Oncologic Emergencies, Including Side Effects of New Therapies

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Disclosures

I have nothing to disclose
Outline

- Updates on oncologic emergencies:
  - Hypercalcemia
  - Tumor lysis syndrome
  - Thrombocytopenia
  - Pleural effusions
- Review of side effects of immunotherapies
- Discussion of your cases and questions

Hypercalcemia | Old and new

- Mr. N: 72M with multiple myeloma.
  - Dx: 5/2015 in setting of long-standing MGUS (since 2003)
  - Prognostic info: IgG kappa, +lytic bone lesions, FISH without high-risk mutations
- Treatment:
  - 6/2015-10/2015: Velcade, cyclophosphamide, dexamethasone
  - PR
  - 10/2015: Lenalidomide, dexamethasone
  - CR

Progressive hip pain and diminished concentration.
Hypercalcemia | Manifestations

- Progressive mental impairment and renal failure.
- A poor prognostic sign.
- Treatment is indicated if hypercalcemia is symptomatic or severe.

<table>
<thead>
<tr>
<th>Calcium (Ca$_{2+}$) mg/dL</th>
<th>Ionized Calcium (ioniz Ca$_{2+}$) mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.0</td>
<td>1.4</td>
</tr>
<tr>
<td>12.0</td>
<td>2.0</td>
</tr>
<tr>
<td>14.0</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Mild

Moderate

Severe
What are the mechanisms of hypercalcemia in malignancy?

What are the main components of therapy for hypercalcemia of malignancy?

<table>
<thead>
<tr>
<th>Hypercalcemia</th>
<th>Mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>type</strong></td>
<td><strong>mechanism</strong></td>
</tr>
</tbody>
</table>
| Humoral | PTHrP | • Squamous cancers (most commonly lung)  
          • Breast cancer  
          • Renal cancer  
          • Ovarian or endometrial cancer |
| Osteolytic | Cytokine mediated and PTHrP | • Multiple Myeloma  
               • Breast cancer  
               • Lymphoma |

![Diagram](image)
**Hypercalcemia | Mechanisms**

<table>
<thead>
<tr>
<th>Type</th>
<th>Mechanism</th>
<th>Associated cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humoral</td>
<td>PTHrP</td>
<td>• Squamous cancers (most commonly lung)</td>
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<tr>
<td></td>
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<td>• Breast cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Lymphoma</td>
</tr>
</tbody>
</table>

**Much less common:**
- 1,25(OH)₂D secreting tumors (lymphomas)
- PTH secreting tumors

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**Hypercalcemia | Review**

**What are the mechanisms of hypercalcemia in malignancy?**

Most commonly, PTHrP mediated. Not necessarily indicative of bone metastases.

**What are the main components of therapy for hypercalcemia of malignancy?**
Hypercalcemia | Review

Which of the following is not an initial component of management?

A. 80 mg IV furosemide
B. 2L Normal Saline
C. IV pamidronate
D. IV calcitonin

volume repletion and supportive care
- NS 200-300 cc/hr
- oral phos repletion (goal 2.5-3 mg/dL)

bring down the calcium
- bisphosphonate +/- calcitonin
- either pamidronate or zoledronate
- response time: hours for calcitonin; about a day with bisphophonate
- duration: up to 4 weeks

treat underlying cause
Hypercalcemia | *New(ish)!*

**Options for treating severe hypercalcemia in AKI (Cr >4.5)**

- Full dose bisphosphonate
- Reduced dose bisphosphonate with slower infusion rate
  - (e.g. 4 mg zoledronic acid over 1 hour or 30 mg pamidronate over 4 hours)
- Calcitonin until kidney function improves
- RANK ligand inhibitor (i.e. denosumab) that is not renally cleared.

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![Graph showing changes in calcium levels with treatments](image-url)
**Hypercalcemia | Review**

What are the mechanisms of hypercalcemia in malignancy?

Most commonly, PTHrP mediated.
Not necessarily indicative of bone metastases.

What are the main components of therapy for hypercalcemia of malignancy?

Volume repletion.
Bisphosphonate +/- calcitonin.
Treatment of underlying cause.
Denosumab for specific situations.

**Outline**

• Updates on oncologic emergencies:
  - Hypercalcemia
  - Tumor lysis syndrome
  - Thrombocytopenia
  - Pleural effusions

• Review of side effects of immunotherapies

• Discussion of your cases and questions
Tumor Lysis Syndrome | Old and New

- **Mr. T**: 70M with newly diagnosed ALL.
  - **Dx**: Two days prior in setting of 1 week fatigue, DOE, diaphoresis, and diffuse body aches.
  - **Prognostic info**: BCR-abl negative. WBC count of 32; uric acid within normal limits; Cr 1.1.
  - **Treatment**: planning for hyper-CVAD

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Tumor Lysis Syndrome | Review

Which of the following is true about the diagnosis and management in this case?

A. This patient is at intermediate risk for complications of tumor lysis syndrome.
B. He should receive rasburicase prior to initiation of therapy.
C. CBC and lytes should be checked once daily.
D. Febuxostat is preferable to allopurinol in this case for prevention of TLS
**Tumor Lysis Syndrome | Review**

Definition: A syndrome resulting from “the metabolic derangements that occur with tumour breakdown following the initiation of cytotoxic therapy.”

— Cairo & Bishop

**Laboratory tumor lysis = 2 or more electrolyte abnl**
- K > 6 mEq/L
- Phos > 4.5 mg/dL
- UA > 8 mg/dL
- Ca < 7 mg/dL

**Clinical tumor lysis = laboratory tumor lysis AND**
- Cr 1.5x ULN or
- cardiac arrhythmia/sudden death or
- seizure

**Tumor Lysis Syndrome | Review + new**

<table>
<thead>
<tr>
<th>HIGH</th>
<th>MEDIUM</th>
<th>LOW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burkitt lymphoma/leukemia</td>
<td>CLL</td>
<td>Multiple Myeloma</td>
</tr>
<tr>
<td>High grade DLBCL</td>
<td>NHL with elevated LDH</td>
<td>CML</td>
</tr>
<tr>
<td>ALL (wbc &gt;100K)</td>
<td>ALL (wbc &lt;100K)</td>
<td>Other solid tumors</td>
</tr>
<tr>
<td>AML (wbc &gt;100K)</td>
<td>AML (wbc &lt;100K)</td>
<td></td>
</tr>
<tr>
<td>CLL with high burden disease + venetoclax</td>
<td>small cell lung cancer</td>
<td></td>
</tr>
<tr>
<td></td>
<td>germ cell tumors</td>
<td></td>
</tr>
</tbody>
</table>
Tumor Lysis Syndrome | Review

- **Fluids**
  - 2-3 L/m2/day. (D5 1/4 NS preferable)

- **Hypouricemic agents**
  - allopurinol if uric acid is wnl
    - exception is patients of Asian descent (due to inheritance of HLA allele that predisposes to severe cutaneous rxns)
  - febuxostat (alternative to allopurinol)
  - rasburicase if high-risk or elevated uric acid in intermediate-risk patients
    - exception is patients with G6PD deficiency
    - In practice, 3 mg dose is commonly used

- **Monitoring**
  - For patients at high-risk, serum K, Cr, Ca, Phos, uric acid, LDH q4-8H (in addition to 4 hours after first rasburicase dose)
  - Urine output (2 ml/kg/hr)

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Thrombocytopenia | Review

- Mr. J: 54M with h/o hypertension, CKD, and sickle cell trait presents with 2 weeks abdominal pain, nausea, and vomiting.

MEDS:
- Atorvastatin
- Amlodipine
- Carvedilol
- Labetalol
- Pantoprazole
- Senna

EXAM:
- AF 192/130  116
- Lungs with bibasilar crackles bilaterally.
- Abd soft, NT, ND.
- Neuro non-focal.
- Skin with petechiae.

IMAGING:
- CT chest/abdomen without acute findings.
- U/S of kidneys with moderate echogenicity bilaterally.

LABS:
- wbc 12.4  hb 7.9  plt 69
- LDH 719 U/ (140-271)
- T bili 1.0 mg/dL (0.1-1.2)
- PT 14.2 s  INR 1.1
- PTT 31.4 s

Smear: “Few schistocytes with additional RBC fragments and blister cells. May be consistent with microangiopathic hemolytic anemia.”

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<table>
<thead>
<tr>
<th>CLINICAL CHARACTERISTIC</th>
<th>PLATELET DEFECT</th>
<th>CLOTTING FACTOR DEFICIENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site of bleeding</td>
<td>Skin, mucous membranes</td>
<td>Deep in soft tissue</td>
</tr>
<tr>
<td>Bleeding after minor cuts</td>
<td>Yes</td>
<td>Not usually</td>
</tr>
<tr>
<td>Petechiae</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Ecchymoses</td>
<td>Small, superficial</td>
<td>Large, palpable</td>
</tr>
<tr>
<td>Hemarthrosis, muscle hematomas</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Bleeding after Surgery</td>
<td>Immediate, mild</td>
<td>Delayed, severe</td>
</tr>
</tbody>
</table>
Thrombocytopenia | Drug induced

New onset thrombocytopenia

Pit <20K?  
Mucocutaneous bleeding?  
Time course: 5-10 days or <1 day?)?

YES!

Known offender?

YES!

Stop the drug.  
Transfuse. Consider IVIG and steroids.  
Call hematology or lab medicine to test for drug dependent platelet antibodies.

Most common:
- Antibiotics:
  - vancomycin
  - penicillin
  - ceftriaxone
  - TMP/SMX
  - rifampin
- Gp IIb/IIIa inhibitors
- ibuprofen
- quinine

Thrombocytopenia | NEW! For TTP…

Median time to response: 4.9 days vs. 3 days

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Outpatient Talc Administration by Indwelling Pleural Catheter for Malignant Effusion


April 5, 2018

Study question: Does talc administration through pleural catheter increase rates of pleurodesis compared with placement of catheter alone?

Design: Randomized study.

Primary outcome: Rates of pleurodesis.


Patients: 154 patients in the UK with malignant pleural effusions (from solid tumors) and a life expectancy of greater than 2 months.
Main finding:
Talc group had higher rates of pleurodesis (43% vs. 23%; hazard ratio 2.2, p<0.008).

Other findings:
- Talc group had significantly higher measures on quality of life assessments.
- No significant difference in mortality or difference in number of days spent in hospital.

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Cancer cell

Immune cell

PD ligand

pembrolizumab

nivolumab

atezolizumab

PD-1 receptor

CTLA-4

ipilimumab

“You don’t look like you’re from around here”

2014 Melanoma
2015 Lung
Renal cell
2016 Head & neck
2017 DNA repair deficiency, MSI-high
What are the most common side effects? And what are the side effects that are unique to checkpoint inhibitors?

When do these side effects typically develop?

How do I manage immune-related adverse events?

Mr. S: 71M with metastatic melanoma.
- Dx: 9/2014 in setting evaluation for anemia and weight loss revealing lung and renal masses.
- Staging: Metastatic. Lung, renal, small bowel, brain, and spine lesions.
- Treatment:
  - 10/2014-2/2015: Ipilimumab
  - PR with progression of disease in brain
  - 3/2015-presentation: Pembrolizumab

Maculopapular rash on back.
Checkpoint inhibitors | Adverse effects

RASH: The most common adverse event

When? Usually within the first few weeks.

Biopsy? Yes. Rule out TEN, DRESS, etc.

Management:
- If less than 30% BSA (grade 1 or 2), topical steroids and emollients. Oral antihistamines.
- If more than 30% BSA (grade 3), discontinue immunotherapy. Consider oral systemic steroids.
- If grade 4 (SJS, TEN), discontinue immunotherapy. Admit. IV methylprednisolone 1-2 mg/kg.

<table>
<thead>
<tr>
<th>Adverse events: General</th>
<th>Adverse events: Immune</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin (7%)</td>
<td>Skin (10%)</td>
</tr>
<tr>
<td>GI (6%)</td>
<td>-rash</td>
</tr>
<tr>
<td>Musculoskeletal (3%)</td>
<td>-pruritis</td>
</tr>
<tr>
<td>Endocrine (2%)</td>
<td>-vitiligo</td>
</tr>
<tr>
<td>Nervous system (2%)</td>
<td>GI</td>
</tr>
<tr>
<td>Respiratory (1%)</td>
<td>Musculoskeletal (2%)</td>
</tr>
<tr>
<td>Blood/lymphatic (1%)</td>
<td>Endocrine (2%)</td>
</tr>
</tbody>
</table>
Checkpoint inhibitors | Adverse effects

• Mr. S: 71M with metastatic melanoma.
  • Dx: 9/2014 in setting evaluation for anemia and weight loss revealing lung and renal masses.
  • Staging: Metastatic. Lung, renal, small bowel, brain, and spine lesions.
  • Treatment:
    • 10/2014-2/2015: Ipilimumab
      • PR with progression of disease in brain
    • 3/2015-11/2017: Pembrolizumab
      • CR!

Acute chest pressure refractory to nitroglycerin.

Checkpoint inhibitors | Adverse effects

• Mr. T: 70M with metastatic lung cancer.
  • Dx: 4/2014 in setting evaluation for anemia and weight loss.
  • Staging: IIIA (4/2014); metastatic (7/2014).
    Bilateral lungs, pleural with effusion.
  • Treatment:
    • 4/2014: Chemoradiation
    • 10/2014: Carboplatin/pemetrexed followed by pemetrexed maint.
      • SD
    • 8/2015: paclitaxel/trastuzumab
      • SD
    • 9/2016: nivolumab

Monitoring labs reveal a transaminitis (2.5 x ULN)
Checkpoint inhibitors | *Adverse effects*

**IMMUNE RELATED HEPATITIS:**
Relatively common ~1-10%.

**When?** Usually within the first few weeks.

**Management depends on degree:**
- **Grade 1 (less than 3x ULN):** No intervention.
- **Grade 2 (3-5x ULN),** Recheck in 3 days. Steroids if LFTs rising.
- **Grade 3 (5-20x ULN) AND normal bili/albumin:** Stop immunotherapy. Oral prednisolone 1 mg/kg/day.
- **Worse than above:** Stop immunotherapy. IV methylprednisolone 2 mg/kg/day.

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### Adverse events: Pembro

- Skin (10%)
  - rash
  - pruritis
  - vitiligo
- GI
  - Musculoskeletal (2%)
  - Endocrine (2%)

### Adverse events: Nivo

- Skin (24%)
- GI (15%)
- Hepatic (12%)
- Pulmonary (5%)
Checkpoint inhibitors | Adverse effects

- Mr. T: 70M with metastatic lung cancer.
  - Dx: 4/2014 in setting evaluation for anemia and weight loss.
  - Bilateral lungs, pleural with effusion.
  - Treatment:
    - 4/2014: Chemoradiation
    - 10/2014: Carboplatin/pemetrexed followed by pemetrexed maint.
      - SD
    - 8/2015: paclitaxel/trastuzumab
      - SD
    - 9/2016: nivolumab
      - SD

Mild increase in fatigue and decreased appetite.
<table>
<thead>
<tr>
<th>ORGAN</th>
<th>FREQUENCY (all grades / severe)</th>
<th>TIMING</th>
<th>MANAGEMENT (mild / moderate / severe)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>33% / &lt;3%</td>
<td>weeks</td>
<td>Topical steroids / oral systemic steroids / IV methylpred</td>
</tr>
<tr>
<td>GI - colitis</td>
<td>33% / &lt;7% or 1%</td>
<td>weeks</td>
<td>Loperamide / IV methylpred + consider infliximab</td>
</tr>
<tr>
<td>GI- hepatitis</td>
<td>&lt;9% or &lt;2%</td>
<td>weeks</td>
<td>Monitor / oral steroids / oral or IV steroids + consider MMF</td>
</tr>
<tr>
<td>Endocrine (hypothalamus, thyroid)</td>
<td>&lt;5%</td>
<td>months</td>
<td>Hypothyroid: levothyroxine Hypophysitis: methylpred/pred, indefinite hormone replacement</td>
</tr>
<tr>
<td>Lung</td>
<td>5% / &lt;1%</td>
<td>Median 2.5 months</td>
<td>Monitor / methylpred + consider infliximab with slow steroid taper</td>
</tr>
<tr>
<td>Kidney</td>
<td>2%</td>
<td>Median 3 months</td>
<td>Monitor / pred / methylpred + consider infliximab, aza, MMF with slow taper</td>
</tr>
<tr>
<td>Eye (uveitis)</td>
<td>variable</td>
<td>variable</td>
<td>Artificial tears / ophthalmic steroid / + systemic steroid with slow taper</td>
</tr>
<tr>
<td>CNS</td>
<td>5% / &lt; 1%</td>
<td>Median 6 weeks</td>
<td>Depends on specific condition</td>
</tr>
<tr>
<td>CV - myocarditis</td>
<td>1%</td>
<td>Median 4 weeks</td>
<td>If severe, methylpred + consider infliximab with slow taper</td>
</tr>
<tr>
<td>MSK - arthralgia</td>
<td>variable</td>
<td>variable</td>
<td>NSAID / pred / methyl pred + consider infliximab with slow taper</td>
</tr>
</tbody>
</table>

~ for additional detail, see nccn.org ~

### Checkpoint inhibitors | Adverse effects

**What are the most common side effects? And what are the side effects that are unique to checkpoint inhibitors?**

Like chemotherapy, fatigue, n/v/d, rash, cytopenias.  

**Immune-related adverse events are unique:**  

**Skin, GI/liver, Endocrine, Lung**

**When do these side effects typically develop?**  

Anytime; from weeks to months after start.

**How do I manage immune-related adverse events?**

Depends. In general, steroids/immunosuppression.  

Enlist multidisciplinary support.
Summary

• New for oncologic emergencies:
  • Denosumab for hypercalcemia of malignancy
  • New therapies for heme malignancies = new risks for TLS
  • Caplacizumab for TTP
  • Outpatient talc for pleural effusions

• Adverse effects of checkpoint inhibitors
  • Although conventional side effects are more common, have a high degree of suspicion for immune-related adverse effects.
    • Most common: skin, GI, hepatic, endocrine, lung
    • Steroids and multidisciplinary care.