Updates on Oncologic Emergencies, Including Side Effects of New Therapies

Gerald Hsu, MD, PhD
Assoc. Clinical Professor of Medicine
University of California, San Francisco

Outline

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

• Review of uses and side effects of immunotherapies

Disclosures

I have nothing to disclose

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.

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>
</tr>
<tr>
<td></td>
<td></td>
<td>• Breast cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Renal cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Ovarian or endometrial cancer</td>
</tr>
<tr>
<td>Osteolytic</td>
<td>Cytokine mediated</td>
<td>• Multiple Myeloma</td>
</tr>
<tr>
<td></td>
<td>and PTHrP</td>
<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

Hypercalcemia | Review

- **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
  - (eg. 4 mg zoledronic acid over 1 hour or 30 mg pamidronate over 4 hours)
- Calcitonin until kidney function improves
- RANK ligand inhibitor (ie. denosumab) that is not renally cleared.

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Tumor Lysis Syndrome | Old and New
- Mr. T: 70M with CLL with wbc count of 150,000/uL, progressive anemia and bulky adenopathy.
- Prognostic info: FISH testing revealed presence of deletion 17p.
- Treatment: Considering ibrutinib or venetoclax with or without rituximab.

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

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>High grade DLBCL</td>
<td></td>
</tr>
<tr>
<td>ALL (wbc &gt;100K)</td>
<td>ALL (wbc &lt;100K)</td>
<td></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>CLL with elevated LDH</td>
<td>Multiple Myeloma</td>
</tr>
<tr>
<td></td>
<td>NHL with elevated LDH</td>
<td>CML</td>
</tr>
<tr>
<td></td>
<td>ALL (wbc &lt;100K)</td>
<td>Other solid tumors</td>
</tr>
<tr>
<td></td>
<td>small cell lung cancer</td>
<td></td>
</tr>
<tr>
<td></td>
<td>germ cell tumors</td>
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</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
    - Caution with patients of Asian descent (due to inheritance of HLA allele that predisposes to severe cutaneous rna)
  - 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-H (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 150/130 116
- Lungs with bibasilar crackles bilaterally.
- Abd soft, NT, N
- Neuro non-focal.
- Skin with petechiae.

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

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

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

- Mr. T: 68M with CLL and new pleural effusion.
  - PET CT revealed fdg avid pleural nodules and hilar adenopathy.
  - Thoracentesis performed and cytology revealed atypical cells suspicious for adenocarcinoma that is confirmed with additional staining.

How should manage the pleural effusion?
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-1 receptor

“Leave me alone. I don’t look like you’re from around here”

PD ligand

Cancer cell

pembrolizumab

nivolumab

atezolizumab

CTLA-4

“Leave me alone. I don’t look like you’re from around here”

2014  Melanoma
2015  Lung
          Renal cell
2016  Head & neck
          Hodgkin lymphoma
2017  DNA repair deficiency, MSI-high
2018  Hepatocellular
          Cervical
2019  Breast Cancer (triple neg)

2018 TOP 5 ONC DRUGS

1. Lenalidomide
2. Nivolumab (+31%)  
   $7.6$ billion
3. Pembrolizumab (+88%)  
   $7.2$ billion
4. Trastuzumab
5. Bevacizumab

Checkpoint inhibitors | Adverse effects

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?
### 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-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.

### Checkpoint inhibitors | Adverse effects

<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>Musculoskeletal (2%)</td>
</tr>
<tr>
<td>Respiratory (1%)</td>
<td>Endocrine (2%)</td>
</tr>
<tr>
<td>Blood/lymphatic (1%)</td>
<td></td>
</tr>
</tbody>
</table>

### 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.

**Adverse events: Pembro**
- Skin (10%)
- -rash
- -pruritis
- -vitiligo
- GI
- Musculoskeletal (2%)
- Endocrine (2%)

**Adverse events: Nivo**
- Skin (24%)
- GI (15%)
- Hepatic (12%)
- Pulmonary (5%)

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  - SD
  - 9/2016: nivolumab
  - SD

* Mild increase in fatigue and decreased appetite.
### Checkpoint inhibitors | Summary of irAEs

<table>
<thead>
<tr>
<th>ORGAN</th>
<th>FREQUENCY</th>
<th>TIMING</th>
<th>MANAGEMENT</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</td>
<td>33% / &lt;5% or 1%</td>
<td>weeks</td>
<td>Loperamide / IV methylpred + consider infliximab</td>
</tr>
<tr>
<td>Liver</td>
<td>&lt;1% or &lt;3%</td>
<td>weeks</td>
<td>Monitor / oral steroids / oral or IV steroids + consider MMF</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Hypothalamic, Pituitary</td>
<td>&lt;5%</td>
<td>months</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>Eye (uveitis)</td>
<td>variable</td>
<td>variable</td>
<td>Artificial tears / ophthalmic steroid + consider infliximab with 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 = new risks for TLS
  - Caplacizumab for TTP
  - Outpatient talc for malignant 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.