Oncologic Emergencies in Children

Jihad N. Zahraa, MD
Pediatric Intensivist
King Fahad Medical City
Oncology in PICU

- **At the time of the diagnosis:**
  - Tumor bulk causing metabolic disturbances
  - Tumor bulk causing obstructive problems

- **After intensive chemotherapy:**
  - Metabolic complications
  - Infectious complications
Complications of oncologic diseases

- Tumor lysis syndrome
- Hyperleukocytosis
- Mediastinal masses/superior vena cava syndrome
- Spinal cord compression
- Septic shock
- Acute hypoxemic respiratory failure
- Outcome?
Tumor Lysis Syndrome
Tumor Lysis Syndrome

- Patients with rapidly growing tumors, bulky disease and chemo sensitive tumors

- Most common with B-cell leukemia (26.4%), Burkitt’s lymphoma (with LDH >= 500 U/l 14.9%), and T-cell leukemia/lymphoma

- Risk of rapid lysis of tumor cells and release of intracellular contents overwhelming kidney’s ability to excrete those products

Tumor Lysis Syndrome

- Can occur at presentation
- More common early after start of chemotherapy (within 12-24 hrs)

Risk of:
- Renal failure and
- Life-threatening electrolyte disturbances
Patients at high risk of TLS who could benefit by rasburicase

<table>
<thead>
<tr>
<th>Tumor factors</th>
<th>Patients factors</th>
<th>Biochemical factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>High tumor burden</td>
<td>Hyperleukocytosis</td>
<td>High uric acid levels</td>
</tr>
<tr>
<td>High tumor growth rate</td>
<td>Pre-existing renal impairment</td>
<td>High LDH levels</td>
</tr>
<tr>
<td>High sensitivity to chemotherapy, especially during early treatment phase</td>
<td>Dehydration</td>
<td>High phosphoreemia levels</td>
</tr>
<tr>
<td>Advanced stage of tumor</td>
<td>Poly-pharmacology</td>
<td>Low pH of urine</td>
</tr>
<tr>
<td>Kind of tumor (haematological malignancies more than solid tumors)</td>
<td></td>
<td>High creatinine levels</td>
</tr>
<tr>
<td>Lymphoma infiltration of kidney</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of monoclonal antibodies and targeted therapies</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cairo-Bishop definition of laboratory tumor lysis syndrome

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uric acid</td>
<td>≥476 μmol/L (8 mg/dL) or 25% increase from baseline</td>
</tr>
<tr>
<td>Potassium</td>
<td>≥6.0 mmol/L (6mEq/L) or 25% increase from baseline</td>
</tr>
<tr>
<td>Phosphorous</td>
<td>≥2.1 mmol/L (children) or ≥1.45 mmol/L (adults) or 25% increase from baseline</td>
</tr>
<tr>
<td>Calcium</td>
<td>≤1.75 mmol/L or 25% decrease from baseline</td>
</tr>
</tbody>
</table>

# Cairo-Bishop grading system for tumor lysis syndrome

<table>
<thead>
<tr>
<th></th>
<th>Grade 0*</th>
<th>Grade I</th>
<th>Grade II</th>
<th>Grade III</th>
<th>Grade IV</th>
<th>Grade V</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LTLS</strong></td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Creatinine</strong></td>
<td>1.5 x ULN</td>
<td>1.5 x ULN</td>
<td>&gt;1.5-3.0 x ULN</td>
<td>&gt;3.0-6.0 x ULN</td>
<td>&gt;6.0 UNL</td>
<td>Death§</td>
</tr>
<tr>
<td><strong>Cardiac arrhythmia</strong></td>
<td>None</td>
<td>Intervention not indicated</td>
<td>Non-urgent medical intervention indicated</td>
<td>Symptomatic and incompletely controlled medically or controlled with device (e.g. defibrillator)</td>
<td>Life-threatening (e.g. arrhythmia associated with CHF, hypotension, syncope, shock)</td>
<td>Death§</td>
</tr>
<tr>
<td><strong>Seizure</strong></td>
<td>None</td>
<td>---</td>
<td>---</td>
<td>One brief generalized seizure; seizure(s) well controlled by anti-convulsants or infrequent focal motor seizures not interfering with ADL</td>
<td>Seizure in which consciousness is altered; poorly controlled seizure disorder; with breakthrough generalized seizures despite medical intervention</td>
<td>Seizure of any kind which is prolonged, repetitive or difficult to control (e.g. status epilepticus, intractable epilepsy)</td>
</tr>
</tbody>
</table>

*No laboratory TLS; ‡Not directly or probably attributable to a therapeutic agent; §Attributive probably or definitely to CTLS. TLS=tumor lysis syndrome; LTLS=laboratory tumor lysis syndrome; ULN=upper limit of normal; CHF=congestive heart failure; ADL=activities of daily living; CTLS=clinical tumor lysis syndrome. © Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification (2004). Originally published in British Journal of Haematology, Blackwell Publishing Ltd. 127, 3-11.
Consequences of TLS

- Hyperkalemia → weakness, dysrhythmias
- Hyperphosphatemia → hypocalcemia, renal failure
- Hypocalcemia → tetany, seizures mental status changes
- Hyperuricemia → “uric acid nephropathy” oliguria, renal failure
Management

- **Monitoring:**
  - Serum creatinine, blood urea nitrogen
  - sodium, potassium, calcium, phosphorous
  - LDH and uric acid levels
  Before therapy and every 4-6 hours for the first 48-72 hours after the initiation of tumor therapy.

- **A baseline ECG**
- **Continuous cardiac monitoring** until the completion of treatment.

- Ideally, **intravenous hydration** 24-48 hours before the initiation of tumor therapy
“The best treatment is prevention”

- **Hydration**
  - Fluid intake = 2-3 L/m²/day enhances uric acid excretion, phosphate excretion
  - Goal of urine specific gravity ≤ 1.010

- **Urine alkalinization** - add NaHCO³ to IVF **not recommended** anymore
  - Hypoxanthine crystals in renal tubules
  - Alkalosis and Ca-PO₄ stones possible

Purine Catabolism Pathway

Purine Catabolism

↓

Xanthine/Hypoxanthine

Allopurinol → Xanthine Oxidase

Uric acid (low urinary excretion)

Urate oxidase

Allantoin (high urinary excretion)
Prevention

Decrease production of uric acid
- **Allopurinol inhibits xanthine oxidase**
  - 300 mg/m²/day divided tid P.O./I.V.
  - Dose reduction in renal insufficiency
  - Long time standard Rx
  - 24-48 hrs before chemo

Conversion of uric acid to more water soluble
- **Rasburicase (Recombinant urate oxidase)**
- Catalyzes conversion of uric acid to allantoin
- Allantoin more soluble, easily excreted by kidneys
- Urine alkalinization unnecessary if used
Recombinant Urate Oxidase

- Rasburicase is more effective than allopurinol in prevention and treatment of hyperuricemia
  - IV at doses up to 0.1-0.2 mg/kg daily 30 minutes infusion for 1-7 days
  - Contraindicated with G-6-PD deficiency

Dialysis for Tumor Lysis Syndrome

- **Indications:**
  - Oliguria,
  - Hyperkalemia
  - Azotemia
  - Hyperphosphatemia
    (correct only symptomatic hypocalcemia)
  - Refractory hyperuricemia

- **Hemodialysis or continuous venovenous hemofiltration with dialysis most effective**

Hyperleukocytosis
Hyperleukocytosis

5-20% of children with new Dx of leukemia have WBC count > 100,000/mm³

These patients at risk of severe complications from hyperviscosity of blood
Early complications in children with acute lymphoblastic leukemia presenting with hyperleukocytosis

Lowe EJ, et al. Department of Hematology-Oncology, St. Jude Children's Research Hospital, Memphis, Tennessee

Pediatr Blood Cancer. 2005 Jul

- 178 children, representing 8% of all children with ALL (2288), had an initial leukocyte count >200 x 10^9/L
- 67 (37.6%) patients had a leukocyte count >400 x 10^9/L.
- Sixteen patients (9%) had neurological complications
- Four patients (2%), all with initial leukocyte counts >400 x 10^9/L, suffered a CNS hemorrhage.
- Pulmonary leukostasis occurred in 11 patients (6%).
- The degree of hyperleukocytosis was significantly predictive of neurological (P=0.006) and respiratory (P=0.014) complications.
- The majority of complications occurred at presentation.
Hyperleukocytosis - Complications

- Blasts interact with endothelium to form aggregates, thrombi in microcirculation
- Most problems in CNS and pulmonary circulation
- Complications more common with AML than ALL (Myeloblasts and monoblasts larger, less deformable, “stickier”)

Pulmonary leukostasis

Pulmonary arteriole with leukostatic thrombus in patient with AML and hyperleukocytosis
Pulmonary leukostasis

- Symptoms:
  - Dyspnea
  - Tachypnea
  - Hypoxemia
  - Acidosis
  - Cor pulmonale

- CXR: diffuse interstitial infiltrates
CNS leukostasis
CNS leukostasis

- Headache, blurred vision, agitation, mental status changes, seizures, coma

- High risk of intracranial hemorrhage, especially with AML and thrombocytopenia
Therapy for hyperleukocytosis

- Decrease blood viscosity (directly related to morbidity)
  - Hydration
  - AVOID use of diuretics
  - AVOID PRBC transfusion (Hb goal < 10 gm/dL for viscosity)
- Transfuse platelets to keep > 20,000/mm³ and treat coagulopathy (common with AML) to decrease risk of intracranial hemorrhage
Therapy for hyperleukocytosis

- Hydration, as with tumor lysis syndrome
- Consider leukopheresis or exchange transfusion (WBCs > 300,000 in ALL)
- PICU supportive care - mechanical ventilation, hemodynamic support, etc
Leukopheresis
Whole blood enters the centrifuge (1) and separates into plasma (2), leukocytes (3), and erythrocytes (4). Selected components are then drawn off (5).

- At diagnosis 11 (14 % ) of 77 children with acute leukemia had hyperleukocytosis.
- 4 patients (2 ALL, 2 AML) received exchange transfusion
- 2 others (1 ALL, 1 AML) underwent leukapheresis.
- Marked cytoreduction was achieved in all patients within 24 h after therapy initiation.
- There were no procedure-related adverse events.
- Symptoms due to hyperleukocytosis markedly improved after cytoreduction.
Mediastinal Masses
<table>
<thead>
<tr>
<th>Lesions</th>
<th>Fluid</th>
<th>Fat</th>
<th>Vascular</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anterior</strong></td>
<td>Thymic Lymphoma</td>
<td>Thymic C</td>
<td>Thyroid Cardiac Coronary</td>
</tr>
<tr>
<td></td>
<td>Germ Cell Goiter</td>
<td>Thymoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pericardial C</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Germ Cell Lymphoma</td>
<td></td>
</tr>
<tr>
<td><strong>Middle</strong></td>
<td>Lymph nodes</td>
<td>Duplication C</td>
<td>Arch anomaly</td>
</tr>
<tr>
<td></td>
<td>Duplicated C</td>
<td>Necrotic nodes</td>
<td>Azygous Vein</td>
</tr>
<tr>
<td></td>
<td>Arch anomaly</td>
<td>Pericard recess</td>
<td>Vascular nodes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Retroperitoneal</td>
<td></td>
</tr>
<tr>
<td><strong>Posterior</strong></td>
<td>Neurogenic Bone and marrow</td>
<td>Neuroenteric C</td>
<td>Desc Aorta</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Schwannoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Meningocele</td>
<td></td>
</tr>
<tr>
<td><strong>&gt;1 comp</strong></td>
<td>Infection Hemorrhage</td>
<td>Lymphangioma</td>
<td>Liposarcoma</td>
</tr>
<tr>
<td></td>
<td>Lung Cancer</td>
<td>Mediastinitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hemangioma</td>
</tr>
</tbody>
</table>
Mediastinal tumors in children

- Anterior
  - Non-Hodgkin’s lymphoma
  - Hodgkin’s disease
  - Teratoma
- Middle
  - Lymphoma
- Posterior
  - Neuroblastoma
Pathophysiology of large mediastinal tumors

- Displacement or obstruction of:
  - Tracheobronchial tree
  - Heart and great vessels
  - SVC
- Superior mediastinal syndrome
Presentation and symptoms

- Often a subacute hx of cough, low-grade fever, dyspnea, ± orthopnea, ± weight loss

- Signs/symptoms of airway obstruction and/or SVC syndrome demand emergency evaluation
  - Airway obstruction -- stridor, wheezing, dyspnea, anxiety, “position of comfort”
  - SVC syndrome -- plethora, engorgement of face & upper extremities; dilatation of veins in area; CNS (in 95% of children it is due to malignancy)
Evaluation of the child with mediastinal mass

- Management/diagnostic decisions difficult and controversial — emergency treatment vs definitive Dx

- Significant stridor, dyspnea usually not present unless airway cross-sectional area narrowed by \( >50\% \)

- Some authors recommend CT scan to evaluate tracheal compression prior to decisions regarding sedation/anesthesia
Evaluation

- Inability to tolerate supine position of grave significance with anterior mediastinal mass

- May result from weight of tumor compressing not only airway, but great vessels and heart (especially RV outflow tract)

- If can tolerate supine position, CT and PFT's may help indicate which children will tolerate anesthesia
  
  - Shamberger, 1991 and 1995
Respiratory symptoms and tracheal area

Note severe tracheal narrowing in patients with orthopnea

Shamberger, 1991
CT Scan of Mediastinal Mass Showing Tracheal Compression at Carina
PFT’s with large mediastinal lymphoma

Shamberger, 1995 -- note dramatic pre-chemotherapy reduction in flow supine vs upright -- due to weight of mass on airways
ANTERIOR MEDIASTINAL MASS ON CHEST X-RAY

DYSPNEA ± POSITIONAL INTOLERANCE

YES

LOCAL ANESTHESIA FOR BIOPSY (BM, EFFUSION)

RADIOSENSITIVE OR CHEMOSENSITIVE TUMOR

YES

THERAPY

NO

GENERAL ANESTHESIA AVAILABLE BRONCHOSCOPY AND CP-BYPASS

ADEQUATE AIRWAY

Respiratory Failure Hemodynamic Collapse

NO

CT SCAN

+ -

F-V LOOP / ECHO UPRIGHT / SUPINE

+ -

LOCAL OR GENERAL ANESTHESIA
Emergent Management

- Keep child in sitting, left lateral decubitus position — helps “lift” mass off airway and RVOT
- IV access (lower extremities preferable due to SVC obstruction)
- Face mask $O_2$, non-invasive PEEP
  - Heli-ox possibly helpful due to large airway obstruction → decreases airway resistance
Emergent Management

- AVOID sedation for procedures unless anesthesiologist present and prepared for VERY difficult intubation
- If impending respiratory failure and requires intubation . . .
  - Awake, bronchoscopic intubation ideal to maintain airway muscle tone, prevent worsened extrinsic compression
  - Ideally, have cardiopulmonary bypass available
  - AVOID neuromuscular blockade - - worsened obstruction even as low as carina
Therapy

- Urgent radiotherapy since most lymphomas are radiosensitive.
- Chemotherapy, including steroids or cyclophosphamide, is a possible alternative to irradiation.
Spinal cord compression
Spinal cord compression

- Occurs in 3-5% of children with cancer, often at diagnosis.

- Can occur with any tumor type, but mostly with neuroblastoma, sarcoma, and Hodgkin’s disease.
Spinal cord compression

- Spinal cord compression for as little as 24 hours can result in permanent sequelae.
Presentation

- **Back Pain**: suspect cord compression when:
  - pain not relieved in supine position or
  - back pain has a radicular component.
- Weakness, sensory abnormalities, and paresis.
- Paraplegia and quadriplegia can occur rapidly if there are neurologic abnormalities.
- Urinary and fecal incontinence.
Diagnosis

- MRI is the imaging procedure of choice (with and without gadolinium enhancement)
Treatment

- Treatment of cord dysfunction: give dexamethasone bolus of 1-2 mg/kg and obtain MRI

- Decompression:
  - surgery, radiation, chemotherapy.

- Surgery indicated:
  - if tumor type is not known or
  - symptoms progress despite radiotherapy.

- Chemotherapy is appropriate for:
  - lymphoma, leukemia, and neuroblastoma.
Sepsis &
Febrile Neutropenia
Febrile Neutropenia

**Definitions:**
- Absolute neutrophil count < 500 cells/mm$^3$
- Fever: Single oral temp $\geq 38.3^\circ C$ or $\geq 38^\circ C$ that persist for more than 1 hour
- Non-infectious etiologies for fever should be considered:
  - Blood product transfusion
  - G-CSF
  - Active primary disease
  - Medications
Risk Factors for Serious Infections (Invasive Bacterial Infections)

- Presence of leukemia as the cancer type
- A temperature of 39°C or higher, occurrence of chills
- ≥ 7 days since last chemotherapy
- Relapse of leukemia
- Hypotension (diastolic)

Labs:
- CRP 90 mg/L
- ANC ≤200/mm³
- AMC < 100/mm³
- Platelet 50,000/mm³
- Gram negative sepsis

Sepsis in Pediatric Cancer Patients

- Same diagnostic criteria as other pts:
  - Fever/hypothermia
  - Tachycardia
  - Tachypnea
  - Hypoperfusion
  - Acidosis
  - Hypotension
    - (SCCM/ACCP Consensus Conference, 1992)

- Common etiologies:
  - Gram + cocci
    - α-hemolytic Strep
    - Staph. Epi
    - Staph aureus
  - Gram - rods
    - Pseudomonas
    - Enterobacter
    - E. coli
  - Fungi
    - Candida spp
  - Viruses
Therapy for Sepsis in Oncology Patients

- Empiric broad-spectrum Abx
- Early consideration of antifungals
- Usual PICU supportive care
  - Mechanical vent
  - Fluids/inotropes
  - Nutrition/blood products, etc

- Consider aggravated cardiac dysfunction if hx of high-dose anthracyclines, radiation
- Risk of adrenal suppression in pts with steroid Rx hx
- Granulocyte transfusion reportedly helpful in fungal sepsis -- but remains controversial
Outcome of Oncology Patients in PICU
Outcomes of intensive care in pediatric oncologic patients

- Shock and respiratory disease are the most frequent indications for PICU admission.
- Survival of oncology patients in PICU historically poor, especially for shock, respiratory failure, and if post-BMT
- Recent studies with more encouraging outcomes, however
# Mechanical Ventilation Survival in Pediatric Oncology

<table>
<thead>
<tr>
<th>Author</th>
<th>Year Range</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butt</td>
<td>79-87</td>
<td>32 %</td>
</tr>
<tr>
<td>Meert</td>
<td>84-88</td>
<td>50 %</td>
</tr>
<tr>
<td>Sivan</td>
<td>86-88</td>
<td>26 %</td>
</tr>
<tr>
<td>van Veen</td>
<td>83-92</td>
<td>45 %</td>
</tr>
<tr>
<td>Hallahan</td>
<td>87-96</td>
<td>72 %</td>
</tr>
<tr>
<td>Keengwe</td>
<td>90-97</td>
<td>58 %</td>
</tr>
<tr>
<td>Ben-Abraham</td>
<td>89-99</td>
<td>36 %</td>
</tr>
<tr>
<td>Heying</td>
<td>95-99</td>
<td>50 %</td>
</tr>
</tbody>
</table>
ICU Survival of Respiratory Failure in Pediatric Oncology Patients at St Jude Children’s Research Hospital (Sillos, 2002)

OR of ICU Survival 99-01 vs 93-98: 1.45 (95% C.I. 1.09, 1.98)


**CONCLUSIONS:**

- Hematopoietic stem cell transplant (HSCT) patients who require mechanical ventilation have worse outcomes than non-HSCT oncology patients.
- Outcomes for both groups have improved over time.
- Allogeneic transplant, higher PRISM score, need for repeated mechanical ventilation, and concomitant organ system dysfunction are risk factors for death.
Predicting Survival

Prognostic factors in pediatric cancer patients admitted to the pediatric intensive care unit.
Dursum O, et al. Turkey
*J Pediatr Hematol Oncol.* 2009

Assessing the risk of mortality in paediatric cancer patients admitted to the paediatric intensive care unit: a novel risk score?
Meyer S, et al. Germany
*Eur J Pediatr.* 2005

Introduction of the oncological pediatric risk of mortality score (O-PRISM) for ICU support following stem cell transplantation in children.
Schneider DT, et al.
*Bone Marrow Transplant.* 2000
Mortality rate was related to:

- leukemia/lymphoma vs Solid organ (P=0.029)
- The number of organ failures (P<0.0001)
- Neutropenia (P=0.001)
- Septic shock (P=0.025)
- Mechanical ventilation (P=0.01)
- Inotropic support (P=0.01).

The strongest predictor for poor outcome was the number of organ failures (P<0.05).
Conclusions

- Pediatric oncology patients experience a broad variety of critical illnesses related to both disease and therapy
- Long-term survival for many pediatric cancers is improving
- ICU outcomes for this patient group is improving
- Good ICU care can benefit children with malignancies
Thank You