    ▫ Higher the ratio, the better the prognosis
• Lab Studies: CBC, liver and kidney function, coags, ferritin, LDH, neuron specific enolase, and urine catecholamines
• Diagnostic Imaging: CT of chest, abdomen, pelvis; MRI of head and spine (if indicated), MIBG scan (bone/soft tissue scan), ECHO, GFR
• Tissue studies: Bilateral bone marrow biopsies and aspirates and tissue from mass large enough for histopathology, N-MYC amplification, cytogenetics

**INSS Staging**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
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<tbody>
<tr>
<td>1</td>
<td>Local tumor with complete gross resection, with or without microscopic residual disease, ipsilateral lymph nodes negative</td>
</tr>
<tr>
<td>2A</td>
<td>Localized tumor with incomplete gross resection, with ipsilateral lymph nodes negative</td>
</tr>
<tr>
<td>2B</td>
<td>Localized tumor with or without incomplete resection, with ipsilateral lymph nodes positive for tumor. Contralateral lymph nodes negative</td>
</tr>
<tr>
<td>3</td>
<td>Unresectable unilateral tumor infiltrating across the midline, with or without regional lymph node involvement</td>
</tr>
<tr>
<td>4</td>
<td>Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin and/or other organs</td>
</tr>
<tr>
<td>4S</td>
<td>Localized primary tumor with dissemination limited to skin/liver and/or bone marrow (usually hyperdiploid and without N-MYC amplification). Limited to infants &lt;1 year of age</td>
</tr>
</tbody>
</table>

At time of diagnosis, 78% of children and 43% of infants have stage 3 or 4 disease.

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**High Risk Neuroblastoma**

Long-term survival is about 34% - 40% with High Risk Group

- INSS Stage 4 > 18 months of age
- INSS Stage 4 with N-MYC, regardless of age
- INSS Stage 4 between 12 – 18 months of age with unfavorable histology and/or diploid DNA content
- INSS Stage 3 with N-MYC amplification, regardless of age
- INSS Stage 3 with unfavorable histology, greater than 18 months of age
- INSS Stage 2 with N-MYC amplification
- INSS Stage 4S with N-MYC amplification

**Prognosis**

- 5 year survival for infants is 83%, children age 1 - 4 years is 55%, and children 5 years and older is 40%
- Two year survival in stage 3 or 4 is 10 - 30%

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**Dinutuximab (Unituxan®)**

- Anti-GD2 monoclonal antibody
- COG studies ANBL0032 and ANBL0931
- Use with granulocyte-macrophage colony-stimulating factor (GM-CSF) interleukin-2 (IL-2) and 13 cis-retinoic acid
- 4 doses of dinutuximab given per cycle for 5 cycles
- Alternating GM-CSF and IL-2 with each cycle
- 13 cis-retinoic acid given in between cycles

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**Dinutuximab**

<table>
<thead>
<tr>
<th>Chakravarty, K.</th>
<th>Randomized, Phase 3 Study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment:</strong></td>
<td>Adjuvance of ch14.18 with GM-CSF and cyclophosphamide/3 days of chemotherapy</td>
</tr>
<tr>
<td><strong>Dose:</strong></td>
<td>13 mg/m2/day for 4 consecutive days during each of five consecutive 4-week cycles</td>
</tr>
<tr>
<td><strong>Duration:</strong></td>
<td>4 weeks for each of the five cycles</td>
</tr>
<tr>
<td><strong>Adverse Effects:</strong></td>
<td></td>
</tr>
</tbody>
</table>

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**Treatment of High Risk Neuroblastoma**

- Patients receive 6 cycles of induction chemotherapy on ANBL0532
  - Cycle 1: Cyclophosphamide/Etoposide/Cisplatin
  - Cycle 2: Cyclophosphamide/Etoposide/Cisplatin
  - Cycle 3: Cyclophosphamide/Etoposide/Cisplatin
  - Cycle 4: Vincristine/Doxorubicin/Cyclophosphamide
  - Cycle 5: Cyclophosphamide/Etoposide/Cisplatin
  - Cycle 6: Vincristine/Doxorubicin/Cyclophosphamide
- Autologous stem cell transplant
  - Two transplants
    - Thiotepa and Cyclophosphamide
    - Carbopeptin, Etoposide, Melphalan
- Radiation

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www.childrensoncologygroup.org

Dinutuximab (Unituxan®)

- **Adverse Reactions**
  - Severe Infusion reactions
    - Hives, rash, fever, chills, rigors
    - Bronchospasm or angioedema
    - Patient should receive diphenhydramine prior to starting
    - Frequent vital sign checks during the 10 hour infusion and for at least 2 hours after


- **Neuropathy/Pain**
  - GD2 is also found on nerve cell
  - IV opioid PCA required during infusion and 2 hours after
  - Consider gabapentin
  - If severe pain, might require a lidocaine infusion


- **Hypotension**
  - Normal saline bolus given prior to infusion
  - Frequent blood pressure monitoring
  - Algorithm for treatment of hypotension
    - Bolus/PRBC/albumin
    - Decrease narcotic doses if possible
    - Potentially needs pressors


Questions?

References

- www.childrensoncologygroup.org
- www.nccn.org
- www.arsdc.org
- Pediatric Melanoma au GdM 2006
- Topp, H., goldsmit, R., stone a.,
- Dinutuximab package insert