Immunotherapy toxicity guidelines

These guidelines cover the management of patients who are treated with:

- CDLA-4 monoclonal antibody - Ipilimumab
- PD-1 monoclonal antibodies: Pembrolizumab & Nivolumab

This information is issued by the Medicines Management Committee on the understanding that it is the best available from the resources at our disposal at the time of preparation.

These guidelines are intended to support clinical judgement. The clinician must use his discretion when following them.

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<th>Dr Satish Kumar (Consultant Oncologist) &amp; Valerie Harris Melanoma CNS</th>
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<td>Immunotherapy Toxicity (CTC grading table)</td>
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Background

**Ipilimumab - Yervoy**® is a cytotoxic T lymphocyte antigen-4 (CTLA4) monoclonal antibody that activates/potentiates T cell responses and in clinical trials have shown to cause a prolonged response – sometimes in years in approximately 15-20% of patients treated for metastatic melanoma. Grade 3 toxicity or above can occur in approx 15-20% of patients – the toxicity is primarily immune related due to recognition of self antigens present in the skin of bowel, liver, neurological or endocrine system.

**Pembrolizumab**: It is a monoclonal antibody that binds to PD-1 receptor & potentiates T cell responses. Pembrolizumab has better responses than ipilimumab in terms of progression free survival & overall survival. The toxicity is again immune related but offers a better tolerability profile than ipilimumab. It is administered at a dose of 2mgs/kg IV over 30mins every 3 weeks until disease progression. It has also shown activity in other cancers eg: lung, prostate & lymphoma.

**Nivolumab** is another monoclonal antibody which potentiates Tcell response. It is administered at a dose of 3mgs/kg IV over 60 mins every 2 weeks until progression or unacceptable side effects.

For all immunotherapies please grade toxicity according to the NCI CTC v4 adverse event grading criteria & follow guidelines for management of toxicities.

Side effects can result in severe immune mediated adverse reactions, the most common are itchy skin rashes, diarrhoea leading to an inflammatory colitis type picture, thyroid, adrenal or pituitary dysfunction, pneumonitis, nephritis, hepatitis, uveitis, paresthesia and neuropathy can all occur.

It is important to recognise and manage these adverse events early to reduce serious patient related morbidity and mortality. The mainstay of immunotherapy toxicity management is corticosteroids which is immunosuppressive and therefore suppresses the T cell activating function of the treatment.

The majority of these side effects manifest during treatment, however some may occur weeks to months after the last cycle due to the long half life of the immunotherapies.

The following serve as a general guide—it is important to inform the treating team as soon as possible or in the event of a hospital admission. It is also important to liaise with medical specialities such as the gastroenterology or endocrine team at UHW, as a proportion of patients may not respond to first line corticosteroids and will have to be admitted to hospital.
Pre treatment

Supportive medication

All supportive medications are prescribed on chemocare with cycle one

- Immodium
- Topical emolient eg Epaderm/Menthol cream/Dermol/Aveeno.
- Topical steroid: Elocon cream (mometasone furoate 0.1%) 30g tube.
- Anti-histamine eg: Non drowsy antihistamines:Cetirizine 10mgs OD or Loratadine 10mgs OD Piriton 4mgs TDS: may cause drowsiness.
- Prednisolone 1mg/kg: Max 60mgs daily & PPI omeprazole 20mgs daily. To be taken only on advice from Velindre.

Patients to be given a supply of microbiology forms & stool pots (in case of need to provide stool sample).

Pre treatment blood tests: Pre treatment bloods are as follows:

- U&Es
- LFTs & bone profile, glucose.
- FBC
- Thyroid function test as baseline & pre each cycle.
- Cortisone levels as baseline & pre each cycle if not on regular steroids.
**Immunotherapy Induced Diarrhoea/Colitis**

**Mild (Grade 1)**
- Increase of up to 3 stools per day.
- No abdominal Pain or blood in stool

**Management Plan:**
- Advise to increase fluid intake
- Loperamide: See section 1.1
- Send stool culture
- Follow up call next day until improvement.

**Symptoms:** WORSEN Or ongoing >1 week

**Moderate (Grade 2)**
- If any of the following symptoms are present:
  - 4-6 stools/day over baseline
  - Mild-moderate abdominal pain, mucus or blood in stool.

**Management Plan:**
- Full assessment of toxicity.
- PO prednisolone 1mg/kg/day (max 60mg/PO/day) with PPI cover.
- Stop loperamide.
- Contact Patients Consultant/team
- Bloods eg: U&Es, LFTs, TFTs, Cortisol, FBC, CRP, blood cultures if pyrexial.
- Stool culture.
- Abdominal XRay +/−CXR if indicated.
- Refer to local gastroenterology team for endoscope & assessment.
- Omit next dose of immunotherapy

**See section 1.2 for further details.**

**Symptoms:** PERSIST ≥5 days or WORSEN or RELAPSE

**Severe or Life-threatening (Grade 3/4)**
- If any of the following symptoms are present:
  - ≥7 stools/day over baseline
  - Severe abdominal pain
  - Fever
  - Dehydration
  - Blood or mucus in stool

**Management Plan:**
- Admit patient under Gastroenterology team for urgent flexi-sigmoidoscopy.
- Abdominal X-Ray/CT abdomen to rule out bowel perforation/peritonitis.
- Inform patients consultant/team.
- High-dose IV corticosteroid therapy (eg, methylprednisolone 1-2 mg/kg/day) if no indication of perforation.
- PPI cover
- Commence IV hydration
- Daily bloods eg; FBC, U&E, LFTs, CRP
- Blood cultures.
- Investigate aetiology- stool cultures.
- Regular obs,NEWS assessment, daily stool chart and fluid balance
- Permanent discontinuation of immunotherapy

**See section 1.3 for further details.**

**Symptoms:** PERSIST ≥3 days IV corticosteroids

**Dr S Kumar & Val Harris September 2016**
Managing Immunotherapy Induced Diarrhoea (Event 1).

Unless alternative aetiology identified signs & symptoms should be considered immune-related. Gastrointestinal immune related adverse events (irAEs) are a common side effect of immunotherapies. It is generally reported as diarrhoea, defined by frequent and watery bowel movements, and/or colitis, defined by inflammation of the colon. Inflammatory responses may broadly involve the GI tract, including small intestine and upper GI tract, and the symptoms and signs of GI inflammation may extend beyond diarrhoea to include abdominal cramping, nausea, vomiting, GI bleeding, fever, fatigue, dyspepsia, leukocytosis, hypoalbuminemia, and serum electrolyte abnormalities.

NCI Common Toxicity Criteria Grading Scale v4.0

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diarrhoea</strong></td>
<td>Increase of up to 3 stools per day over baseline. (Mild increase in ostomy output)</td>
<td>Increase of 4-6 stools per day over baseline (moderate increase in ostomy output)</td>
<td>Increase of 7 or more stools per day over baseline, or incontinence or need for parenteral rehydration (severe increase in ostomy output)</td>
</tr>
<tr>
<td><strong>Colitis</strong></td>
<td>Asymptomatic; intervention not indicated</td>
<td>Abdominal pain; mucus or blood in stool</td>
<td>Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs</td>
</tr>
</tbody>
</table>

1.1: Grade 1:

Mild diarrhoea or suspected mild colitis (e.g. abdominal pain or blood in stools) may remain on immunotherapy. Also exclude infectious aetiology, send stool sample if possible. If out of hours, please send on next working day. Unless alternative aetiology identified signs & symptoms should be considered immune-related.

- Encourage increased oral fluid intake, and commence symptomatic antidiarrheal management for management of Grade 1 diarrhoea only.
  - Loperamide 4mg PO stat dose followed by 2mg after each loose stool or every 2 hours to a maximum 16mg daily.
- Needs follow-up call within 24 hours to ensure symptoms are not progressing, and advise patient to ring chemo pager. If any associated abdominal cramps, stop loperamide & follow guidelines for Grade 2.

If symptoms fail to improve within 5-7 days of antidiarrheal treatment then follow guidelines for Grade 2.
Severe colitis should be suspected when the frequency of diarrhoea only meets grade mild criteria but patients have associated systemic signs and symptoms, including:

- blood per rectum
- cramps
- fever
- nausea
- elevated white blood cell count
- low albumin
- electrolyte abnormalities

1.2: Grade 2: Moderate diarrhoea:

- Assess for other toxicities. If no other toxicity & patient well encourage increased fluid intake. Consider hospitalisation & IV fluids if other toxicities.
- Bloods eg: U&Es, LFTs, TFTs, Cortisol (if not on steroids), FBC, CRP, blood cultures if pyrexial.
- Stool culture.
- Abdominal XRay +/-CXR if indicated.
- Stop Loperamide
- Commence corticosteroid therapy 0.5-1 mg/kg/day PO (max. 60mg/day prednisolone)
- PPI cover
- Refer to local gastroenterology team for endoscope & assessment.
- Consider prophylactic antibiotics for opportunistic infections
- Contact Patients Consultant/team or on call SPR and omit next dose of immunotherapy.

If an improvement in symptoms to mild/grade 1: The initial steroid dose should be maintained for ≥7 days, once symptoms resolve, steroids should be tapered over 3-6 weeks.

If moderate symptoms persist for >5 days, treat as per Grade 3.

1.3: Grade 3: Severe diarrhoea:

- Inform patients consultant/ team and admit patient under Gastroenterology team for assessment & urgent flexi sigmoidoscopy
- Abdominal X-Ray / CT abdomen to rule out bowel perforation/peritonitis.
- Commence high-dose IV corticosteroid therapy (eg, methylprednisolone 1-2 mg/kg/day or IV hydrocortisone 100mgs QDS) if no indication of perforation with PPI cover.
- Commence IV hydration
- Daily bloods eg; FBC, U&E, LFTs, CRP
- Blood cultures.
- Investigate aetiology- stool cultures if not already sent.
- Antibiotics are not indicated unless a concern re possible infection.
- Regular obs,NEWS assessment, daily stool chart and fluid balance
- Refer to dietician if indicated.
- Use analgesia for abdominal pain with caution as may mask symptoms of perforation and peritonitis.
- Permanent discontinuation of immunotherapy.
Patients that respond to steroids:
Regardless of improvement, the initial steroid dose should be maintained for ≥ 7 days, but can be converted to oral administration when the patient is discharged from the hospital. Once symptoms resolve, steroids should be tapered over 3-6 weeks with weekly monitoring for recurrence of symptoms as doses are reduced.

Patients with refractory colitis:
Patients with severe colitis who have persistent symptoms despite intravenous steroids for ≥ 3 days should be evaluated for evidence of GI perforation or peritonitis and a repeat endoscopy should be considered. In some patients, doubling the dose of systemic corticosteroids may be sufficient to resolve the symptoms.

1.4: Persistant symptoms:
If symptoms persist for >3 days on IV corticosteroids with blood in stools, significant bowel inflammation seen on imaging, or clinical deterioration, urgent assessment by the gastroenterology team should be considered, as endoscopy and anti-TNFα therapy (Infliximab) may be indicated.

Agents such as infliximab at 5 mg/kg or other tumour necrosis factor (TNF)-blocking agents are usually effective when steroids fail. If concomittant hepatitis use Mycophenylate. Infliximab therapy can be repeated approximately every 2 weeks, although some patients will require an escalated dose to 10 mg/kg and up to a total of 3-4 doses before the colitis resolves. The steroid taper can be continued after initiation of infliximab.

Admission to UHW:
- Admit to UHW if possible. Contact on call registrar & if no beds on ward, patient will be reviewed on MAU.
- Telephone call to MAU & advise to put patients name on Gastroenterology retrieval board. UHW provides a 7 day gastroenterology cover.
- E mail Dr Durai & Dr Khan to inform them of admission or if any advice is needed.
- Communicate with AOS team & advise them of admission. Important to maintain links with AOS team throughout patients admission.
- If other DGH, contact Medical Registrar on call. Ensure access to VCC Immunotherapy guidelines.

Guidelines developed in consultation with Gastroenterology team in UHW: Dr Dharmaraj Durai dharmaraj.durai@wales.nhs.uk & Dr Mohid Khan mohid.khan@wales.nhs.uk.
Adverse Event 2: Dermatitis:

Immunotherapy induced rash and pruritus should be managed based on severity.

Grade 1:

- Use emollients eg: epaderm, aveeno cream topically to dry skin.
- For pruritis prescribe an antihistamines eg; Cetirizine 10mgs daily or alternative.
- Patients may remain on immunotherapy with symptomatic treatment.

Grade 2:

- Consider using topical steroids to red/inflamed areas eg: Elocon cream or Dermovate cream BD.
- Continue with emollients & antihistamines if pruritis.
- For mild to moderate rash or pruritus that persists for 1 to 2 weeks and does not improve with topical corticosteroids, oral corticosteroid therapy should be initiated e.g. prednisone 1 mg/kg once daily (max dose 60mgs /day).
- Resume immunotherapy if dermatitis resolves or improves to mild symptoms.

Grade 3:

- The scheduled dose of immunotherapy should be withheld.
- Commence oral steroids, prednisolone 1mg/kg/day with PPI cover (max 60mgs/daily).
- Refer for Dermatology assessment team for advice & monitoring.

Grade 4:

- Admit patient for regular observations, Fluid chart & IV fluids.
- Continue emollients & antihistamine.
- Commence systemic high-dose intravenous corticosteroid therapy (e.g. methylprednisolone 2 mg/kg/day) for a total of 5 days. Once rash or pruritus is controlled, initiation of corticosteroid taper should be based on clinical judgment. Tapering should occur over a period of at least 1 month.
- Dermatology consultation.
- Treatment must be permanently discontinued.
Management of Skin Toxicities

Grade 1
Macules/papules covering <10% BSA with or without symptoms (e.g., pruritus, burning, tightness)
Management plan: Observation
Emollients, Antihistamines for pruritus

Grade 2
Macules/papules covering 10-30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL
Management Plan:
Topical steroids eg: Elocon cream/Dermovate cream BD.
Emollients, Antihistamines for pruritis.

Grade 3
Macules/papules covering >30% BSA with or without associated symptoms; limiting self care ADL
Management Plan:
Commence oral steroids: Prednisolone 1mg/kg/day (max 60mgs daily) & PPI cover.
Hold immunotherapy.
Continue emollient & antihistamine if needed.
Refer to Dermatology

Grade 4
Skin sloughing covering >=30% BSA with associated symptoms (e.g., erythema, purpura, or epidermal detachment
Management Plan:
Admission & Dermatology assessment
IV steroids eg: Methylprednisolone 2mgs/kg/day & PPI.
Permanent discontinuation of immunotherapy.

Antihistamines:
Piriton 4mgs TDS; causes drowsiness
Non drowsy antihistamines: Cetirizine 10mgs daily
Loratadine 10mgs daily

Continue as needed for management of pruritis.
Guidelines for Management of Immunotherapy Induced Endocrinopathy

Immunotherapy can cause inflammation throughout the endocrine system. Hypocortisolism, hypothyroidism and hypogonadism are the most frequent endocrine adverse effects found in patients with Immunotherapy-induced Hypophysitis (IIH). Hypocortisolism is the most important pathology to rapidly identify and treat.

Common symptoms:

Endocrine pathology may present with vague signs and symptoms such as: headache, fatigue, visual impairment, loss of appetite, nausea, vomiting, erectile dysfunction, amenorrhoea, hypotension, hyponatraemia and hypoglycemia. These symptoms often resemble other disease-related causes such as brain metastasis or progression of underlying disease. A low threshold for investigation into possible endocrine abnormalities in patients on immunotherapy is therefore required.

- Fatigue and headache are the most prevalent symptoms related to Immunotherapy-induced hypophysitis. Check when last dose of immunotherapy was given as high risk during immunotherapy & within 6 months of completion of immunotherapy.
- Check cortisol & TFTs.

Hypophysitis is a very rare disease but is seen with high frequency in patients treated with immunotherapy and if left undiagnosed can be fatal.

Adrenal insufficiency due to ACTH deficiency appears to be the earliest change found in patients with IIH. This does not appear to recover in response to immunosuppressive doses of steroids. Therefore the priority is to recognise and treat any hormone deficiency.

Diagnosis and Treatment of Immunotherapy-induced Hypophysitis.

1. All patients should have TSH, FT4, cortisol, electrolytes and glucose at baseline and prior to the start of every cycle as long as patient is not on any steroids.

2. If Hypophysitis is suspected (either symptomatically or on the basis of test abnormalities e.g. hyponatraemia, hypoglycaemia, low FT4, low cortisol [see below]) then they should have a full pituitary profile which includes ACTH, serum cortisol, TSH, FT4, LH, FSH, prolactin, IGF1, testosterone (men) / oestradiol (women). Endocrine advice should be sought at this stage.

3. MRI of the pituitary is helpful but not mandatory for the diagnosis of hypophysitis. An important differential diagnosis of IIH is occurrence of brain metastases and an MRI is indicated primarily to rule this and other pituitary masses out. A normal appearance of the pituitary gland on MRI does not rule out a diagnosis of IIH.

A short synacthen test during the acute phase can be misleading as adrenocortical responses to ACTH (synacthen) can be preserved for a few weeks after pituitary insult. In the acute phase a paired ACTH and 9am serum cortisol measurement should be performed. **A 9am serum cortisol of <100 nmol/L is virtually diagnostic of adrenal insufficiency.** Values between 100 – 450 nmol/L are indeterminate and
should be discussed with the on-call endocrinologist. Values of > 450nmol/L usually indicate an intact Hypothalamic Pituitary Adrenal axis (HPA). Synacthen test (250 micrograms IV, measuring cortisol at 0 and 30 mins) will ultimately be needed to confirm adrenal insufficiency in nearly all patients but this should only be performed on recommendation from Endocrinology.

**Treatment:**

1. After bloods have been taken for serum cortisol and ACTH, commence high dose intravenous steroids (Hydrocortisone 100mg tds). **Do not wait for blood results before commencing treatment in unwell patients.** Liaise with biochemistry to request urgent processing of the cortisol sample.

2. Continue treatment with intravenous hydrocortisone in confirmed cortisol deficiency as follows:

   Day 1 Hydrocortisone 100mg, iv tds  
   Day 2 Hydrocortisone 50mg, po, tds  
   Day 3 Hydrocortisone 25mg, po, bd  
   Day 4 Hydrocortisone 10mg, po, bd

   (Reduce dose of steroids every 24 hours).

3. Thyroid function tests may show secondary hypothyroidism (i.e. low FT4, low/normal TSH). **Delay thyroxine replacement until cortisol deficiency is either excluded or corrected if present.**

4. Thyroxine 50 micrograms od can be commenced once the patient is safely established on steroids for > 24hours.

5. Correction of cortisol deficiency with glucocorticoids may unmask diabetes insipidus, therefore urine output should be monitored closely in the first 1-2 days after commencing glucocorticoids. If the urine output is > 4 L/24 hours, this may suggest DI. Please seek advice from the Endocrine team on the need for testing and DDAVP replacement.

6. **Seek Endocrinology input for advice on further management and long-term follow-up.**

**Prior to discharge patient should be given advice on:**

1. Sick day rules regarding steroids (available at [www.addisons.org.uk](http://www.addisons.org.uk)).  
2. Issue a steroid card and advise to obtain a steroid alert bracelet or pendant.  
3. Emergency hydrocortisone pack – refer to Endocrine Outpatient Clinic.

**Adrenal crisis**

Adrenal crisis is a medical emergency, and should be suspected if a patient presents with unexplained severe dehydration, hypotension or shock, particularly if electrolyte disturbance (hyponatraemia / hyperkalaemia), nausea, and/or non-specific abdominal pain is present.
1. Patient should be admitted for IV fluid resuscitation (4-6 L may be required in 24 hours) and commenced on IV hydrocortisone 100mg tds.

2. Send blood samples for TFTs and serum cortisol prior to starting IV hydrocortisone. **If adrenal insufficiency is suspected, do not wait for results before commencing IV steroids.**

3. If co-existent immune toxicity of any grade is also present (such as diarrhoea, hepatitis, etc), use IV Dexamethasone.

4. Treat any co-existent sepsis with appropriate antibiotics.

**Hypothyroidism**

1. Hypothyroidism usually presents with symptoms of weight gain, lethargy, cold intolerance, constipation and low mood.

2. This is not usually an acute presentation, but should be considered if patient presents with suggestive symptoms.

3. Check TSH, FT4, serum cortisol levels and TPO Ab.

4. Delay thyroxine replacement until cortisol deficiency is excluded.

5. Seek endocrinology input regarding dosing and long-term follow-up.

**Hyperthyroidism**

Hyperthyroidism is often due to an acute autoimmune thyroiditis, which may progress to hypothyroidism eventually. Medication such as carbimazole should therefore be avoided initially, unless on endocrine advice.

Patient may present with classical symptoms such as hyperactivity, tremors, palpitations, insomnia, heat intolerance, unexplained weight loss or diarrhoea.

1. Send blood samples for TSH, FT4, FT3, TRAb (TSH receptor antibodies) and serum cortisol levels.

2. Treat symptomatically with propanolol 10mg QID initially (dose can be increased up to 40mg QID).

3. Steroid therapy is not indicated, unless other concurrent immune toxicities or hypoadrenalism are present.

4. Seek endocrinology input.
Guidelines compiled by Chandan Kamath, Peter Taylor, Ravikumar Ravindran, Aled Rees.

University Hospital Wales, Cardiff.

For further information regarding these guidelines please email ReesDA@cardiff.ac.uk

Reference

Hepatitis:

<table>
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<tr>
<th>Liver enzymes abnormality</th>
<th>Initial Management</th>
<th>Plan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td></td>
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<tr>
<td>ALT &lt;3 ULN</td>
<td>Monitor LFTs weekly</td>
<td>Exclude other causes of hepatic injury.</td>
</tr>
<tr>
<td>Bilirubin &lt;1.5ULN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST or ALT &gt;3-&lt;5x ULN</td>
<td>Hold treatment</td>
<td>Resume treatment if AST &amp; ALT &lt;3x ULN &amp; bilirubin &lt; 1.5x ULN.</td>
</tr>
<tr>
<td>Bilirubin &gt;1.5-&lt;3 xULN</td>
<td>Monitor LFTs weekly</td>
<td>If persists for &gt;5-7 days or worsens commence oral prednisolone 0.5-1mg/kg/day. Taper steroids slowly.</td>
</tr>
<tr>
<td>Grade 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST or ALT &gt;5x ULN</td>
<td>Permanently discontinue immunotherapy.</td>
<td>Inform gastroenterology/hepatology team UHW. After discussion, initiate high dose Intravenous corticosteroids eg Methylprednisolone 1-2mg/kg/day. Monitor LFTs until return to normal.</td>
</tr>
<tr>
<td>Bilirubin &gt;3 xULN</td>
<td>Admit to hospital</td>
<td>Symptoms resolving &amp; LFTs improving, taper corticosteroids over at least 1 month. Any elevations in LFTs during taper, manage with increasing dose of corticosteroids &amp; a slower taper of steroids. If no improvement or steroids contraindicated, contact gastroenterology for further advice about transfer/alternative therapy with mycophenolate.</td>
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</tbody>
</table>

Once symptoms have resolved and LFTs show sustained improvement or return to baseline, the initiation of corticosteroid taper should be based on clinical judgment. Tapering should occur over a period of at least 1 month. Elevations in LFTs during taper may be managed with an increase in the dose of corticosteroid and a slower taper.

For patients with significant LFT elevations that are refractory to corticosteroid therapy, addition of an alternative immunosuppressive agent to the corticosteroid regimen may be considered. In clinical trials, mycophenolate mofetil was used in patients without response to corticosteroid therapy, or who had an LFT elevation during corticosteroid tapering that was not responsive to an increase in the dose of corticosteroids.
Neurological Toxicity:

Paraesthesia: Definition: A disorder characterized by functional disturbances of sensory neurons resulting in abnormal cutaneous sensations of tingling, numbness, pressure, cold, and warmth that are experienced in the absence of a stimulus.

Progressive signs of motor neuropathy must be considered immune-related and managed accordingly. Immunotherapy must be permanently discontinued in patients with severe (Grade 3 or 4) motor neuropathy regardless of causality.

<table>
<thead>
<tr>
<th>Severity of neuropathy</th>
<th>Management</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1: mild symptom</td>
<td>Continue therapy &amp; monitor.</td>
<td>If worsens treat as Grade 2</td>
</tr>
<tr>
<td>Grade 2: moderate symptoms.</td>
<td>Withhold treatment.</td>
<td>Resume treatment when symptoms resolve or return to baseline.</td>
</tr>
<tr>
<td></td>
<td>Appropriate medical intervention: consider corticosteroids 0.5-1mg/kg/day</td>
<td>If symptoms worsen see below.</td>
</tr>
<tr>
<td>Grade 3-4: Severe symptoms.</td>
<td>Permanently discontinue immunotherapy</td>
<td>Inform treating team.</td>
</tr>
<tr>
<td>New onset or worsening severe motor or sensory neuropathy</td>
<td>Initiate high dose Intravenous corticosteroids eg Methylprednisolone 2mg/kg/day</td>
<td>If not improving, Contact neurology team UHW for further advice, and to consider transfer for further therapy.</td>
</tr>
</tbody>
</table>
**Pneumonitis:**

Assess for other causes of respiratory symptoms eg infections, tumour progression.

Initial CXR, if suspected pneumonitis confirm with an urgent high resolution CT chest.

Signs & symptoms may include:

- Breathing difficulties or cough.
- Radiological changes: eg focal ground glass opacities, patchy infiltrates.
- Dyspnoea
- Hypoxia.

Once confirmed, treat according to CTC grade below:

<table>
<thead>
<tr>
<th>Grade</th>
<th>Management</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic; intervention not indicated</td>
<td>Continue therapy &amp; monitor.</td>
<td>If worsens treat as Grade 2</td>
</tr>
<tr>
<td><strong>Grade 2:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic; medical intervention indicated; limiting instrumental ADL</td>
<td>Delay treatment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Add antibiotics if concurrent infection suspected.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Commence oral prednisolone 1mg/kg/day with ppi cover.</td>
<td></td>
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<tr>
<td></td>
<td>Consider hospitalisation</td>
<td></td>
</tr>
<tr>
<td><strong>Grade 3:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe symptoms; limiting selfcare ADL; oxygen indicated</td>
<td>Permanently discontinue treatment</td>
<td>If improves taper steroids.</td>
</tr>
<tr>
<td><strong>Grade 4:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Life-threatening respiratory compromise</td>
<td>Admission to hospital &amp; Respiratory consultation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IV Methylprednisolone 2-4mgs/kg/day.</td>
<td></td>
</tr>
</tbody>
</table>
**Nephritis**

- Exclude other causes of renal injury eg diarrhoea or vomiting, tumour related renal obstruction or concomitant medication
- Urinalysis for haematuria & proteinuria
- Assess grade of nephritis

<table>
<thead>
<tr>
<th>Grade</th>
<th>Management</th>
<th>Follow up</th>
</tr>
</thead>
</table>
| Grade 1  
Creatinine level creatinine 1.5 - 2.0 x above baseline | Continue treatment  
Treat any associated symptoms eg vomiting, diarrhoea.  
Monitor creatinine weekly  
Encourage increased oral fluids. | Monitor bloods until return to normal.  
If worsens treat as grade 2. |
| Grade 2:  
Creatinine 2 - 3 x above Baseline | Delay treatment  
Arrange US renal tract to exclude obstructive cause.  
Consider autoimmune nephritis & commence Prednisolone 0.5-1mg/kg/day with PPI cover. | Renal team input  
If condition deteriorates treat as grade 3. |
| Grade 3:  
Creatinine >3 x baseline or >4.0 mg/dL; hospitalization indicated | Permanently discontinue treatment  
Admit to hospital & seek Nephrology advice.  
Start IV methylprednisolone 1-2mgs/kg/day | If improves taper steroids slowly. |

**Other immune-related adverse reactions:**

The following immune related adverse effects can occur:

- Uveitis
- eosinophilia
- lipase elevation
- glomerulonephritis
- iritis
- haemolytic anaemia
- amylase elevations
- multi-organ failure

If severe (Grade 3 or 4), these reactions may require immediate systemic high-dose corticosteroid therapy and discontinuation of immunotherapy.

For immunotherapy-related uveitis, iritis, or episcleritis, topical corticosteroid eye drops should be considered as medically indicated. Urgent referral to Ophthalmologist is indicated.
Infusion reaction

There were isolated reports of severe infusion reactions in clinical trials. In case of a severe infusion reaction, treatment must be discontinued and appropriate medical therapy administered. Patients with mild or moderate infusion reaction may receive treatment with close monitoring. Premedication with antipyretic and antihistamine may be considered.

Drug interactions

Corticosteroids

The use of systemic corticosteroids at baseline, before starting immunotherapy, should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of treatment. However, systemic corticosteroids or other immunosuppressants can be used after starting immunotherapy to treat immune-related adverse reactions. The use of systemic corticosteroids after starting treatment does not appear to impair the overall efficacy.

Anticoagulants

The use of anticoagulants is known to increase the risk of gastrointestinal haemorrhage. Since gastrointestinal haemorrhage is an adverse reaction with immunotherapy, patients who require concomitant anticoagulant therapy should be monitored closely.

References


<table>
<thead>
<tr>
<th>ECOG performance status</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry out all pre-disease performance without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of self care, but unable to carry out any work activities. Up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self care, confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any self care. Totally confined to bed or chair</td>
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</tbody>
</table>

Eastern Cooperative Oncology Group (ECOG)
<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diarrhoea</strong></td>
<td>Increase of up to 3 stools per day over baseline. <em>(Mild increase in ostomy output)</em></td>
<td>Increase of 4-6 stools per day over baseline <em>(moderate increase in ostomy output)</em></td>
<td>Increase of 7 or more stools per day over baseline, or incontinence or need for parenteral rehydration <em>(severe increase in ostomy output)</em></td>
</tr>
<tr>
<td><strong>Colitis</strong></td>
<td>Asymptomatic; intervention not indicated</td>
<td>Abdominal pain; mucus or blood in stool</td>
<td>Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs</td>
</tr>
<tr>
<td><strong>Fatigue</strong></td>
<td>Fatigue relieved by rest</td>
<td>Fatigue not relieved by rest; limiting instrumental ADL</td>
<td>Fatigue not relieved by rest, limiting self care ADL</td>
</tr>
<tr>
<td><strong>Nausea</strong></td>
<td>Nausea but able to eat almost as normal</td>
<td>Unable to eat normal amount but no significant weight loss</td>
<td>Eating and drinking almost nothing. Weight loss noticeable</td>
</tr>
<tr>
<td><strong>Vomiting</strong></td>
<td>1 episode in 24 hours</td>
<td>2-5 episodes in 24 hours</td>
<td>6 or more episodes in 24 hours or need for parenteral rehydration</td>
</tr>
<tr>
<td><strong>Rash</strong></td>
<td>Macules/papules covering&lt;10% BSA with or without symptoms <em>(e.g., pruritus, burning, tightness)</em></td>
<td>Macules/papules covering 10-30% BSA with or without symptoms <em>(e.g., pruritus, burning, tightness)</em>; limiting instrumental ADL</td>
<td>Macules/papules covering &gt;30% BSA with or without associated symptoms; limiting self care ADL</td>
</tr>
<tr>
<td><strong>Toxic epidermal necrosis</strong></td>
<td>-</td>
<td>-</td>
<td>Skin sloughing covering &gt;30% BSA with associated symptoms <em>(e.g., erythema, purpura, or epidermal detachment)</em></td>
</tr>
<tr>
<td>Condition</td>
<td>Grade 1</td>
<td>Grade 2</td>
<td>Grade 3</td>
</tr>
<tr>
<td>------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Stephens-Johnson</strong></td>
<td></td>
<td></td>
<td><strong>Skin sloughing covering &lt;10% BSA with</strong> associated signs (e.g., erythema, purpura, epidermal detachment and mucous membrane detachment)</td>
</tr>
<tr>
<td><strong>syndrome</strong></td>
<td></td>
<td></td>
<td><strong>Skin sloughing covering &gt;30% BSA and associated with pruritus; limiting self care ADL</strong></td>
</tr>
<tr>
<td><strong>Dry skin</strong></td>
<td><strong>Covering &lt;10% BSA and no associated erythema or pruritus</strong></td>
<td><strong>Covering 10 - 30% BSA and associated with erythema or pruritus; limiting instrumental ADL</strong></td>
<td><strong>Covering &gt;30% BSA and associated with pruritus; limiting self care ADL</strong></td>
</tr>
<tr>
<td><strong>Pruritis</strong></td>
<td><strong>Mild or localized; topical intervention indicated</strong></td>
<td><strong>Intense or widespread; intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL</strong></td>
<td><strong>Intense or widespread; constant; limiting self care ADL or sleep; oral/corticosteroid or immunosuppressive therapy indicated.</strong></td>
</tr>
<tr>
<td><strong>Adrenal insufficiency</strong></td>
<td><strong>Asymptomatic; clinical or diagnostic observations only; intervention not indicated</strong></td>
<td><strong>Moderate symptoms; medical intervention indicated</strong></td>
<td><strong>Severe symptoms; hospitalization indicated</strong></td>
</tr>
<tr>
<td><strong>Hypothyroidism</strong></td>
<td><strong>Asymptomatic; clinical or diagnostic observations only; intervention not indicated</strong></td>
<td><strong>Symptomatic; thyroid replacement indicated; limiting instrumental ADL</strong></td>
<td><strong>Severe symptoms; limiting self care ADL; hospitalization indicated</strong></td>
</tr>
<tr>
<td><strong>Paraesthesia</strong></td>
<td><strong>Mild symptoms</strong></td>
<td><strong>Moderate symptoms; limiting instrumental ADL</strong></td>
<td><strong>Severe symptoms; limiting selfcare ADL</strong></td>
</tr>
<tr>
<td><strong>Pneumonitis</strong></td>
<td><strong>Asymptomatic; clinical or diagnostic observations only; intervention not indicated</strong></td>
<td><strong>Symptomatic; medical intervention indicated; limiting instrumental ADL</strong></td>
<td><strong>Severe symptoms; limiting selfcare ADL; oxygen indicated</strong></td>
</tr>
<tr>
<td>Disease</td>
<td>Grade 1</td>
<td>Grade 2</td>
<td>Grade 3</td>
</tr>
<tr>
<td>-----------------------</td>
<td>----------------------------------------------</td>
<td>----------------------------------------------</td>
<td>----------------------------------------------</td>
</tr>
<tr>
<td><strong>Hepatitis</strong></td>
<td>ALT &lt;3.0 x ULN</td>
<td>AST or ALT &gt;3-&lt;5x ULN</td>
<td>AST or ALT &gt;5x ULN</td>
</tr>
<tr>
<td></td>
<td>Bilirubin: &lt;1.5 x ULN</td>
<td>Bilirubin &gt;1.5-&lt;3 xULN</td>
<td>Bilirubin &gt;3 xULN</td>
</tr>
<tr>
<td><strong>Acute kidney injury</strong></td>
<td>Creatinine level creatinine 1.5 - 2.0 x above baseline</td>
<td>Creatinine 2 - 3 x above Baseline</td>
<td>Creatinine &gt;3 x baseline or &gt;4.0 mg/dL; hospitalization indicated</td>
</tr>
</tbody>
</table>

Based on NCI-CTCAE v4