OPTIMAL MANAGEMENT OF IMMUNE-RELATED ADVERSE EVENTS ASSOCIATED WITH CHECKPOINT INHIBITORS

Alberto Fusi
Charité Comprehensive Cancer Centre
Berlin, Germany
• Immune check point blockade with CTLA-4, anti-PD-1 and anti-PD-L1 is a major advance in cancer management

• Associated with novel immune mediated toxicity different from other classes of antineoplastic agents

• Require specialised management
Points to consider

- Treatment (drug, dose, frequency of side effects, onset pattern of side effects)

- Patient factor (allergy, atopic patients)

- Exclude other causes (irAEs are less common than AEs with chemotherapy or targeted treatment)
### Frequency of irAE

<table>
<thead>
<tr>
<th></th>
<th>Ipilimumab</th>
<th>Pembrolizumab</th>
<th>Nivolumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All % (G3/4 %)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>37 (6.9)</td>
<td>18 (2)</td>
<td>13 (1)</td>
</tr>
<tr>
<td>Colitis</td>
<td>8 (4.9)</td>
<td>1 (0.2)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Rash</td>
<td>33.2 (2.5)</td>
<td>&lt;1</td>
<td>15 (0)</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>0.7 (0.7)</td>
<td>0.5 (0.2)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>2.7 (2.1)</td>
<td>0.5 (0.2)</td>
<td>&lt;1 (&lt;1)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>&lt;2</td>
<td>2.9 (0.2)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Thyroid dysfunction</td>
<td>Hypo 1.8 (0.1)</td>
<td>Hyper 1.2 (0.2)</td>
<td>Hyper 1 (&lt;1)</td>
</tr>
<tr>
<td></td>
<td>Hypo 8.3 (0.2)</td>
<td></td>
<td>Hypo 4 (&lt;1)</td>
</tr>
<tr>
<td>Nephritis</td>
<td>&lt;2</td>
<td>0.7 (0.5)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Neuropathies</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

Ibrahim JCO 2011
Pembrolizumab PI, 2014
Nivolumab, safety management BMS, 2014
Toxicity Patterns - Ipilimumab
Toxicity Patterns - Anti-PD-1 Mab

- Rash
- Pneumonitis
- Hypothyroidism
- Hepatitis

Graph showing intensity over weeks to symptoms.
Effective management is dependent on:

- Early recognition
- Appropriate monitoring
- Initiation of immunosuppressive therapy
- Patient education
- Utilization of treatment algorithms
## General Management Algorithm

<table>
<thead>
<tr>
<th>CTCAE grade</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Supportive treatment</td>
</tr>
<tr>
<td></td>
<td>Increased monitoring of symptoms</td>
</tr>
<tr>
<td></td>
<td>Exclude infection</td>
</tr>
<tr>
<td></td>
<td>Patient education</td>
</tr>
<tr>
<td>2</td>
<td>As per grade 1 but in addition:</td>
</tr>
<tr>
<td></td>
<td>Withhold immunotherapy until toxicity has resolved to grade 1 or less</td>
</tr>
<tr>
<td></td>
<td>Consider oral steroids if persistent symptoms &gt;5 days</td>
</tr>
<tr>
<td>3</td>
<td>Supportive therapy</td>
</tr>
<tr>
<td></td>
<td>Commence intravenous steroids (typical dose 1–2 mg/kg methyprednisolone)</td>
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<tr>
<td></td>
<td>If not resolving within 48 h consider addition of other immunosuppressants (e.g. infliximab, mycophenolate)</td>
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<tr>
<td></td>
<td>Consider system specific investigations (e.g. colonoscopy)</td>
</tr>
<tr>
<td></td>
<td>Seek expert opinion of relevant specialist</td>
</tr>
<tr>
<td></td>
<td>Investigate and treat infection</td>
</tr>
<tr>
<td></td>
<td>Withhold immunotherapy, consider restarting if toxicity grade 1 or less on individual basis</td>
</tr>
<tr>
<td></td>
<td>Steroids will need to be tapered over 3–6 weeks</td>
</tr>
<tr>
<td>4</td>
<td>As for grade 3 but permanently discontinue immunotherapy</td>
</tr>
</tbody>
</table>
Diarrhoea

- G3-4 Diarrhoea occurs in 7% of pts on ipilimumab and around 2% of pts on anti-PD-1 antibodies
- Colitis was observed in 5% of pts on ipilimumab (dose-dependent) and around 1.5% of patients on anti-PD-1 antibodies
- Grade 1 and 2 diarrhoea should be managed with antidiarrheal medications, oral hydration and electrolyte supplements
- Persistent (>5 days) grade 2 diarrhoea should be treated with oral steroids (0.5 mg/kg of prednisolone or equivalent)
- **Grade 3-4 diarrhoea** should be treated with high dose intravenous steroids (methylprednisolone 1–2 mg/kg/day or equivalent) and consider further immunosuppresion (e.g infliximab, etc) if symptoms not improve within 2-3 days.
- Colonoscopy should be considered to assess ulceration and need for more aggressive immunosuppression (! risk of perforation)
- Steroids and infliximab are **contraindicated** if perforation is suspected
Skin Toxicity

- **Rash** (maculopapular), **pruritus** and occasionally vitiligo and depigmentation
- Most common irAE with ipilimumab (40% any grade; 2% G3-4)
- Rash common with anti-PD-1 inhibitors (nivolumab > pembrolizumab)
- Grade 1 and 2 skin toxicity should be managed supportively with emollients, steroid creams (1% hydrocortisone) and topical or oral antihistamines.
- Grade 3 or 4 toxicity may manifest as **Stevens-Johnson syndrome** or toxic epidermal necrolysis and requires evaluation by a dermatologist and treatment with iv high dose steroids.
Hepatic Toxicity

- Hepatotoxicity is reported in 3–9% of patients receiving ipilimumab and in 4–10% of patients receiving anti-PD-1 antibodies, with grade 3 or 4 toxicity in 1%
- On biopsy hepatic inflammation with ballooning degeneration with diffuse lymphocytic infiltrates. Immunohistochemistry demonstrated predominantly CD4+ cells in the periportal regions and CD8+ cells in hepatic lobules
- Exclude other causes (viral, disease, etc)
- Grade 1 and 2 hepatic toxicity requires close monitoring of the LFTs and in case of grade 2 hepatic toxicity persisting for more than 5-7 days intermediate dose steroids and liver biopsy should be considered
- **Grade 3 or 4** should be treated with iv high dose steroids. If no improve within 48 h immunosuppression with mycofenolate mofitil should be considered.
- A case report describes successful use of anti-thymocyte globulin in a patient with severe ipilimumab related hepatic failure
Endocrine Toxicity

- Endocrine toxicity can easily be overlooked, grade 1 endocrine irAE are asymptomatic and identified by routine testing

- **Monitor of thyroid function tests reccomended**

- For ipilimumab, the most commonly reported endocrine toxicities are hypopituitarism, hypothyroidism and adrenal insufficiency; grade 3 or 4 toxicity occurred in <2%

- For anti-PD-1 antibodies the most commonly reported endocrine toxicity is thyroid dysfunction. Grade 3 or 4 toxicites in <1%

- Grade 1 or 2 endocrine toxicity may be monitored and hormone replacement therapy instituted where appropriate.

- Grade 3 or 4 toxicities requires hospitalisation, institution of high dose iv steriods and review by an endocrinologist to direct hormone replacement. Patients with hypopituitarism may present with **headache, fatigue and visual disturbance**. Diagnosis is confirmed with pituitary dedicated MR imaging and assessment of pituitary hormones

- Endocrine damage is usually **irreversible**

- Once a patient’s hormone replacement needs are addressed, **immunotherapy can be resumed**
Pneumonitis

- Rare with ipilimumab; it occurs in 9% of the patients on anti-PD-1 antibodies (3% grade 3 or 4)
- Grade 3-4 toxicities more common for pts who received thoracic radiotherapy or concurrent chemotherapy (up to 7%)
- Can present with dyspnoea, cough, fatigue or respiratory failure
- Exclude other causes (! pts with lung cancer or pulmonary metastases)
- Grade 1 pneumonitis (asymptomatic radiological changes) may be monitored with no change in immunotherapy treatment. For grade 2 toxicity, immunotherapy therapy should be withheld and oral steroids commenced
- 17% of grade 2 pneumonitis can re-occur
- Grade 3 or 4 pneumonitis requires hospitalisation, review by a respiratory physician, together with high dose intravenous steroids. If no benefit from steroids consider bronchoscopy to refine diagnosis and additional immunosuppression
- For grade 3 or 4 pneumonitis treatment should be permanently discontinued
What might impact the occurrence of AEs with immune checkpoint inhibitors?

- PD-L1 expression ✗
- Previous treatment with an immunotherapeutic agent ✓
- Atopic subjects ✓
- EGFR, ALK, BRAF, NRAS status ✗
- Dose, drug levels achieved ✓
- Combination with chemotherapy, radiotherapy or other immunotherapeutic agents ✓
Illustrative case study

54yo lady
3.5mm melanoma excised scalp 04/2013
Satellite recurrence 11/2013
Metastatic disease liver, lung, bones 12/2013
First line treatment as part of a clinical trial with pembrolizumab
Second line ipilimumab commenced 08/2014 due to progressive lung metastases
Hx – admission August 2014

Presented for C2 ipilimumab

Symptoms: Fatigue and fevers

CXR – suspicious left basal consolidation

Commenced treatment with antibiotics for CAP

- Ongoing fevers
- Oxigen-dependent
- CXR showing progressive changes
- Microbiology and serology negative

CT scan suggestive of pneumonitis
Pulmonary Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.

Grade of Pneumonitis (NCI CTCAE v4)

Grade 1
Radiographic changes only

Grade 2
Mild to moderate new symptoms

Grade 3-4
Severe new symptoms; New/worsening hypoxia; Life-threatening

Management

- Consider delay of I-O therapy
- Monitor for symptoms every 2-3 days
- Consider Pulmonary and ID consults
- Delay I-O therapy per protocol
- Pulmonary and ID consults
- Monitor symptoms daily, consider hospitalization
- 1.0 mg/kg/day methylprednisolone IV or oral equivalent
- Consider bronchoscopy, lung biopsy
- Discontinue I-O therapy per protocol
- Hospitalize
- Pulmonary and ID consults
- 2-4 mg/kg/day methylprednisolone IV or IV equivalent
- Add prophylactic antibiotics for opportunistic infections
- Consider bronchoscopy, lung biopsy

Follow-up

- Re-image at least every 3 weeks
  If worsens:
  - Treat as Grade 2 or 3-4
- Re-image every 1-3 days
  If improves:
  - When symptoms return to near baseline, taper steroids over at least 1 month and then resume I-O therapy per protocol and consider prophylactic antibiotics
  If not improving after 2 weeks or worsening:
  - Treat as Grade 3-4
- If improves to baseline:
  - Taper steroids over at least 6 weeks
  If not improving after 48 hours or worsening:
  - Add additional immunosuppression (e.g. infliximab, cyclophosphamide, IVIG, or mycophenolate mofetil)

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
Rx

Commenced 2mg/kg methylprednisolone

Appropriate prophylaxis with aciclovir/septrin/fluconazole

Antibiotics ceased

Clinical and CXR surveillance of response
Rx

Two weeks of high dose steroids

Slow symptomatic improvement with decreased O2 requirements

Fevers settled

Switched oral prednisolone 1mg/kg
**Hx**

24 hours after commencement of oral steroids

Worsening SOB

Recurrent high grade fevers

**Rx**

- **Rx**
  - Felt to be immune-related hepatitis and further rapid immunosuppression required
  - Liver biopsy considered but patient declined
  - IV ATG administered over 2 days without incident

- **Rx**
  - Steroids re-escalated with good response and tacrolimus added as a steroid sparing agent
  - Ongoing CMV serology monitoring to exclude reactivation as a cause of deterioration

**Rx**

- Recommendation for mycophenolate 1g BD
  - Repeat CMV serology to assess for reactivation in view of immunosuppression
  - Continue monitoring rate of rise in LFTs
Pulmonary Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.

Grade of Pneumonitis (NCI CTCAE v4)

Grade 1
Radiographic changes only
- Consider delay of I-O therapy
- Monitor for symptoms every 2-3 days
- Consider Pulmonary and ID consults

Management

- Delay I-O therapy per protocol
- Pulmonary and ID consults
- Monitor symptoms daily, consider hospitalization
- 1.0 mg/kg/day methylprednisolone IV or oral equivalent
- Consider bronchoscopy, lung biopsy

Grade 2
Mild to moderate new symptoms

- Discontinue I-O therapy per protocol
- Hospitalize
- Pulmonary and ID consults
- 2-4 mg/kg/day methylprednisolone IV or IV equivalent
- Add prophylactic antibiotics for opportunistic infections
- Consider bronchoscopy, lung biopsy

Follow-up

- Re-image every 1-3 days
  - If improves:
    - When symptoms return to near baseline, taper steroids over at least 1 month and then resume I-O therapy per protocol and consider prophylactic antibiotics
    - If not improving after 2 weeks or worsening:
      - Treat as Grade 2 or 3-4

Grade 3-4
Severe new symptoms; New/worsening hypoxia; Life-threatening

- Re-image at least every 3 weeks
  - If worsens:
    - Treat as Grade 2 or 3-4

- If improves to baseline:
  - Taper steroids over at least 6 weeks
  - If not improving after 48 hours or worsening:
    - Add additional immunosuppression (e.g. infliximab, cyclophosphamide, IVIG, or mycophenolate mofetil)

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
Re-escalation to IV steroids

Re-imaged: pneumonitis unchanged

Bronchoscopy and washings considered but patient declined

Infliximab given
Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.

<table>
<thead>
<tr>
<th>Grade of Liver Test Elevation</th>
<th>Management</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 (AST or ALT &gt; ULN -2.5 x ULN and/or T. bili &gt; ULN - 1.5 x ULN)</td>
<td>Continue I-O therapy per protocol</td>
<td>Continue LFT monitoring per protocol if worsens; Treat as Grade 2 or 3-4</td>
</tr>
<tr>
<td>Grade 2 (AST or ALT &gt; 2.5 to ≤ 5 x ULN and/or T. bili &gt; 1.5 to ≤ 3 x ULN)</td>
<td>Delay I-O therapy per protocol; Increase frequency of monitoring to every 3 days</td>
<td>If returns to baseline: Resume routine monitoring, resume I-O therapy per protocol; If elevations persist &gt; 5-7 days or worsen: 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol</td>
</tr>
<tr>
<td>Grade 3-4 (AST or ALT &gt; 5 x ULN and/or T. bili &gt; 3 x ULN)</td>
<td>Discontinue I-O therapy*; Increase frequency of monitoring to every 1-2 days; 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent**; Add prophylactic antibiotics for opportunistic infections; Consult gastroenterologist</td>
<td>If returns to grade 2: Taper steroids over at least 1 month; If does not improve in &gt;3-5 days, worsens or rebounds: Add mycophenolate mofetil 1 g BID; If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines</td>
</tr>
</tbody>
</table>

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g., prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

*I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN and T.bili ≤ 5 x ULN.

**The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.
**Rx**

**Recommendation for mycophenolate 1g BD**

Repeat CMV serology to assess for reactivation in view of immunosuppression.

Concerns regarding rate of rise of LFTs

**Reassessed after 72 hours and LFTs continued to worsen**

**Hx – admission August 2014**

- Presented for C2 ipilimumab
- Symptoms: Fatigue and fevers
- CXR – suspicious left basal consolidation
- Commenced treatment with antibiotics for CAP
  - Ongoing fevers
  - Oxygen-dependent
  - CXR showing progressive changes
  - Microbiology and serology negative
  - CT scan suggestive of pneumonitis

**Level of immunosuppression**
Rx

Felt to be immune related hepatitis and further rapid immunosuppression required

Liver biopsy considered but patient declined

IV ATG administered over 2 days without incident

Hx – admission August 2014
Presented for C2 iplimumab
Symptoms: Fatigue and fevers
CXR – suspicious left basal consolidation
Commenced treatment with antibiotics for CAP
Ongoing fevers
Oxygen-dependent
CXR showing progressive changes
Microbiology and serology negative
CT scan suggestive of pneumonitis

Hx
24 hours after commencement of oral steroids
Worsening SOB
Recurrent high grade fevers

Differential:
- Immune related hepatitis
- Infliximab toxicity
- USS abdomen – normal liver
Significant steroid complications

Steroid induced diabetes

Significant proximal myopathy affecting mobility

Suppression of HPA axis

Prioritised steroid wean  worsening LFTs
**Rx**

Steroids re-escalated with good response and tacrolimus added as a steroid sparing agent

Ongoing CMV serology monitoring to exclude reactivation as a cause of deterioration

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**Hx – admission August 2014**

- Presented for C2 plasmablast
- Symptoms: Fatigue and fevers
- CXR - suspicious left basal consolidation
- Commenced treatment with antibiotics for CAP
  - Ongoing fevers
  - Oxygen-dependent
  - CXR showing progressive changes
  - Microbiology and serology negative
  - CT scan suggestive of pneumonitis

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**Re-escalation to IV steroids**

**Re-imaged: pneumonitis unchanged**

**Bronchoscopy and washings considered but patient declined**

**Infliximab given**
Time

Intensity

Immunosuppression

Pneumonitis

IV steroids

Oral steroids

IV steroids + infliximab

ATG

↓ iv steroids

IV steroids + infliximab + mycophenolate

iv steroids + mycophenolate + tacrolimus
Time

Intensity

- IV steroids
- Oral steroids
- IV steroids + infliximab
- IV steroids + infliximab + mycophenolate
- iv steroids + mycophenolate + tacrolimus
- ATG

Immunosuppression

Pneumonitis

Hepatitis
Progress

Three month inpatient admission

Failure to cease immunosuppression 14 months since ipilimumab

Currently requiring maintenance with prednisolone 10 mg and mycophenolate 750mg BD
<table>
<thead>
<tr>
<th>Time</th>
<th>Tumor burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV steroids</td>
<td>□◉☉</td>
</tr>
<tr>
<td>Oral steroids</td>
<td>□◉☉</td>
</tr>
<tr>
<td>IV steroids + infliximab</td>
<td>□◉☉</td>
</tr>
<tr>
<td>IV steroids + infliximab + mycophenolate</td>
<td>□◉☉</td>
</tr>
<tr>
<td>ATG</td>
<td>□◉☉</td>
</tr>
<tr>
<td>iv steroids + mycophenolate + tacrolimus</td>
<td>□◉☉</td>
</tr>
</tbody>
</table>

- **Response:**
  - **PD:** Progression of disease
  - **PR:** Partial response
  - **PD:** Progressive disease
  - **PR:** Partial response

- **Graph:**
  - **Tumor burden** vs. **Time**
  - **Response** indicated by PR and PD markers.
Response

07/2014

10/2014
Response
Response

12/2014

08/2015
What this case demonstrates

Complex case with multiple organ systems involved

Multiple lines of immunosuppression required

Multiple episodes of rebound

Aggressive immunosuppression has affected efficacy
Take home points

- educate pts
- exclude other causes
- start promptly i.v. steroids if G3-G4 toxicity
- consider adding further immunosuppressants if symptoms do not resolve within 2-3 days from iv steroids or as steroid spare agents if pts on long term steroidal treatment or severe steroid-related AE
- Add immunoprophylaxis for opportunistic infections
- taper down steroids slowly (risk of rebound)
- monitor pts closely
- seek expert advice
THANK YOU