Pulmonary Toxicity of (Lung) Cancer Therapies

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Disclosure Statement

I will discuss off label use and/or investigational use of the following drugs/devices:

Prednisone

The following relevant financial relationships exist related to my role in this session:

No relationships to disclose
I'm having trouble breathing.
Outline: Treatment Related Pulmonary Toxicity

- Potential Etiologies / Patterns
  1. Chemotherapy (docetaxel, gemcitabine, bleomycin)
  2. Targeted therapy (EGFR inhibitors, mTOR inhibitors, PD-1 and PD-L1 inhibitors)
  3. Radiation therapy

- Diagnosis / Grade of Pneumonitis

- Management
The importance of this challenge

- Many new therapies being developed / approved
- We must be aware of these therapies and understand their mode of action
- Important to learn to recognize, diagnose and effectively manage their toxicities
Case 1:
Special Thanks to UCSF Clinical Fellow
Alyssa Perez
Case 1

- 75 M with a history of A-fib s/p ablation, HTN, and metastatic prostate CA on treatment with docetaxel who presents with hypoxemic respiratory failure requiring high flow nasal cannula
Case 1

- Onset of SOB 10 days prior
- Rapidly progressed
- On day of presentation, EMS was called after home O2 sat in the 60s
- In ED, hypoxemic and tachypneic in the 30s, placed on HFNC FiO2 100%, 40LPM
**Case 1**

**PMHx/PSHx:**
1. Metastatic Prostate CA: dx 2006, metastatic in 2013, s/p XRT, anti-hormone agents, pembrolizumab x 2 (last 1/2017), and now on docetaxel
2. HTN
3. A-fib s/p cardioversion,
4. Appendectomy in 2011
5. Laminectomy with fusion in 2013 for metastatases

**Family History:** father with prostate CA

**Social History:** never smoker, 1 glass wine nightly, no illicits, no exposures

**Home Meds:**
1. cholecalciferol
2. omega-3 fish oil
3. Dexamethasone

**Allergies:** none
Case 1

EXAM:
Vitals:  T: 37.2 HR: 115 BP: 80/60 RR: 30 O2 Sat: 91% (on 100% FiO2)
General: increased work of breathing
CV: irregularly, irregular, tachycardic, S1, S2, no murmurs
Resp: bilateral crackles diffusely
Ext: 2+ pitting edema to the mid shin b/l, +DP and TP pulses
Case 1

LABS:

BUN      41
Creat    1.13
WBC      4.4
Hgb      7.6
Trop     < 0.04
BNP      484
LDH      382
Case 1: Hospital course

Day 1:
- Started on vancomycin and ertapenem
- Boluses of normal saline → BPs normalized.
- Pan cultured (blood, urine, sputum) & Resp viral panel sent
- Diuresed with lasix
Case 1: Hospital course

Day 2:

- TTE normal (EF 60%)
- Antibiotics broadened to include pseudomonal and atypical coverage. Diuresis continued.
- Micro: cultures remain NGTD, including Resp viral panel
- Remains afebrile, normotensive. Continues on HFNC with FiO2 100% on 40L, sats in low 90s
- CT scan obtained.
Case 1

Differential diagnosis?
Case 1: Hospital course

- Pulmonary Consulted.

Questions
  - What is the diagnosis?
  - Could this be Drug (Docetaxel) induced pneumonitis?
  - Should we give steroids?
Diagnostic algorithm of pneumonitis

- History/Clinical examination
  - Lung co-mobidities
  - Type and dose of agent
  - Symptoms (Cough, Fever, Dyspnoea, Hypoxia)
Drug induced Lung Injury

- Unknown prevalence, thought to be under recognized globally

- Can be acute, sub-acute, or chronic

- Pathogenesis:
  - Direct damage to pneumocytes
  - Capillary leak syndrome
  - Acute or delayed hypersensitivity reaction

Pre-disposing characteristics

- Receiving prior chemotherapy
- Autoimmune diseases (RA, IBD),
- Extremes of age
- Prior radiation
- Pre-existing lung disease
- Smoking history
Histologic patterns

- NSIP
- OP
- Interstitial granulomas
- UIP
- DAH +/- capillaritis
- DAD
- PVOD
- DIP
- LIP
- PAP
- Eosinophilic pneumonia

Diagnostic algorithm of pneumonitis

Recommended work-up depending on pneumonitis grade:

- Chest X-ray
- Arterial blood gases
- HRCT
- Bronchoscopy with BAL +/- biopsy
- PFT

Rule out:

- Pulmonary infection
- Metastatic disease (lymphangitis carcinomatosa)
- Cardiogenic pulmonary oedema
- Pulmonary embolus, etc
### Evaluation of patient with possible Drug Induced Lung Injury

<table>
<thead>
<tr>
<th>Steps</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PFTs</strong></td>
<td>• Lung volumes and DLCO (for baseline and monitoring)</td>
</tr>
</tbody>
</table>
| **Chest CT scan**                              | • Exclude other possible diagnoses (tumor progression, pleural effusion, PE)  
• Assess pattern / monitor for change         |
| **Bronchoscopy**                               | • BAL may be useful to rule out infection (particularly in fever / infection suspected) or to assess the lung inflammation profile  
• TBBx may help to obtain histology, assess for lymphangitic disease |
| **Diagnostic tests to exclude opportunistic infections** | • Bacterial pneumonia (typical acute lobar pneumonia)  
• Viral pneumonia (Respiratory Viral PCR)  
• Other bacterial infections (including *Legionella* infection, particularly in hospitalized patients)  
• Invasive fungal infections (e.g., *Pneumocystis jiroveci*, *Pneumocystis carinii* infection, Aspergillosis) |
| **Consider other causes**                      | • Pulmonary edema / Heart failure                                         |
Day 2 continued:

- All micro data NGTD including blood, sputum, urine, and RVP

- Not improving despite diuresis and Echo did not suggest heart failure

- Bronchoscopy considered but deferred given oxygen requirement and DNR/DNI status
Drug induced Lung Injury


Radiologic and Pathologic Findings with Docetaxel Induced Lung Injury:

- Acute ILD
- Subacute ILD
- Transient Infiltrates
- Pulmonary Edema
- ARDS
- DAH
- DAD

**Docetaxel induced pneumonitis**

**Docetaxel** = taxane used to treat solid tumors

Proposed Mechanisms of Injury:
- **Acute: Type 1 Hypersensitivity reaction**
  - Dyspnea, bronchospasm, hypotension
  - Incidence is 30% of patients; decreases to 1-3% of patients with steroid pre-medication

- **Acute-Subacute: Type IV Hypersensitivity reaction**
  - Few hours to 2 weeks
  - Characterized by bilateral pulmonary opacities

Docetaxel induced pneumonitis

Acute-Subacute: Type IV Hypersensitivity reaction

- Presents as insidious onset
- Symptoms: dyspnea, malaise, chest pain, cough, and fever
- Also associated with edematous state: edema and pleural effusions
- Imaging generally shows bilateral pulmonary infiltrates
  - Most common pattern = NSIP, DAD, pleural effusions

Docetaxel induced pneumonitis

- Factors that increase likelihood of developing severe pneumonitis:
  - Schedule > Dose
  - Combination therapy with gemcitabine
  - Radiation treatment

- A 2012 retrospective study found increased incidence of pneumonitis in patients with NSCLC treated with docetaxel who had baseline pulmonary dysfunction
  - 25.9% vs 4.6% general incidence
  - Recommended against the use of docetaxel in patients with pre-existing lung disease

Docetaxel induced pneumonitis

- Thought to be a steroid responsive process but case reports range from steroid responsive pneumonitis to steroid unresponsive pneumonitis to development of fibrosis

- General recommendation is prompt treatment with steroids
  - No consensus on dose

Case 1: Hospital course

Day 3:
- Started on methylprednisolone 125 mg IV Q6 hours
- Patient subjectively feels improved

Day 4:
- Improvement in oxygen requirement to 50% FiO2 40L HFNC
- Patient continues to feel better, no longer tachypneic at rest
- Chest CT repeated
Case 1: Hospital course

Day 5:
- Ongoing improvement, down to 6L NC
- Steroids changed to prednisone 40 mg PO daily

Day 6:
- Discharged home
- Plan for slow taper of prednisone
Take away points

- Need to consider drug induced lung injury in patients on chemotherapy

- Docetaxel is a rare but well-associated cause of pneumonitis, most commonly presenting with subacute dyspnea and bilateral ground glass opacities
  - Treatment is prompt initiation of steroids, 0.5-0.7 mg/kg prednisone likely sufficient

- Consider avoiding docetaxel in patients with pre-existing lung disease
Case 2:
Case 2

67 y.o. man with metastatic Prostate Cancer (bone, testes, brain). Initially diagnosed in 2005, s/p multiple treatments. Referred to pulmonary for complaints of dyspnea on exertion, dry cough x 3 weeks and an abnormal chest CT scan.

SpO2 at rest 96% on RA
Case 2 – What is your differential diagnosis?

- Metastases to lung
- Pulmonary emboli
- Infections
- Pulmonary edema
- Pneumonitis due to drugs or RT
Case 2 Baseline in 3/2017
Case 2 Baseline in 3/2017
Case 2 Baseline in 3/2017
Case 2 in 9/2017
Case 2 in 9/2017
Case 2

- Treated with XRT and adjuvant docetaxel (completed 12/2007)
- 2 years on Goserelin (LHRH analogues) and Bicalutamide (antiandrogens) until 2009
- Multifocal symptomatic brain mets s/p CK
- Carboplatin/taxotere → 11/2016 – 1/2017
- New brain mets s/p CK
- Started on pembrolizumab in 3/2017
Diagnostic algorithm of pneumonitis

Rule out:
- Pulmonary infection
- Metastatic disease (lymphangitis carcinomatosa)
- Cardiogenic pulmonary oedema
- Pulmonary embolus, etc

Yes

Consider drug related pneumonitis

No

Treat as appropriate
So let's consider these newer targeted agents?

1. TKIs: EGFR
2. mTOR inhibitors
3. PD-1 and PD-L1 inhibitors
**TKIs and ILD**

- 1st case reported in 2003 in Lancet – Gefitinib
- Multiple reports since then

<table>
<thead>
<tr>
<th></th>
<th>DAD</th>
<th>BO</th>
<th>COP</th>
<th>HP</th>
<th>IP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gefitinib</td>
<td>++</td>
<td></td>
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<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Erlotinib</td>
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<td>+</td>
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<tr>
<td>Sorofenib</td>
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</table>

mTOR inhibitors

- Sirolimus
- Everolimus
- Temsirolimus
**PD-1**

Anti-PD-1 monoclonal antibodies
- Nivolumab
- Pembrolizumab (previously lambrolizumab)
- Pidilizumab

Anti-PD-L1 mAbs
- Durvalumab
- Atezolizumab
PD-1 and PD-L1 mAbs

Toxicities with anti-PD-1/PD-L1 mAbs appear to be less common and less severe

7% to 12% in patients receiving single-agent anti-PD-1/PD-L1 mAbs
PD-1 and PD-L1 mAbs

Adverse events of anti-PD-1/PD-L1 therapy

- Fatigue
- Pyrexia, chills, infusion reactions
- Skin rash (maculopapular, papulopustular, Sweet's syndrome, follicular, or urticarial dermatitis)
- Diarrhea/colitis
- Endocrine toxicities (hypophysitis, hypothyroidism, hyperthyroidism, thyroiditis, and adrenal insufficiency)
- Hepatic toxicities (elevations in AST and ALT levels)
- Pneumonitis
Time to development of pneumonitis after starting PD-1 or PD-L1 inhibitor

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5559901/
## Radiographic pattern of pneumonitis on PD-1 or PD-L1

<table>
<thead>
<tr>
<th>Radiologic Subtypes</th>
<th>Representative Image</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cryptogenic organizing pneumonia-like</strong></td>
<td><img src="cryptogenic.jpg" alt="Image" /></td>
<td>Discrete patchy or confluent consolidation with or without air bronchograms</td>
</tr>
<tr>
<td><em>(n = 5, 19%)</em></td>
<td></td>
<td>Predominantly peripheral or subpleural distribution</td>
</tr>
<tr>
<td><strong>Ground glass opacities</strong></td>
<td><img src="ground_glass.jpg" alt="Image" /></td>
<td>Discrete focal areas of increased attenuation</td>
</tr>
<tr>
<td><em>(n = 10, 37%)</em></td>
<td></td>
<td>Preserved bronchovascular markings</td>
</tr>
<tr>
<td><strong>Interstitial</strong></td>
<td><img src="interstitial.jpg" alt="Image" /></td>
<td>Increased interstitial markings, interlobular septal thickening</td>
</tr>
<tr>
<td><em>(n = 6, 22%)</em></td>
<td></td>
<td>Peribronchovascular infiltration, subpleural reticulation</td>
</tr>
<tr>
<td><strong>Hypersensitivity</strong></td>
<td><img src="hypersensitivity.jpg" alt="Image" /></td>
<td>Honeycomb pattern in severe patient cases</td>
</tr>
<tr>
<td><em>(n = 2, 7%)</em></td>
<td></td>
<td><strong>Hypersensitivity</strong>&lt;br&gt;Centrilobular nodules&lt;br&gt;Bronchiolitis-like appearance&lt;br&gt;Tree-in-bud micronodularity</td>
</tr>
<tr>
<td><strong>Pneumonitis not otherwise specified</strong></td>
<td><img src="pneumonitis.jpg" alt="Image" /></td>
<td>Mixture of nodular and other subtypes&lt;br&gt;Not clearly fitting into other subtype classifications</td>
</tr>
</tbody>
</table>
Grade of pneumonitis on PD-1 or PD-L1 inhibitor

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5559901/
Clinical algorithm of drug-induced pneumonitis/pulmonary fibrosis

**Grade 1**
Asymptomatic, only radiological changes

- Clinical monitoring every cycle
- Lung CT scan every two cycles until return to baseline

No dose adjustment

**Grade 2**

- Clinical monitoring every cycle
- Lung CT scan every two cycles until return to baseline

**Grade 2A**
Minor respiratory symptoms (slight cough)

- Close clinical monitoring
- Lung CT scan after 2 weeks if symptoms persist
- Consider steroids after infection is ruled out

No dose adjustment

**Grade 2b**
Severe cough and dyspnoea

- Interruption of the drug; consider re-start with 50% DR if recovery to ≤G1 within 2 weeks and the drug is a targeted agent
- Permanent withdrawal if the drug is a chemotherapeutic

**Grade 3**
Interference with ADL

- Admission to hospital
- Perform bronchoscopy with BAL +/- biopsy
- Consider IV steroids
- Consider O2 and IV antibiotics

**Grade 4**
Life-threatening

- Permanent withdrawal

If recurs consider permanent discontinuation

Case 2 – Follow up

- Treated with **Prednisone** – initially 70 mg (1 mg / kg) daily and slowly tapered over 4 months
- 1/2018 **pembrolizumab** restarted
Case 2 – October 2017
Take Home Points from Diagnosis / Management of Drug Induced Pneumonitis

A question for you…

54 year old woman who has been responding to treatment with pembrolizumab for lung cancer now develops Grade 1 drug induced pneumonitis. Which of the following is the most appropriate recommendation?

A. Stop pembrolizumab permanently
B. Hold pembrolizumab. If symptoms imaging improves within 1 week, resume therapy.
C. Continue pembrolizumab with 50% dose reduction.
D. No dose adjustment if needed. Continue to monitor clinically and with repeat chest CT scans.
A question for you…

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<tr>
<th>Grade</th>
<th>Presentation</th>
<th>Diagnostic Testing</th>
<th>Management</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Asymptomatic with Radiographic changes only</td>
<td>Chest CT scanning Consider Bronch +/- other microbial assessment</td>
<td>Continue therapy Monitor sx q3 days</td>
<td>Repeat Chest CT after every cycle or if develops sx.</td>
</tr>
<tr>
<td>2</td>
<td>Mild / Moderate new symptoms</td>
<td>HOLD therapy Monitor sx daily Oral prednisone (1mg/kg/d)</td>
<td>If improves to &lt; Grade 1 w/in 3 days, resume therapy. If persists, stop therapy. Taper steroids over 1+ mo.</td>
<td></td>
</tr>
<tr>
<td>3-4</td>
<td>Severe or life threatening Worsening hypoxia</td>
<td>STOP therapy Hospitalize IV methylpred 2-4 mg/kg/d</td>
<td>After sx improve to &lt; Grade 1, taper steroids over 6+ wks If worsens, consider additional immunosuppression</td>
<td></td>
</tr>
</tbody>
</table>
Case 3:
Special Thanks to UCSF Clinical Fellow
Shoshana Zha
Case 3: 78 year-old man presenting with worsening dyspnea

- 2004: Adenocarcinoma stage IA RLL lobectomy
- February 2017: Biopsy proven adenocarcinoma
- December 2016: Enlarging right middle lobe nodule
- March 20th – 24th 2017: SBRT 5000 cGy in 5 fractions
- June 22nd 2017: Admitted to UCSF
- June 2017: Dry cough, low grade fever and progressive dyspnea 7-day treatment for CAP

Special thanks to Shoshana Zha, MD for case / slides
# Case 3: Additional History

**PMH**
- Type-II DM
- CAD s/p CABG 6/2016, persistent L pleural effusion
- CHF (EF 50-55%)
- A-fib & sick sinus with pacemaker
- HTN
- CKD stage IV
- COPD: FEV1 1.4 (67%)

**MEDICATIONS**
- ASA
- Atorvastatin
- Metoprolol XL
- Bumex 2mg BID
- Coumadin
- Glargine
- Pioglitazone
- Repaglinide
- Spiriva daily,
- Albuterol PRN

**SH:**
- Smoked 50-60 pack years, quit ~2003
- Occasional alcohol
- No illicit drug use

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Case 3: Differential diagnosis

- Infection
- Radiation pneumonitis
- Organizing pneumonia
- Diffuse alveolar hemorrhage
- Hypervolemic
- Malignancy

Special thanks to Shoshana Zha, MD for case / slides
Case 3: Workup/management

- Started steroids 60mg/day and levofloxacin
- Bronchoscopy without sign of infection or DAH
- Began to improve
- Steroids tapered: 60mg x 6 days → 40mg x 3 days → 20mg daily in setting of rapid improvement + difficult glycemic control
- Discharged on 20mg/day to be taken until follow-up

Special thanks to Shoshana Zha, MD for case / slides
Case 3: To ED 34 days later

- 2-weeks of worsening dyspnea on exertion
- Low-grade fever
- Non-productive cough
- Chest pressure
- In ED, hypoxic to 82% on room air

Special thanks to Shoshana Zha, MD for case / slides
Case 3: Physical exam

- Vitals: BP 104/53, HR 84, RR 20, O2 Sat 96% on 10LPM supplemental oxygen

- CV: Irregularly irregular. PMI displaced laterally. No murmurs. JVD 7 cm at 30 degrees. Trace edema BLE.

- Resp: Speaking in 3-4 word sentences. Bibasilar crackles.

Special thanks to Shoshana Zha, MD for case / slides
Case 3: Laboratories/data

VBG (ABG not obtained): 7.46 / PCO2 45/

BUN 30, Cr 1.55 (baseline 1.3), Electrolytes WNL

WBC 12.2 with 10.45 N, 0.68 L, 0.84 M, 0.15 E

LFTs WNL

Troponin 0.1, EKG without significant changes

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Case 3 - progression

- Day after admission, O2 titrated up to 10-12LPM
- On review with wife, prednisone had been discontinued

Special thanks to Shoshana Zha, MD for case / slides
Case 3 - improvement

- Started on prednisone 40mg/day and down to 2LPM within 4 days
- Discharged to take 20mg/day x 2 weeks, then 15mg/day until follow-up

Special thanks to Shoshana Zha, MD for case / slides
## Radiation induced lung injury

<table>
<thead>
<tr>
<th>Radiation Pneumonitis</th>
<th>Radiation Induced Organizing Pneumonia</th>
<th>Radiation Induced Fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 6 months</td>
<td>3 – 6 months</td>
<td>&gt;6 months</td>
</tr>
<tr>
<td>Dry cough</td>
<td>Dry cough</td>
<td>May be asymptomatic</td>
</tr>
<tr>
<td>Progressive dyspnea</td>
<td>Progressive dyspnea</td>
<td></td>
</tr>
<tr>
<td>Low-grade fevers or chills</td>
<td>Low-grade fevers or chills</td>
<td>High chronic inflammation → circulating platelet-derived and basic fibroblast growth factor</td>
</tr>
<tr>
<td>Malaise</td>
<td>Malaise</td>
<td></td>
</tr>
<tr>
<td>Pleuritic chest pain</td>
<td>More diffuse disease</td>
<td></td>
</tr>
<tr>
<td>Immediately capillary leakiness, delayed exudative alveolitis</td>
<td>Priming of lymphocytes</td>
<td></td>
</tr>
</tbody>
</table>

Murray et al, 2012. Radiation oncology, 7123
Ding et al. 2013 Curr drug targets. 14, 1247-1356
**Imaging and Radiological grading scale (RTOG)**

**Radiation Pneumonitis**
- I – GGO without fuzziness of subjacent pulmonary vessels
- II – GGO extending beyond radiation field or consolidations
- III – focal consolidation +/- elements of fibrosis
- IV – dense consolidation, traction bronchiectasis, volume loss

**Radiation-induced organizing pneumonia**
- Outside radiation field → Often more pronounced in contralateral lung
- Migrates
- Relapses

*Oie et al, 2013. Radiation Oncology. 856*
*Kouloulias et al 2014, Asian Pacific J Cancer Prev, 14, 2717-22*
*Murai et al, 2012. Radiat Oncology 7:123*
Risk/Associated factors

- Smoking History
- Age >65
- Underlying lung disease
- Tumor location: mid-lower lung
- Adjuvant chemotherapy
- Risk with stereotatic (SBRT) 5-10% (up to 28% in older trials)
  - Often lower grade disease
  - Risk stage III with larger tumor
- Expression of Krebs Von den lungen-6

Corticosteroids

- Mainstay of therapy since 1950s
- No standard, but initial dose often Prednisone 0.5 – 1 mg/kg
- High risk of relapse, thus slow / prolonged taper is important
  - Literature dating back to 1960s note relapse with rapid withdrawal of steroids
  - Textbooks recommend decrease of 10mg q2weeks – no trials/data of support this recommendation

Experimental approaches

- Pentoxyphylline – reduced fibrosis in rats (Sterreicher et al. 2001)
- Prophylactic anti-inflammatory agents
- Inhaled steroids
- Case reports of azathioprine and cyclosporine

Hekenberens et al., 2016. Radiation Oncology 11:12
Radiation induced lung injury summary

- Important to try to differentiate Radiation Pneumonitis from Radiation Induced Organizing Pneumonia

- If significantly hypoxic, consider steroids but TAPER VERY SLOWLY
Take Home Points

- A single drug can be associated with multiple lung injury patterns
  - Variety of histologic and radiographic patterns
  - Histologic patterns don’t correlate well with imaging findings

- In most situations, must rely on
  - **temporal relationship** between the administration of drug and the onset of lung injury,
  - along with the exclusion of other potential causes, particularly infections and metastatic disease
Take Home Points

- Grade the degree of lung injury to determine the next steps in therapy / management

- If has also received XRT or SBRT, consider Radiation induced lung injury patterns:
  - Radiation Pneumonitis
  - Radiation Induced Organizing Pneumonia
  - Radiation Induced Fibrosis