Immunotherapy Related Toxicities And Their Management

What the Oncology Pharmacist Needs to Know ..

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Outlines:

- To provide an overview of the main immunotherapy side effects
  - Anti CTLA-4 monoclonal antibodies
  - Anti PD-1/PD-L1 monoclonal antibodies

- To outline how these toxicities are best managed according to current evidence and practice.
Immunotherapy has spread rapidly from melanoma to solid tumors, and now Hodgkin’s lymphoma is being treated with checkpoint inhibitors.
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• The side effects of immunotherapies are in some cases unique, different than what many oncologists have experienced with chemotherapy or targeted drugs.

• These side effects can be understood on the basis of immune mechanisms that lead to hyperactivation of T-cells.
The most common immune-related adverse events include: colitis, dermatitis, hepatitis, nephritis, pneumonitis and endocrinopathies.

Most of these occur during the first 12 weeks of therapy but they can occur at any time.

The rate is low, but when they occur, they can be severe and even fatal.
Effective Surveillance, Recognition And Intervention Minimizes the Potential Impact of ADs

- Proactive monitoring
- Early recognition and reporting
- Appropriate management
- Vigilant follow-up
A Team Approach .. Communication is KEY!
Before starting treatment, patients should be assessed in terms of susceptibility to develop AEs.

Patients should be informed of the potential AEs of immunotherapy before treatment initiation.

In all cases, patients should report directly to the treating physician or team member.

Once AEs have developed, prompt work-up is required and action should be taken to prevent further aggravation of AEs.
Anti CTLA-4 Monoclonal Antibodies: Ipilimumab (Yervoy®)
• Approved indication: Melanoma

• Toxicities are dose related

• The onset of these toxicities varies but usually starts within the first 8 to 12 weeks of initiation of treatment.

Figure 1. Timing of occurrence of immune-related adverse events following ipilimumab treatment.
Immune Mediated Toxicities:

- Dermatological
- Gastrointestinal
- Hepatotoxicity
- Endocrinopathies
- Neurological toxicity
- Ocular toxicity
- Pancreatitis
- Renal toxicity

From trials: 60% patients will experience an AE with around 20% of these developing a severe or life threatening toxicity.
PD-1 Checkpoint Inhibitors
Nivolumab (OPDIVO®)
• Approved indications:
  • Metastatic melanoma
  • 2nd line metastatic NSCLC
  • 2nd line metastatic RCC
  • Classical Hodgkin’s disease.
  • Recurrent or metastatic SCCHN
  • Locally advanced or metastatic UCC

• The toxicities are similar at doses ranges from 0.3 to 10 mg/kg.
• High-grade toxicities are less common than for the CTLA4 blocking agent ipilimumab.

• Toxicities with PD-1/PD-L1 agents may be slower to resolve than with ipilimumab, so long-term surveillance is advised.

• PD-1/ PD-L1 antibodies rarely cause infusion reactions.
PD-L1 Checkpoint Inhibitors
Pembrolizumab (KEYTRUDA®)
Approved indications:

- Metastatic melanoma
- 2nd line metastatic NSCLC
- 1st line metastatic NSCLC
- Classical Hodgkin’s disease
- Locally advanced or metastatic UCCc

High-grade toxicities are less common than for the CTLA4 blocking agent ipilimumab.

Toxicities with PD-1/PD-L1 agents may be slower to resolve than with ipilimumab, so long-term surveillance is advised.
A. Immune-related skin toxicity
- The most frequent AEs observed by patients develop **early** in the course of treatment (within the first few weeks after initiation).

- The most frequent skin AEs are rash, pruritus and vitiligo, but the latter is seen mostly in patients treated for melanoma.
• Rash and Pruritis were reported more frequently in patients treated with ipilimumab than anti-PD-1/PD-L1 MoAbs.

• Vitiligo is reported in about 8% of patients with melanoma treated with anti-PD-1 MoAbs, but is more rarely reported with ipilimumab.

• The occurrence of vitiligo was significantly associated with the clinical response to the drug.
- More rarely, other skin AEs have been reported with checkpoint inhibitors:

- Alopecia areata.
- Xerosis cutis
- Photosensitivity.
- Exacerbation of psoriasis
- Stevens Johnson syndrome
Determine Severity

Mild or Moderate
Grade 1 or 2: localised, papules/pustules <10-30% body surface

Management

Symptomatic treatment
Administer symptomatic treatment e.g. antiH2’s, topical corticosteroids
Monitor patient
Continue Ipilimumab therapy

Follow-Up
(a) Symptoms controlled
(b) Ongoing mild symptoms 1-2 wks
(a) Continue Ipilimumab therapy
(b) Administer systemic corticosteroid therapy and continue Ipilimumab
Determine Severity

| Severe | Grade 3: rash, pruritus |

Management

| Omit scheduled Ipilimumab dose | Consider oral corticosteroid therapy |

Follow-Up

| (a) Symptoms controlled  
(b) Ongoing moderate to severe symptoms | (a) Resume Ipilimumab at next scheduled dose if symptoms improve to G0-1 or baseline  
(b) Continue to omit Ipilimumab until resolves then as above |
Determine Severity

- Very severe
  - Grade 4: rash, pruritis

Management

- Permanently discontinue Ipilimumab
- Administer high dose IV corticosteroid therapy

Follow-Up

- Symptoms controlled
  - Consider initiating corticosteroid tapering based on clinical judgement
B-Gastrointestinal toxicity
- It is well described for anti-CTLA4 Abs.

- Diarrhea occurs in 27%–54%.

- The frequency of colitis ranges from 8% to 22%.

- Colon perforation occurred in 1.5-6 %. 
- Onset of GI symptoms may occur at any time during 1-10 infusions of anti-CTLA4.

- Enterocolitis may even occur several months after the last dose of ipilimumab.

- The half life of ipilimumab is 2 weeks; however, the biological effect may persist long after drug clearance.
Management:

- Non-severe diarrhea (grade 1):
  - ICPI can be continued.
  - Treatment with antidiarrheal medication (e.g. loperamide).
• **Grade 2 diarrhea:**

- ICPi should be interrupted.

- Start with oral corticosteroids 1 mg/kg and taper over 8-12 weeks.

- If no improvement within 3–5 days, colonoscopy should be carried out and, in the case of colitis, infliximab 5 mg/kg should be administered.
• Severe diarrhea (grade 3 to 4):

- Permanently discontinue ICPi.

- Admit patient to the hospital and initiate methylprednisone 2 mg/kg i.v.

- Add MMF if no improvement is observed within 2–3 days.
- Consult a GI consultant if no improvement under double immunosuppression.

- Other immunosuppressive drugs to consider are ATG and tacrolimus.

- Taper over 6 weeks under close monitoring.
**Figure 8. ICPI-related toxicity: management of diarrhoea and colitis.**

**Symptom Grade**
- **Mild (G1):** i.e. < 3 liquid stools per day over baseline, feeling well. ICPI can be continued.
- **Moderate (G2):** i.e. 4-6 liquid stools per day over baseline or abdominal pain or blood in stool or nausea or nocturnal episodes. Outpatient management if appropriate. If unwell, manage as per severe. ICPI to be withheld.
- **Severe (G3/4):** i.e. > 6 liquid stools per day over baseline or if episodes within 1h of eating. Requires hospitalisation and isolation until infection excluded. ICPI to be withheld.

**Management escalation pathway**
- Symptomatic patients: oral fluids, loperamide, avoid high fibre/fermented diet.
- G1 and persists for > 14 days or G2 and persists for > 3 days or worsens:
  - Prednisolone 0.5-1 mg/kg (non-enteric coated) or consider oral budesonide 9 mg od if no bloody diarrhoea.
  - Do not wait for sigmoidoscopy/colonoscopy to start.
  - No improvement in 72h or worsening or absorption concern.
- At clinician discretion: gastroenterology input and ensure sigmoidoscopy/colonoscopy is requested.
  - No improvement in 72h or worsening.
  - Infliximab 5 mg/kg. If no perforation/sepsis/TV/hepatitis/NYHA III/IV CHF can repeat 2 weeks later. Must have had flexisigmoidoscopy prior. Other immunosuppressive treatment options: MMF 500-1000 mg bd or tacrolimus.

**Assessment and Investigations**
- Baseline Investigations: FBC, U/E, LFTs, CRP, TFTs. Stool microscopy for leucocytes/ova/parasites, culture, viral PCR, *Clostridium difficile* toxin and cryptosporidia. Culture for drug-resistant organisms.
- Inpatients: Test as above, including sigmoidoscopy/colonoscopy. Consider CT abdomen/pelvis, repeat Abdominal X-ray as indicated. Review diet (e.g. nothing by mouth, clear fluids, TPN). Early surgical review if bleeding, pain or distension.

**Medications:**
- (Meth)prednisolone 1-2 mg/kg i.v.
- Loperamide 4 mg 1st dose then 2 mg 30min before each meal and after each loose stool until 12h without diarrhoea (max 16 mg/day).
C. Immune-related Hepatotoxicity
• Incidence of Hepatitis occurs in 5%–10% of patients during therapy with ipilimumab, nivolumab, and pembrolizumab.

• Hepatitis is usually asymptomatic and detected on such routine blood monitoring.

• If hepatitis develops, disease-related causes, concomitant drug administration (including alcohol) and infectious causes, particularly viral hepatitis, should be ruled out.
Management:

Grade 1:
ALT or AST > ULN-3x ULN

Continue treatment

If > ULN-3x ULN repeat in 1 week

Grade 2:
ALT or AST 3-5x ULN

Withhold ICPI treatment
If rising ALT/AST when re-checked start oral prednisdone 1 mg/kg

Re-check LFTs/ANR/albumin every 3 days
Review medications, e.g. statins, antibiotics and alcohol history
Perform liver screen: Hepatitis A/B/C serology, Hepatitis E PCR, anti-ANA/SMA/LKM/SLA/LP/LC1, iron studies
Consider imaging for metastases/clot
Grade 3:
ALT or AST 5-20x ULN

Cease treatment
ALT/AST < 400 and normal bilirubin/INR/albumin: oral prednisolone 1 mg/kg
ALT/AST > 400 or raised bilirubin/INR/low albumin: i.v. (methyl)prednisolone 2 mg/kg

Grade 4:
ALT or AST > 20x ULN

i.v. (methyl)prednisolone 2 mg/kg
Permanently discontinue treatment

As above; daily LFTs/INR/albumin
Perform US with Doppler
Low threshold to admit if clinical concern

As above; hepatology consult
Consider liver biopsy

Steroid wean:
- G2: once G1, wean over 2 weeks; re-escalate if worsening; treatment may be resumed once prednisolone ≤ 10 mg
- G3/4: 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 on oral change to i.v. (methyl)prednisolone
- If on i.v. add MMF 500-1000 mg bd
- If worse on MMF, consider addition of tacrolimus
- A case report has described the use of anti-thymocyte globulin in steroid + MMF-refractory fulminant hepatitis [31]
D. Immune-related pneumonitis
The incidence of pneumonitis is higher (1.5–2) times more frequent, in patients receiving anti-PD-1 compared with ipilimumab.

Acute interstitial pneumonitis/diffuse alveolar damage syndrome (DADS) is the most acute, life-threatening event.

Inflammatory pneumonia, as well as a sarcoidosis-like pulmonary granulomatosis have been described and may result in difficulties in differential diagnosis with progression of disease.
• Pneumonitis tends to occur later than other irAEs, commonly several months after treatment was initiated.

• The rate of grade 3 to 4 pneumonitis is similar across tumor types and irrespective of dosage.

• Pneumonitis occurred irrespective of the line of therapy in which immunotherapy was received.
Management

- In grade 1 and 2 pneumonitis:
  - Interrupt ICPi therapy.
  - Try to rule out infection and start with prednisone (1–2 mg/kg orally).
  - Taper over 4–6 weeks.
In grade 3 and 4 pneumonitis:

- Discontinue ICPI permanently.

- Admit the patient to the hospital and immediately start high-dose methylprednisone 2–4 mg/kg i.v.

- Add infliximab, MMF or cyclophosphamide in the case of deterioration under steroids.
- Taper over a period of 4–6 weeks.

- Reintroduction of the checkpoint inhibitor should be delayed until the daily dose of steroids equals 10mg of oral prednisone per day or less.
E. Immune-related Endocrinopathies
I. Thyroid gland disorders

- Both hyper- and hypothyroidism have been reported, although hypothyroid disorders are more common than hyperthyroidism.

- Thyroid dysfunction is most common upon treatment with anti-PD-1/PD-L1.
- In hypothyroidism, substitution with thyroid hormone should be considered.

- Hormone replacement therapy (HRT) is usually long lasting.

- In the case of hyperthyroidism, treatment with beta-blockers should be started (propranolol or atenolol). Rarely, carbimazole or steroids are required.

- In those cases, treatment with Immunotherapy should be interrupted until recovery from symptoms.
II. Hypophysitis

-Hypophysitis: an inflammation of the anterior lobe of the pituitary gland, was extremely rare.

-Anti-CTLA4 lead to mononuclear cell infiltration in the pituitary gland, anti-pituitary antibodies and activation of the complement cascade, causing inflammation of the gland.

-Hypophysitis is very rare in patients treated with anti-PD-1 and anti-PD-L1.
Management:

- In any grade 2 or higher hypophysitis: treatment with ICPis should be interrupted and treatment consisting of HRT should be instigated immediately.

- In the case of headaches and other neurological problems, high dose steroids should be given.

- In most cases, the immune checkpoint inhibition can be continued.

- Long-term HRT is required in most patients.
III. Type 1 Diabetes Mellitus

- De novo diabetes induced by ICPis occurs at low frequency (<1%).

- DM appears to be more common with PD-1 and PD-L1 blockade than with ipilimumab.

- It is recommended that blood glucose levels are regularly monitored in patients treated with ICPis.

- Once the patient has been regulated with insulin substitution, restarting treatment with ICPis may be considered.
Rare Immune Related Toxicities
• Neurological toxicity
• Ocular toxicity
• Pancreatitis
• Renal toxicity
• Cardiotoxicity
KEEP IN MIND
• The key to successful management of checkpoint antibody toxicities is:

✓ Early diagnosis.
✓ High suspicion.
✓ Excellent patient-provider communication.
✓ Rapid and aggressive use of corticosteroids and other immune suppressants.
Conclusion:

- These immune therapies are a major breakthrough in our approach to cancer treatment.

- They require a unique approach in educating patients, monitoring & managing toxicity.

- Remember non-cytotoxic doesn’t = non-toxic

- As a member of the MDC, challenge yourself to contribute to the management of these patients.
Thank You
Ocular Toxicity:

- Rare and occur in <1% of patients treated with ICPis.
- These AEs can be divided into ocular inflammation, such as peripheral ulcerative keratitis, uveitis and Vogt–Koyanagi–Harada syndrome, orbital inflammation, including thyroid-associated orbitopathy and idiopathic orbital inflammation (scleritis, myositis, neuritis, dacryadenitis) and retinal and choroidal disease (choroidal neovascularisation and melanoma-associated retinopathy).
• Treatment of these rare toxicities depends on their severity
• With topical corticosteroids in the case of episcleritis and anterior uveitis
• OR systemic corticosteroids in the case of severe ocular inflammation and orbital inflammation.
• Intravitreal anti-vascular endothelial growth factor (VEGF) is indicated for choroidal neovascularisation.
With CTLA-4 agents, adverse effects can include rash, pruritus, diarrhea, hepatitis, endocrinopathies, neurotoxicity, pancreatitis, and hematologic effects. Adverse events associated with anti–PD-1 agents include diarrhea, colitis, hepatitis, endocrinopathies, pneumonitis, and pancreatitis.

Adverse events that can occur with anti–PD-L1 include fatigue, rash, nausea, loss of appetite, pruritus, colitis, and endocrinopathies.
Blocking CTLA-4 and PD-1

CTLA-4 Blockade (ipilimumab)

PD-1 Blockade (nivolumab)

Activation (cytokines, lysis, proliferation, migration to tumor)

Tumor Microenvironment
Diagnosis: NSCLC

Protocol: Pembrolizumab

Ht: _______ cm  Wt: _______ kg  BSA: _______ m²

Before each cycle: CBC & diff, Chem 18.

This medication is restricted to:
☐ Restricted for second line treatment of metastatic non-small cell lung cancer patients with tumors that have high PD-L1 expression (Tumor Proportion Score [TPS] ≥50%), as determined by an approved test.

Dose modification for:
☐ Hematology
☐ Other Toxicity ______

Premedications:
1. Paracetamol 1000 mg PO 30 minutes before Pembrolizumab.
2. Chlorpheniramine 10 mg IV 30 minutes before Pembrolizumab.

Therapy:
Pembrolizumab: 200 mg IV in 100 ml normal saline over 30 minutes.

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Symptom Grade

Grade 1:
- skin rash, with or without symptoms, < 10% BSA (see Figure 4)

Management escalation pathway

Avoid skin irritants, avoid sun exposure, topical emollients recommended

Topical steroids (mild strength) cream od +/- oral or topical antihistamines for itch

Proceed with treatment

Grade 2:
- rash covers 10%-30% of BSA (see Figure 4)

Supportive management, as above

Topical steroids (moderate strength) cream od or (potent) cream bd +/- oral or topical antihistamines for itch

Proceed with ICPI treatment

Assessment and Investigations

Physical examination
- Exclude other causes, e.g. viral illness, infection, other drug rash

As above
- Consider dermatology referral and skin biopsy

Grade 3:
- rash covers > 30% BSA (see Figure 4)
- or grade 2 with substantial symptoms

Withhold ICPI

Topical treatments as above (potent)

Initiate steroids:
- If mild to moderate 0.5-1 mg/kg prednisolone od for 3 days then wean over 1-2 weeks;
- or if severe iv. (methyl)prednisolone 0.5-1 mg/kg and convert to oral steroids on response, wean over 2-4 weeks;
- recommence ICPI at G1/mild G2 after discussion with patient and consultant

As for Grade 1
- Dermatology review
- Consider punch biopsy and clinical photography

Grade 4:
- skin sloughing > 30% BSA (see Figure 4)
- with associated symptoms (e.g. erythema, purpura, epidermal detachment)

i.v. (methyl)prednisolone 1-2 mg/kg

Seek urgent dermatology review

Discontinue ICPI treatment

As for Grade 1
- Dermatology review
- Punch biopsy
- Clinical photography
Pharmaceutical Research and Development Dept.

“We’ve run out of things to name our drugs. It’s time to invent some new alphabet letters.”
As a part of multidisciplinary team, oncology clinical pharmacist has major role in assuring:

- Safe
- Effective
- Cost effective

Aim of pharmaceutical care
I. Neurological toxicity:

- Incidence 3.8% in patients receiving anti-CTLA4, 6.1% in patients receiving anti-PD-1 agents.

- The time to onset varies from 6 to 13 weeks.
Range of neurological events have been described, including:

- Polyneuropathy
- Facial nerve palsy
- Demyelination
- Myasthenia gravis
- Guillain Barre’s syndrome
- Transverse myelitis
- Encephalitis
- Aseptic meningitis
Management

- **Mild neurological AEs:**
  - Withhold ICPi and perform work-up (MRI scan, lumbar puncture) to define nature of neurotoxicity.

- **In the case of deterioration or severe neurological symptoms:**
  - Admit the patient
  - Start methylprednisone 1–2 mg/kg orally or i.v.

- **In the case of myasthenia-like symptoms,** consider adding plasmapheresis or IVIG.
II. Cardiac toxicity

- The incidence of cardiac AEs is <1%.
- Wide range of toxicities including myocarditis, pericarditis, arrhythmias, cardiomyopathy and impaired ventricular function.

When a myocarditis is suspected:
- Admit the patient.
- Immediately start high-dose methylprednisolone 1–2 mg/kg.
- In the case of deterioration, consider adding another immunosuppressive drug (MMF or tacrolimus).
III. Renal toxicity

- Renal dysfunction is rare with ipilimumab and with anti-PD-1 therapies, occurring in <1% of treated patients.

- Serum sodium, potassium, creatinine and urea should be measured before every infusion of checkpoint inhibitor.
Management:

- In case of nephritis:
  - Rule out other causes of renal failure first.
  - Interrupt or permanently discontinue ICPi depending on the severity of the renal insufficiency.
  - Stop other nephrotoxic drugs.
  - Start (methyl)prednisone 1–2 mg/kg.
  - Consider renal biopsy to confirm diagnosis.