Oncologic Emergencies

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Objectives

• Review the pathophysiology, clinical presentation and diagnosis for four types of oncologic emergencies: superior vena cava syndrome, spinal cord compression, hypercalcemia of malignancy, and tumor lysis syndrome
• Outline the appropriate pharmacologic and non-pharmacologic treatment of patients presenting with an oncologic emergency
• Apply the clinical data supporting therapeutic treatment recommendations for patients presenting with an oncologic emergency

Superior Vena Cava Syndrome (SVCS)

• Occurs in ~15,000 persons/year in the U.S.
• Constellation of symptoms and signs resulting from obstruction of the SVC
• Cerebral edema caused by SVCS may lead to headache, confusion, and coma
• Obstruction of the SVC due to malignant conditions account for ~65% of cases
• Most common malignant causes - non-small cell lung cancer (50%), small-cell lung cancer (25%), lymphoma and metastatic lesions (10% each)
• Non-malignant causes include thrombosis

Diagnosis of SVCS

Diagnosis made with signs and symptoms and diagnostic tests

<table>
<thead>
<tr>
<th>Signs</th>
<th>Symptoms</th>
<th>Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous distention in head, neck, and arms</td>
<td>Cough</td>
<td>Chest X-ray</td>
</tr>
<tr>
<td>Facial plethora</td>
<td>Hoarseness</td>
<td>CT scan neck and chest</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>Dyspnea</td>
<td>Venography</td>
</tr>
<tr>
<td></td>
<td>Stridor</td>
<td>Biopsy</td>
</tr>
<tr>
<td></td>
<td>Dysphagia</td>
<td></td>
</tr>
</tbody>
</table>

Management of SVCS

• Involves both treatment of the cancer and relief of the symptoms of obstruction
• Supportive care and medical management
  – Elevate the patient’s head to decrease hydrostatic pressure
  – Oxygen for dyspnea and tachypnea PRN
  – Corticosteroids to decrease inflammation
  – Loop diuretics and low salt diet to reduce edema
Management of SVCS

- Radiation therapy
- Chemotherapy
- Thrombolytic therapy and anticoagulation
- Expandable wire stents
- Balloon angioplasty
- Surgical bypass


Scenario Treatment Strategy

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Treatment Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgically-managed tumor (e.g., thymoma)</td>
<td>Surgery</td>
</tr>
<tr>
<td>Chemo/radio-sensitive tumor (e.g., SCLC, NHL)</td>
<td>Treat the same as without SVCS</td>
</tr>
<tr>
<td>Intermediate sensitivity (e.g., NSCLC)</td>
<td>Treat the same as without SVCS</td>
</tr>
<tr>
<td>Poor treatment options</td>
<td>Consider stent, early RT</td>
</tr>
<tr>
<td>Severe symptoms / Life-threatening</td>
<td>Urgent stent placement (thrombolytic if thrombus)</td>
</tr>
</tbody>
</table>


Spinal Cord Compression (SCC)

- Compression of the dural sac and its contents (spinal cord and/or cauda equina) by an extradural tumor mass
- One of the most devastating neurologic complications
- May result in permanent paraplegia or quadriplegia if left untreated
- Affects 5% to 10% of patients with cancer
- Most common cancers associated with SCC
  - Breast, lung, prostate, lymphoma

Devita et al. Cancer: Principles & Practice of Oncology, 9th ed

Pathophysiology of SCC

- Tumors reach the spinal column through
  - Direct arterial embolization of tumor cells
  - Direct growth into the spinal canal through an intervertebral foramen
  - Intramedullary, subdural or leptomeningeal metastases (rare)
- Damage to spinal cord occurs through
  - Vascular compromise
  - Destabilization of the spinal column

Expert Rev Anticancer Ther 2010; 10:697-708

SCC Clinical Presentation

- Back pain most common complaint (88%)
  - May be exacerbated by sneezing / coughing
  - Aggravated by the recumbent position (maximum pain intensity on awakening)
  - Can be local, referred, radicular or all three

Devita et al. Cancer: Principles & Practice of Oncology, 9th ed

SCC Clinical Presentation

- Other signs/symptoms
  - Radiculopathy
  - Weakness
  - Sensory changes
  - Sphincter incontinence
  - Autonomic dysfunction (e.g., urinary hesitancy, retention)
- Frankel grading system
  - A = complete paraplegia
  - B = only sensory function
  - C = non-ambulation
  - D = ambulation
  - E = no neurological signs/symptoms

Devita et al. Cancer: Principles & Practice of Oncology, 9th ed
Diagnosis of SCC

- Severe symptoms → sphincter dysfunction or paraparesis
- MRI preferred diagnostic test
- Biopsy preferred prior to treatment if SCC initial cancer presentation
- Lumbar puncture is of no diagnostic value
- CT myelogram if MRI non-diagnostic for any reason

Management of SCC

- Goals
  - Relieve pain
  - Preserve or improve neurologic function
  - Provide local tumor control
  - Stabilize spine
- Most important factor determining neurologic status after treatment is the neurologic status prior to treatment

Cancer-related Hypercalcemia

- Occurs in up to 20-30% of patients with cancer at some time during the course of their disease
- Leads to progressive mental impairment, including coma, as well as renal failure
- Poor prognosis: ~50% of patients die within 30 days

Classification of Hypercalcemia

<table>
<thead>
<tr>
<th>Type</th>
<th>Frequency (%)</th>
<th>Bone Metastases</th>
<th>Causal Agent</th>
<th>Typical Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local osteolytic hypercalcemia</td>
<td>20</td>
<td>Common, extensive</td>
<td>Gastrointestinal, PTHrP</td>
<td>Breast cancer, multiple myeloma, lymphoma</td>
</tr>
<tr>
<td>Humoral hypercalcemia of malignancy</td>
<td>80</td>
<td>Minimal or absent</td>
<td>PTHrP</td>
<td>Squamous-cell cancer (e.g., of head and neck, esophagus, cervix, or lung), renal, ovarian, breast, endometrial</td>
</tr>
<tr>
<td>1,25(OH)2D-secreting lymphomas</td>
<td>&lt;1</td>
<td>Variable</td>
<td>1,25(OH)2D,D</td>
<td>Lymphoma (all types)</td>
</tr>
<tr>
<td>Ectopic hyperparathyroidism</td>
<td>&lt;1</td>
<td>Variable</td>
<td>PTH</td>
<td>Variable</td>
</tr>
</tbody>
</table>
Pathophysiology of cancer-related hypercalcemia

- Osteolytic - occurs as a result of focal bone destruction
  - Bone destruction mediated by local (paracrine) factors secreted by tumor cells that infiltrate bone (cytokines and growth factors)
- Humoral paraneoplastic syndrome – caused by tumor-produced factors that affect bone resorption or tubular calcium reabsorption
  - Parathyroid hormone-related protein (PTHrP)
  - Various cytokines (e.g., IL-1, IL-6, TGF-α, TNF-α)
  - 1,25 dihydroxyvitamin D
- Hypercalcemia induces an osmotic diuresis while inhibiting antidiuretic hormone
  - Polyuria & nausea/vomiting  dehydration  reduced glomerular filtration & increased calcium reabsorption

De Vita et al. Cancer: Principles & Practice of Oncology, 8th ed

Diagnosis

- Rule out other causes of hypercalcemia
- Ideally, an ionized calcium level would be drawn
- If total serum calcium levels are used, need to correct for albumin
  Corrected Ca²⁺ = measured Ca²⁺ + 0.8 X (4 – measured albumin)
- Severity of hypercalcemia
  - Mild = Serum Ca²⁺ 10.5 – 11.9 mg/dL (2.6–2.9 mmol/L)
  - Moderate = Serum Ca²⁺ 12 – 13.9 mg/dL (3–3.4 mmol/L)
  - Severe = Serum Ca²⁺ ≥ 14 mg/dL (3.5 mmol/L)


Management of Hypercalcemia

- Therapy for cancer is ultimate management
- General supportive measures
  - Remove calcium from parenteral feeding solutions
  - Discontinue oral calcium supplements in enteral feeding solutions
  - Discontinue medications that may independently lead to hypercalcemia (e.g., lithium, clacitriol, vitamin D, and thiazides)
  - Increase weight-bearing mobility of the patient (if possible)
  - Discontinue sedative drugs, including analgesics, if possible
  - Maintain normal serum phosphorus (PO better than IV)
  - Maintain serum creatinine level in the normal range


Pharmacologic Therapy for Hypercalcemia

- Normal saline hydration
  - MDA – dilutional effect as dehydration corrected, then increased renal calcium excretion
  - Onset - minutes to hours
  - Duration – during infusion
  - e.g., 0.9% NaCl @ 200-500 mL/hr
- Loop diuretics
  - MDA - increase urinary calcium excretion (only use after dehydration resolved)
  - Onset – Hours
  - Duration – during therapy
  - e.g., furosemide 20-40 mg IV


Pharmacologic Therapy for Hypercalcemia

- Calcitonin
  - MDA – inhibits bone resorption and increases urinary calcium excretion (rapid tachyphylaxis)
  - Onset – 4-6 hours
  - Duration – 48 hours
  - e.g., calcitonin 4-8 IU SubQ or IM every 12 hours
- Bisphosphonates
  - MDA – inhibit bone resorption via interference with osteoclast recruitment and function
  - Onset – 24-72 hours
  - Duration – 2-4 weeks
  - e.g., pamidronate 60-90 mg IV over 2-24 hrs or zoledronic acid 4 mg IV over 15 min

Pharmacologic Therapy for Hypercalcemia

- Other agents
  - Corticosteroids
    - e.g., prednisone 60 mg PO x 10 days
    - Onset 3-5 days
    - Primarily useful in lymphoproliferative malignancies
  - Gallium nitrate
    - MOA: inhibits bone resorption
    - Onset 24 hours
    - Due to inconvenience of a 5-day infusion and the toxicity, it is usually reserved for bisphosphonate failures
  - Denosumab
    - MOA: inhibits bone resorption (RANK inhibitor)
    - Onset not yet well described
    - Consider in patients that have failed a bisphosphonate

Tumor Lysis Syndrome (TLS)

- Most common disease-related emergency in patients with hematologic cancers
- Most commonly associated with non-Hodgkin’s lymphoma or acute leukemia
- Typically occurs 12-72 hours after initiation of anticancer therapy
- Incidence ranges from 3-25%
Risk Assessment

• Prevention of TLS relies on identification of at-risk patients
• TLS risk factors
  – Age
  – Type of malignancy
  – Tumor burden
  – WBC
  – Renal dysfunction

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>Low Risk (&lt;1%)</th>
<th>Intermediate Risk (1-5%)</th>
<th>High Risk (&gt;5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL</td>
<td>N/A</td>
<td>WBC &lt;100K and LDH &lt;2XULN</td>
<td>WBC &gt;100K and/or LDH &gt;2XULN</td>
</tr>
<tr>
<td>AML</td>
<td>WBC &lt;25K and LDH &lt;2XULN</td>
<td>WBC 25-100K or LDH &gt;2XULN</td>
<td>WBC &gt;100K</td>
</tr>
<tr>
<td>NHL</td>
<td>Adult intermediate-grade NHL and LDH &lt;2XULN</td>
<td>Burkitt lymphoma and LDH &gt;2XULN</td>
<td>LL Stage II/IV and/or LDH &gt;2XULN</td>
</tr>
<tr>
<td></td>
<td>Indolent NHL Adult ALC/L</td>
<td>Burkitt lymphoma and LL stage I/II and LDH &gt;2XULN</td>
<td>Burkitt lymphoma stage II/IV and/or LDH &gt;2XULN</td>
</tr>
<tr>
<td>CLL</td>
<td>Most patients, unless: WBC &gt;50K or tx w/fludarabine/rituximab</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

Management of TLS

Goals
• Preservation of renal function
• Prevention of cardiac dysrhythmias, neuromuscular irritability, seizures, death

Management of TLS

• Initiate appropriate TLS prophylactic / treatment regimen prior to start of anticancer therapy
  – Assess patient for clinical or laboratory TLS
  – Assign to risk category (low, intermediate, high)
  – Assess for presence of renal dysfunction / involvement by the malignancy
• Manage the complications of TLS

Management of TLS

• Patient monitoring
• Hydration
• Anti-hyperuricemic therapy
  – Allopurinol
  – Rasburicase
  – Treatment duration of 5 to 7 days
• Management of electrolyte abnormalities

• Urinary alkalinization
  – Not proven to be of therapeutic benefit
  – Increased risk of precipitating hypoxanthine and xanthine
  – Increased risk of overt, clinical hypocalcemia
  – Urinary precipitation of calcium phosphate
• Leukapheresis
  – Rapidly reduces peripheral WBC
  – Has not proven to improve long-term prognosis
Management of TLS

- **Low Risk**
  - IV/oral fluids
  - +/- Allopurinol
  - Daily labs

- **Intermediate Risk**
  - IV fluids
  - Allopurinol
  - Q8-12 hour labs

- **High Risk**
  - IV fluids
  - Rasburicase
  - Q6-8 hour labs

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**Rasburicase**

- Recombinant form of urate oxidase
- Urate oxidase is an enzyme that metabolizes urate to allantoin, a substance 5-10x more soluble than uric acid
- FDA-approved dosing: 0.2 mg/kg IV infusion over 30 min daily for up to 5 days
- Rasburicase typically administered at lower doses (3-6 mg flat dose) and for <5 days in adults due to high cost
- Adverse effects: N/V, pyrexia, peripheral edema, anxiety, HA, GI, hypersensitivity, ataxia, anemia, hemolysis, antibody formation
- Contraindicated in patients with G6PD deficiency

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**Allopurinol**

- Xanthine analog
- Converted to oxypurinol, which acts as a competitive inhibitor of xanthine oxidase, thereby blocking conversion of purine metabolites to uric acid
- Dosing: 200-400 mg/m²/day in 1 to 3 divided doses (max of 800 mg/day)
- Adverse effects: hypersensitivity reactions, Stevens-Johnson syndrome, immune hypersensitivity reaction, myelosuppression, reduced clearance of methotrexate

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**Rasburicase vs Allopurinol**

- 200 patients with active leukemia at potential/high risk for TLS
- Rasburicase 0.2 mg/kg/day ± 5 days
- Rasburicase 0.2 mg/kg/day on days 1-2, then allopurinol 300 mg PO on days 3-5
- Allopurinol 300 mg PO daily ± 5 days

Primary endpoint: Percent of patients achieving and maintaining plasma uric acid <7.5 mg/dL during days 3-7 of chemo
Management of TLS

- Increased hydration and close monitoring for all patients at risk of TLS
- Allopurinol (start 72 hours prior to start of antineoplastic therapy) for all patients at intermediate and high risk for TLS
- Rasburicase for patients with persistent hyperuricemia in the setting of established TLS despite adequate hydration and/or allopurinol (off-label dosing studies support one time doses of 3-6 mg with frequent monitoring of uric acid levels in adults)

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