EMERGENCIES IN HEMATOLOGY AND ONCOLOGY

South Dakota ACP Meeting
September 14, 2018
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Objectives

- Discuss common emergencies in the care of patients with oncologic and hematologic diseases including:
  - Febrile neutropenia
  - Malignant Spinal Cord Compression
  - Brain Metastases with Increased Intracranial Pressure
  - Tumor Lysis Syndrome
  - Hyperviscosity/Leukostasis
Febrile Neutropenia (FN)

• Definition
• Who is affected?
• Most common infections
• Evaluation
• Treatment
• Use of growth factors
Febrile Neutropenia

- Fever
  - Single temp of 101 or higher OR
  - Temp of 100.4 sustained over an hour
  - Avoid axillary and rectal measurement

- Neutropenia
  - ANC <500 cells/mm3 OR
  - ANC expected to decrease to <500 cells/mm3 in the next 48 hours
  - Profound neutropenia = ANC <100 cells/mm3
  - Functional neutropenia = circulating neutrophils are ineffective due to hematologic malignancy
Who is affected?

- Risk varies by type of malignancy
  - AML/MDS 85-95%
  - Soft tissue sarcoma 27%
  - NHL/myeloma 26%
  - Germ cell tumors 23%
  - Hodgkin lymphoma 15%
  - Ovarian carcinoma 12%
  - Lung cancer 10%
  - Colorectal cancer 5%
  - Breast cancer 5%
  - Prostate cancer 1%
Who is affected?

- Risk increased with:
  - Age $\geq 65$ years
  - Performance status $\geq 2$
  - Albumin $< 3.5$ g/dL
  - Prior episode of febrile neutropenia
  - Comorbidities
Most Common Infections

• Clinically documented infections occur in just 20-30% of episodes of febrile neutropenia

• Of those, infections of the GI tract, lungs, and skin are most common

• Bacteremia occurs in 10-25% of patients, primarily in those with prolonged or profound neutropenia
Most Common Infections

• Most common organisms isolated:
  • Gram positive
    • Coag-negative staph
    • Staph aureus (including MRSA)
    • Enterococcus species (including vancomycin resistant strains)
    • Viridans group strep
    • Strep pneumoniae
    • Strep pyogenes
Most Common Infections

• Gram negative
  • E coli
  • Klebsiella
  • Enterobacter species
  • Pseudomonas aeruginosa
  • Citrobacter species
  • Acinetobacter species
  • Stenotrophomonas maltophilia
Initial Assessment

• Gather history focusing on:
  • Type of cancer and chemotherapy
  • Comorbid illnesses
  • Time since last chemotherapy
  • Recent antibiotic therapy/prophylaxis
  • Devices (lines, catheters, etc.)
  • Exposures (tobacco smoke, etc.)
Initial Assessment

• CBC with differential, creatinine, BUN, electrolytes, transaminases, bilirubin

• At least 2 sets of blood cultures (set = 2 bottles), one from line and one peripheral or 2 separate peripheral sites if no line is present

• Other cultures as clinically indicated

• CXR and UA as clinically indicated for symptoms
Risk Evaluation

- High risk for complications/morbidity and mortality:
  - Inpatient at time of fever development
  - Significant comorbidities or clinically unstable
  - Allogeneic HCT
  - Prolonged severe neutropenia expected ($\leq 100$ cells/$\mu$L for $\geq 7$ days)
  - Hepatic insufficiency (transaminases $\geq 5x$ ULN)
  - Renal insufficiency (creatinine clearance $< 30$ mL/min)
Risk Evaluation

- High risk for complications/morbidity and mortality
  - Uncontrolled/progressive cancer (AML not in remission or other cancer progressing after more than 2 courses of chemotherapy)
  - Pneumonia or other complex infection at presentation
  - Alemtuzumab
  - Mucositis grade 3 or 4
  - MASCC Risk Index score <21
Risk Evaluation

• Low risk for complications/morbidity and mortality:
  • No high risk features
  • Outpatient at time of fever development
  • No associated acute comorbid condition requiring admission in its own right
  • Anticipated short duration of severe neutropenia ≤100 cells/μL for <7 days
  • Good performance status (ECOG 0-1)
  • No hepatic insufficiency
  • No renal insufficiency
  • MASCC Risk Index score ≥21
# MASCC Risk Index

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>POINTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>No or Mild Symptoms</td>
<td>5</td>
</tr>
<tr>
<td>Moderate Symptoms</td>
<td>3</td>
</tr>
<tr>
<td>No Hypotension</td>
<td>5</td>
</tr>
<tr>
<td>No COPD</td>
<td>4</td>
</tr>
<tr>
<td>Solid Tumor or Hematologic Malignancy with No Previous Fungal Infection</td>
<td>4</td>
</tr>
<tr>
<td>No Dehydration</td>
<td>3</td>
</tr>
<tr>
<td>Outpatient Status</td>
<td>3</td>
</tr>
<tr>
<td>Age &lt;60 Years</td>
<td>2</td>
</tr>
</tbody>
</table>
Initial Empiric Therapy

• High Risk:
  - NCCN guidelines list Cefepime, Imipenem/cilastin, meropenem, and piperacillin/tazobactam as category 1 options for monotherapy.
  - Ceftazidime should be avoided unless it is the only available option because of weak gram positive coverage and increased breakthrough infections.
  - Meta-Analysis of 44 trials published in Cochrane Review in 2010 showed an increased risk for all cause mortality with cefepime compared with other beta-lactams (RR 1.39, CI 1.04-1.86) and a lower mortality with zosyn (RR 0.56, CI 0.34-0.92).
  - IV Vancomycin should only be added in appropriate situations including suspected line infection, disseminated papules or other lesions, suspicion for MRSA, or periorbital cellulitis.
Initial Empiric Therapy

- Low Risk:
  - Consider oral antibiotics in outpatient setting
    - Ciprofloxacin + amoxicillin/clavulanate (category 1)
    - Moxifloxacin (category 1)
    - Levofloxacin
  - Oral regimen not recommended if patient received prior quinolone prophylaxis
Management of Outpatients

- 24 hour caregiver
- Access to telephone
- Access to emergency facilities
- Adequate home environment
- Distance of ≤ 1 hour from medical facility
- Able to tolerate oral antibiotics (no nausea/vomiting)
- Telephone follow up within 12-24 hours recommended
Duration of Therapy

• Empiric antibiotics should be continued until ANC is $\geq 500 \text{cells/mcL}$ as long as fever has resolved.

• If an infection is documented, antimicrobials should be de-escalated and continued for the duration appropriate for that infection.
Growth Factors

• Prophylactic growth factors:

  • Chemotherapy regimens with a >20% risk for febrile neutropenia

  • Considered based on patient characteristics in regimens with 10-20% risk
Growth Factors

• Therapeutic growth factors should be considered:
  • Sepsis
  • Age >65
  • ANC <100
  • Neutropenia expected to be >10 days
Growth Factors

• Therapeutic growth factors should be considered:
  • Pneumonia or other documented infection
  • Invasive fungal infection
  • Hospitalization at time of fever
  • Prior episode of febrile neutropenia
Malignant Spinal Cord Compression (MSCC)

- Who is affected?
- Symptoms
- Evaluation
- Treatment
Who is affected?

- 5-10% of all patients with cancer will experience MSCC
- 20% of patients diagnosed have no prior diagnosis of cancer
- May occur with any type of cancer
- Most cases are due to breast, lung or prostate cancer
- Cancers with the highest likelihood of causing MSCC are non-Hodgkin lymphoma and multiple myeloma with prostate cancer a distant third
Symptoms

- Most patients have back pain
- Back pain is mild or absent in 5-15%
- Pain is typically localized to the spine, radicular, or both
- Pain is typically acute in onset, progressive and is often nocturnal
- Pain may be worsened by increase in intra-abdominal pressure
Symptoms

• Weakness is the 2\textsuperscript{nd} most common symptom

• Up to 70\% of patients are unable to walk at the time of diagnosis

• Sensory deficits typically occur after motor deficits

• Autonomic symptoms such as loss of bladder and bowel function occur later in the course
Evaluation

- MRI should be obtained in patients with cancer who present with relatively acute back pain, especially if it is progressive.

- Entire spine should be imaged whenever possible as up to 40% of patients may have multiple levels of involvement.

- If unable to image entire spine, image suspected area emergently and image the remaining spine as soon as able.

- If MRI is contraindicated, obtain CT with or without myelography.

- Plain x-rays and bone scans are not sensitive for cord compression.

- PET CT is also not detailed enough to diagnose MSCC.
Treatment

• Therapy should be started immediately when MSCC is suspected to try to preserve neurologic function

• The best predictor of neurologic function after treatment is motor function prior to treatment

• Steroids may be started before imaging can be obtained if there is a delay in ability to obtain imaging

• Dexamethasone is used most commonly
  
  • Dosing: 10-16 mg IV initially followed by 4 mg every 4-6 hours
Treatment

• Most patients should be evaluated urgently for surgical decompression

• A randomized multi-institution trial published in The Lancet in 2005 compared surgery followed by radiation to radiation alone, along with steroids, with primary endpoint being ability to ambulate after treatment
  
  • Study was stopped early with significantly more surgical patients being able to walk after therapy (84% vs 57%)
  
  • Surgical patients were also able to walk for a longer period after treatment (122 days vs 13 days)
  
  • Of 32 patients who were unable to walk at the time of trial enrollment, 10/16 surgical patients regained the ability to walk while 3/16 non-surgical patients regained the ability to walk
  
  • Need for steroids and opioids were also reduced in the surgical group
  
  • Patients with very radiosensitive tumors, including lymphomas, leukemia, multiple myeloma, and germ-cell tumors, were excluded from the study
Brain Metastases with Increased Intracranial Pressure

- Who is affected?
- Symptoms
- Initial therapy
- Definitive therapy
- Is anticoagulation safe?
Who is affected?

- 10-20% of adults with cancer
- All types of cancer can potentially spread to the brain
- Lung cancer, breast cancer, renal cell carcinoma and melanoma are the most common
Symptoms

- Symptoms depend on area of brain affected
  - 80% of mets are in the cerebral hemispheres
  - 15% affect the cerebellum
  - 3% are in the brainstem
- Headache is the most common symptom
Symptoms

- Other common symptoms include
  - Motor and sensory deficits
  - Speech disturbance
  - Unsteadiness
  - Cognitive decline

- Seizures affect up to 10-20% of patients with brain mets and are more often seen in patients with multiple metastases

- Sudden severe symptoms can be seen with hemorrhage into a metastatic lesion
Diagnosis

- Contrast enhanced MRI is the test of choice
- Contrast enhanced CT is less sensitive but can be used when MRI is contraindicated
- Non-contrast CT is useful to look for hemorrhage
Treatment

- Increased intracranial pressure most often seen with peritumoral edema
Treatment

• Steroids needed right away if symptomatic and/or peritumoral edema present
  • Dexamethasone used most commonly
  • Optimal dose unknown but reasonable to start with 4-8 mg/day in 2 divided doses
  • Can consider 16 mg/day if more severe symptoms
  • Taper over 3-4 weeks following more definitive therapy

• Steroids not necessary if no symptoms or peritumoral edema
Treatment

• Seizures should be treated as they would be for patients without brain metastases

• Prophylactic AEDs are not recommended

• Prophylaxis can be considered following resection of metastases with rapid tapering
Treatment

• Definitive therapy involves radiation and/or surgical resection

• Choice of therapy depends on size and number of mets

• Multiple mets = whole brain radiation

• 1-3 lesions, less than 3-4 cm = stereotactic radiosurgery (SRS)

• Solitary lesion and/or lesion(s) >4 cm = surgical resection +/- postoperative radiation
Treatment

- Whole brain radiation (WBRT)

- Used for multiple mets, oligometastases with poor systemic control, mets too large for SRS, reirradiation, or following surgery or SRS

- Increases median survival with multiple mets from 1-2 months to 3-6 months

- Decreases symptoms

- Given as 10 daily treatments of 3 Gy each

- May cause significant progressive cognitive decline in those who survive longer than 6 months but cognitive symptoms from tumor progression are worse
Treatment

- SRS may be used alone or in combination with WBRT
- Combination lowers likelihood of recurrent brain mets in the following year but is associated with more cognitive decline
- First line SRS followed by salvage WBRT if needed has been shown to be cost effective
- Role of SRS in >3 mets is less clear
- ~10% of patients develop radiation necrosis after SRS
- SRS may also be used after surgical resection
Treatment

• Two studies have looked at resection vs SRS in 1-2 mets

• Showed no difference in survival between SRS and resection for 1 or 2 mets

• One study showed more distant brain recurrences in the SRS group

• Surgery is beneficial if a tissue diagnosis is needed
Anticoagulation

• A 1994 study showed anticoagulation to be more effective than IVC filter in treating thrombosis in patients with brain metastases

• Incidence of serious CNS hemorrhage was 7% and was most often associated with supratherapeutic anticoagulation

• Anticoagulation is generally felt to be safe as long as over-anticoagulation does not occur

• Anticoagulation is safest once the brain mets have been treated
Tumor Lysis Syndrome (TLS)

- Definition
- Who is affected?
- Prevention
- Treatment
Tumor Lysis Syndrome

- Release of large amounts of intracellular contents into the bloodstream due to death of large numbers of malignant cells
- Most commonly occurs after initiation of anticancer therapy but may occur spontaneously
- Cairo and Bishop Classification
<table>
<thead>
<tr>
<th>Metabolic Abnormality</th>
<th>Criteria for Classification of Laboratory Tumor Lysis Syndrome</th>
<th>Criteria for Classification of Clinical Tumor Lysis Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperuricemia</td>
<td>Uric acid &gt;8.0 mg/dl (475.8 μmol/liter) in adults or above the upper limit of the normal range for age in children</td>
<td>Cardiac dysrhythmia or sudden death probably or definitely caused by hyperkalemia</td>
</tr>
<tr>
<td>Hyperphosphatemia</td>
<td>Phosphorus &gt;4.5 mg/dl (1.5 mmol/liter) in adults or &gt;6.5 mg/dl (2.1 mmol/liter) in children</td>
<td>Cardiac dysrhythmia, sudden death, seizure, neuromuscular irritability (tetany, paresthesias, muscle twitching, carpopedal spasm, Trousseau’s sign, Chvostek’s sign, laryngospasm, or bronchospasm), hypotension, or heart failure probably or definitely caused by hypocalcemia</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>Potassium &gt;6.0 mmol/liter</td>
<td>Increase in the serum creatinine level of 0.3 mg/dl (26.5 μmol/liter) (or a single value &gt;1.5 times the upper limit of the age-appropriate normal range if no baseline creatinine measurement is available) or the presence of oliguria, defined as an average urine output of &lt;0.5 ml/kg/hr for 6 hr</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>Corrected calcium &lt;7.0 mg/dl (1.75 mmol/liter) or ionized calcium &lt;4.5 mg/dl (1.12 mmol/liter)†</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

* In laboratory tumor lysis syndrome, two or more metabolic abnormalities must be present during the same 24-hour period within 3 days before the start of therapy or up to 7 days afterward. Clinical tumor lysis syndrome requires the presence of laboratory tumor lysis syndrome plus an increased creatinine level, seizures, cardiac dysrhythmia, or death.

† The corrected calcium level in milligrams per deciliter = measured calcium level in milligrams per deciliter + 0.8 x (4 – albumin in grams per deciliter).

‡ Acute kidney injury is defined as an increase in the creatinine level of at least 0.3 mg per deciliter (26.5 μmol per liter) or a period of oliguria lasting 6 hours or more. By definition, if acute kidney injury is present, the patient has clinical tumor lysis syndrome. Data about acute kidney injury are from Levin et al.¹¹
Who is Affected?

• Most common in aggressive heme malignancies including acute leukemias and high grade lymphomas
• Can also occur with other rapidly proliferating tumors
• With more effective treatments, risk is increased in other tumors as well
• Patient factors also increase risk including
  • Increasing age
  • Underlying kidney disease
  • Use of drugs/substances including aspirin, thiazides, caffeine, and alcohol
## Risk and Prophylaxis

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Malignant Disease</th>
<th>Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low</strong></td>
<td>Solid Tumor</td>
<td>Daily labs</td>
</tr>
<tr>
<td></td>
<td>Multiple Myeloma</td>
<td>IV fluids (3 L/m²/day)</td>
</tr>
<tr>
<td></td>
<td>CML</td>
<td>Consider allopurinol</td>
</tr>
<tr>
<td></td>
<td>CLL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Indolent NHL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hodgkin Lymphoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AML (WBC &lt;25K and LDH &lt;2x ULN)</td>
<td></td>
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<tr>
<td><strong>Intermediate</strong></td>
<td>AML (WBC 25-100K)</td>
<td>Labs every 8-12 hours</td>
</tr>
<tr>
<td></td>
<td>AML (WBC &lt;25K and LDH ≥2x ULN)</td>
<td>IV fluids (3L/m²/day)</td>
</tr>
<tr>
<td></td>
<td>Intermediate grade NHL (LDH ≥2x ULN)</td>
<td>Allopurinol up to 7 days</td>
</tr>
<tr>
<td></td>
<td>ALL (WBC &lt;100K and LDH &lt;2x ULN)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Burkitt lymphoma (LDH &lt;2x ULN)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lymphoblastic NHL (LDH &lt;2x ULN)</td>
<td></td>
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<tr>
<td><strong>High</strong></td>
<td>ALL (WBC ≥100K and/or LDH ≥2x ULN)</td>
<td>Labs every 6-8 hours</td>
</tr>
<tr>
<td></td>
<td>Burkitt lymphoma (stages III/IV and/or LDH ≥2x ULN)</td>
<td>IV fluids (3L/m²/day)</td>
</tr>
<tr>
<td></td>
<td>Lymphoblastic NHL (stages III/IV and/or LDH ≥2x ULN)</td>
<td>Rasburicase</td>
</tr>
<tr>
<td></td>
<td>Int risk disease with renal dysfunction or involvement</td>
<td></td>
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<tr>
<td></td>
<td>Int risk disease with elevated uric acid, K, and/or phos</td>
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Treatment

• Prevention is best (see last slide)

• Prephase treatment with steroids or low dose Cytoxan, vincristine, and steroids can debulk some tumor and decrease risk

• Allopurinol does not break down uric acid that has already been produced

• Rasburicase rapidly decreases uric acid levels

• Rasburicase should be avoided in patients with G6PD deficiency as they can develop methemoglobinemia and hemolytic anemia
Treatment

- IV fluids are preferred for increasing urine output but loop diuretics may be needed
- Target urine output of 2 ml/kg/hr
- Urine alkalinization should be avoided because it decreases calcium phosphate solubility
- Limit K and phos intake
Treatment

• Oral sodium polystyrene sulfonate (Kayexalate)

• Standard therapies for managing hyperkalemia to avoid arrhythmias

• Treat hypocalcemia with the lowest doses of calcium that relieve symptoms to avoid calcium phosphate crystallization

• Lower threshold for renal replacement therapy
Hyperviscosity/Leukostasis

- Hyperviscosity vs Leukostasis
- Who is affected?
- Management of hyperviscosity in myeloma or WM
- Management of leukostasis
Hyperviscosity Causes

- Sluggish flow of blood due to elevated monoclonal proteins or blood cells
- Multiple myeloma
- Waldenstroms macroglobulinemia
- Severe erythrocytosis
- Severe thrombocytopenia
Hyperviscosity

- Typically caused by IgM which are larger than IgG and IgA and remain intravascular
- Level required to cause symptoms varies but most likely with IgM levels > 3 g/dL
Hyperviscosity Symptoms

- Headache
- Dizziness
- Altered Mental Status
- Seizures
- Hearing and vision changes
Hyperviscosity Symptoms

- Mucocutaneous bleeding
- Dyspnea
- Congestive heart failure
- Priapism
- Eye and CNS symptoms are most common
Hyperviscosity Management

- Blood viscosity measurement may be difficult to get urgently in many hospitals, so treatment should be initiated urgently before confirmation available

- Plasmapheresis very effective, especially with high IgM

- May phlebotomize and give saline while arranging for pheresis if severely symptomatic

- Avoid red cell transfusions which can worsen symptoms

- Need systemic therapy for underlying disease
Leukostasis Causes

- Microvascular obstruction due to large number of large ‘sticky’ blast cells
- Acute leukemia, particularly AML
- Very rare to see in CLL or CML despite very high WBC counts
- May see in blast phase of CML
Leukostasis Symptoms

- Can have all the same symptoms of hyperviscosity but also:
  - Focal neuro deficits
  - Intracranial hemorrhage
  - Hypoxia
  - Pulmonary infiltrates
  - Chest pain
Leukostasis Symptoms

- MI
- Fever
- Renal failure
- Thrombosis
- DIC
Leukostasis Management

• Leukapheresis quickly lowers the white count, improving symptoms

• Hydrea can also rapidly lower the white count

• Urgent initiation of systemic chemotherapy is needed and is typically curative intent
Questions?
References


References


