MANAGEMENT OF IMMUNE-RELATED ADVERSE EVENTS IN
PATIENTS
TREATED WITH IMMUNE CHECKPOINT INHIBITOR THERAPY

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Learning Objectives

At the end of the presentation the learner will be able to:

- Discuss the toxicities and management issues associated with the immune checkpoint inhibitors
- Increase awareness of pneumonitis, colitis toxicity in the NSCLC population
Mechanism:

- Works by blocking pathways called checkpoints. These checkpoint pathways are mechanisms for the human immune system to control the immune response.
ICPis Approved

- Ipilimumab – Advance Melanoma
- Pembrolizumab and nivolumab – Advance melanoma, metastatic NSCLC, head and neck squamous cancers, urothelial carcinoma, gastric adenocarcinoma, and Hodgkin lymphoma.
- Combination Ipilimumab and nivolumab- Advanced melanoma and Lung cancer
- Atezolizumab – NSCLC and urothelial cancers
- Durvalumab- Urothelial cancers
- Avelumab – Merkel cell carcinoma and urothelial cancer
Selected Adverse Events

Presented By Shirish Gadgeel at 2018 ASCO Annual Meeting
Common Toxicities

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<table>
<thead>
<tr>
<th>Toxicities</th>
<th>Any Grade (%)</th>
<th>Grade 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>16-20</td>
<td>1</td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>10-14</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Rash</td>
<td>9-13</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>8-11</td>
<td>1</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>2-5</td>
<td>2</td>
</tr>
</tbody>
</table>

Hyperthyroidism, Myocarditis, Adrenal insufficiency, Myositis, Type I diabetes, Hepatitis. *Reviewed data from Checkmate 057, Keynote 10 and OAK.
Guidelines

- Electrolytes, TSH, LFT’s and Kidney function and CBC to be evaluated before each cycle
- Educated patients and colleagues
- Consults
Guidelines Management

- irAEs higher with CTLA4 (exceptions: hypothyroidism, type I DM)

- Grade 1- symptomatic management, continue ICI

- Grade 2- Steroids 0.5-1.0mg prednisone, hold ICI, restart once grade 1 and prednisone at 10mg daily.

- Grade 3- Steroids 1-2mg prednisone, Infliximab. Steroid taper over 4-6 weeks. May restart PD-(L)-1 drugs with high level of caution.

- Grade 4- Steroids 1-2mg prednisone, Infliximab, other immunosuppressants, discontinue ICI (exception: endocrinopathies)

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Pneumonitis

- Incidence of pneumonitis 5%: 10% with PDL-1 AND and CTLA4 combinations (higher in combinations 10% vs 3%)
- No clear association with prior chest RT.
- Median time onset: 2.8 months (9d-19.2m)
- 88% G1/G2
Pneumonitis: Management Algorithm

- **G 1** - No symptoms, radiographic changes only
- **G 2** - NO improvement in 48 hrs. with steroids → Manage as G3
- **G 3/4** – IV steroids, bronchoscopy/empiric antibiotics/consider Ifliximab
Clinical case

- 64 year old male
- Smoker
- PMH: emphysema, GERD, HTN, obesity
- Adenocarcinoma of the lung stage IV with left adrenal metastasis 10/2014
- Non actionable mutations
- First line: chemotherapy and maintenance until progression on 6/13/2016
- SBRT left adrenal mass 8/2016
- Second line therapy palliative immunotherapy # 4 cycles until developed bilateral pneumonitis on 11/2016
- 11/2016 worsening dyspnea. CT chest scattered areas of patchy opacity and consolidation extent bilaterally since last CT 10/2016. Negative cultures and viral panel.
- Treatment: HOLD immunotherapy. IV antibiotics for possible community acquired pneumonia + IV steroids high dose (methylprednisolone). D/C immunotherapy.
- Patient on remission since then.
Types of rash:
Dermatitis, dermatitis acneiform, dermatitis bullous, erythema, pruritus allergic, rash erythematous, rash generalized, rash macular, rash popular and rash pruritic
Skin Rash Management

- Incidence: PD-1 20%/ CTLA4 40%
- G3-4/ 1-3%
- Pruritus without rash may occur
- OS longer in patients with rash
- Bullous Dermatology consult/bx

Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treat and follow-up† Ann Oncol. 2017

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Diarrhea Management

- Incidence: PD-1 10% - CTLA4 40%
- Routine evaluation diarrhea (C. diff)
- If starting steroids/ CT scans and Colonoscopy

Grade of Diarrhea/Colitis (NCI CTCAE v4)

- Grade 1
  - Diarrhea: 4 stools/day over baseline; Colitis: asymptomatic
  - Management: Continue I-O therapy per protocol; Symptomatic treatment
  - Follow-up: Close monitoring for worsening symptoms; Educate patient to report worsening immediately if worsens; Treat as Grade (G) 2 or 3/4

- Grade 2
  - Diarrhea: >4 stools/d over baseline; IV fluids indicated <24 hours (hrs); not interfering with ADL; Colitis: abdominal pain; blood in stool
  - Management: Delay I-O therapy per protocol; Symptomatic treatment
  - Follow-up: If improves to grade 1:
    - Resume I-O therapy per protocol if persists > 5-7 days or recur:
      - 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent
      - When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol.
    - If worsens or persists > 3-5 days with oral steroids:
      - Treat as grade 3/4

- Grade 3-4
  - Diarrhea (G3): >7 stools per day over baseline; incontinence; IV fluids >24 hrs; interfering with activities of daily living (ADL); Colitis (G3): severe abdominal pain, medical intervention indicated, perineal signs
  - Management: Intermittent I-O therapy per protocol; 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent
  - Add prophylactic antibiotics for opportunistic infections
  - Consider lower endoscopy
  - Follow-up: If improves:
    - Continue steroids until grade 1, then taper over at least 1 month
    - If persists > 3-5 days or recur after improvement:
      - Add infliximab 5 mg/kg (if no contraindication), Note: Infliximab should not be used in cases of perforation or sepsis

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• 71 y/o female former smoker
• Adenocarcinoma of the lung stage IV 10/2018 with bone metastases
• Non actionable mutations
• First line chemotherapy +immunotherapy
• Sx: Nausea, diarrhea more than 6 for 3 days and no appetite and fever on 2/2019. Imodium at home without improvement.
• C. diff negative. CT abdomen: Inflammation involving the rectosigmoid. Sigmoidoscopy: Active colitis.
• Treatment: Hold immunotherapy. Loperamide + high dose steroid + electrolyte replacement. D/C immunotherapy.
**Management of Hepatic Toxicities**

1. Incidence - 5-10%
2. Asymptomatic rising liver enzymes - start steroids
3. Infliximab not used
4. Steroid refractory - Mycophenolate mofetil, tacrolimus

**Symptom Grade**

- **Grade 1:** ALT or AST > ULN-3x ULN
  - Management: Continue treatment
  - Assessment: If > ULN-3x ULN repeat in 1 week

- **Grade 2:** ALT or AST 3-5x ULN
  - Management: Withhold IPI treatment. If rising ALT/AST when re-checked start oral prednisolone 1 mg/kg
  - Assessment: Re-check LFTs/TNR/albmin every 3 days. Review medications, e.g. statins, antibiotics and alcohol history. Perform liver screen: Hepatitis A/B/C serology, Hepatitis E PCR, anti-JAHA/SM/MK/LSA/ILP/LD, iron studies. Consider imaging for metastases/cot

- **Grade 3:** ALT or AST 5-20x ULN
  - Management: Case treatment. ALT/AST ≤ 400 and normal bilirubin/TNR/albumin: and prednisolone 1 mg/kg. ALT/AST > 400 or raised bilirubin/TK/low albumin: i.v. methylprednisolone 2 mg/kg
  - Assessment: As above; daily LFTs/TNR/albmin

- **Grade 4:** ALT or AST > 20x ULN
  - Management: i.v. methylprednisolone 2 mg/kg. Permanently discontinue treatment
  - Assessment: As above; hepatology consult. Consider liver biopsy

**Steroid use:**
- G2: once G1, wean over 2 weeks; re-escalate if worsening; treatment may be resumed once prednisolone ≤ 10 mg
- G3/G4: once improved to G2, can change to oral prednisolone and wean over 4 weeks; for G3, rechallenge only at consultant discretion
- Worsening despite steroids:
  - If oral change to i.v. methylprednisolone
  - If on i.v. add MMF 500-1000 mg bd
  - If Unable to MMF, consider addition of tacrolimus
  - A case report has described the use of anti-thymocyte globulin in steroid + MMF-refractory fulminant hepatitis [11]
Management of Thyroid Dysfunction

1. Incidence- 10%

2. Hyperthyroidism- 2%

3. Regular TFT testing

4. TSH > 10mIU/L start thyroid hormone therapy.

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Most common musculoskeletal toxicities:

- Inflammatory arthritis, Myositis and Polymyalgia like syndrome.
- Incidence: 40% more frequent with PD1/PD-L1 antagonist
- NSAIDs alone are not sufficient add corticosteroids (Prednisone 1-2 mg /kg /daily and synthetic DMARDs might be required
- Myositis may be lethal / Cardiac muscle/ referral rheumatologist or neurologist.
Case Scenario

A 62 year old male patient diagnosed with poorly differentiated adenocarcinoma of the neck (base of the tongue) treated with cisplatin high dose and radiation therapy on 4/2017. On 1/2018 PET scan showed lung metastases biopsy proven. Case was presented on tumor board and it was agreed to treat him with Cyber knife on the lung lesion and immunotherapy. Patient has a history of Psoriasis under treatment with Apremilast, well controlled. After given him cycle # 2 immunotherapy patient developed an exacerbation of his psoriatic lesions.

Question

What will be your next step on treatment?

a) Permanently discontinue ICPI
b) Continue ICPI + steroids
c) Hold ICPI + reevaluate to decided further treatment
Re-challenge with PD-(L)-1 after irAEs

- 482 lung cancer patients at MSKCC; 15% (70) patients developed irAE

- 38 (54%) were re-challenged

- 24% developed same irAE; 26% developed new irAE

- 16 were treated successfully; 2 (5%) deaths

- Among patients who had response before irAE no difference whether ICP therapy re-started or not.

Conclusion

- ICPi agents may cause immune related side effects
- Close monitoring is very important
- Referral...Referral... Referral
- Side effects respond to steroids

