

# Clinical Pharmacology & Toxicology Pearl of the Week

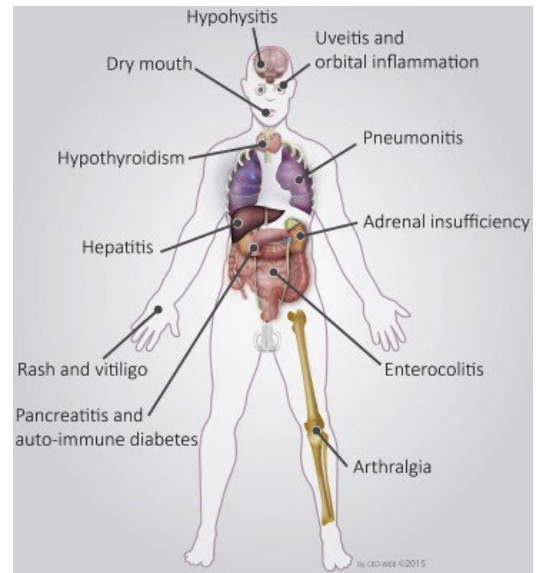
## Immune Checkpoint Inhibitors Part 2: Toxicity

### Case

- ✓ A 64 y/o male presents to the ED with increasing headaches, decreased libido, and erectile dysfunction.
  - PMHx: HTN, dyslipidemia, and Stage III melanoma on the back of his neck treated 6 months prior with nivolumab (anti-PD-1) and ipilimumab (anit-CTLA-4)
  - Physical exam is unremarkable aside from bitemporal hemianopsia and orthostatic hypotension
  - Laboratory work demonstrates hyponatremia (125), hyperkalemia (5.7). A non-contrast head CT is unremarkable.
  - Internal medicine is consulted for concerns of adrenal insufficiency and neurology is consulted.
- ✓ How do we proceed to manage this patient?

### Toxicity

- ✓ Toxicity can occur within **ANY organ system**, and can often present as any immune-related disease
  - Dermatologic is most common, followed by colitis, then hepatitis, pneumonitis and other endocrinopathies
  - Dermatologic toxicity generally, presents as erythematous maculopapular rash, though can also involve isolated pruritis, vitiligo, or Steven-Johnson Syndrome
  - Myasthenia Gravis, Guillain-Barré and IDDM are possible autoimmune effects
- ✓ Incidence of toxicity is high. 90% for CTLA-4 inhibitors and 70% for the rest
  - Fortunately, **toxicity is generally associated with a good outcome for cancer treatment**
- ✓ Toxicity is not dose dependent and is unpredictable
- ✓ Patients on combination immune checkpoint inhibitor therapy are at higher risk of more severe toxicity



Source: Michot et al, Eur J Cancer 2016, 55:1, 129-148

### Grading of toxicity:

- ✓ Grading of immune checkpoint inhibitor toxicity is organ specific, though are based on degree of symptoms, degree of end organ damage, and effect of activities of daily living
- ✓ Consensus guidelines are available from the Society for Immunotherapy of Cancer (SITC) Toxicity Management working group ([Puzanov et al, J Immunother Cancer 2017 Nov 21, 5\(1\):95](#)) and Cancer Care Ontario ([Cancer Care Ontario Clinical Practice Guideline](#))

**Table 4.** General treatment recommendations of immune related adverse events per the ASCO guidelines [17].

Grade	Definition*	Treatment	Disposition
1	Mild; asymptomatic or mild symptoms; Clinical or diagnostic observations only Intervention not indicated.	Symptomatic treatment	Discharge, if possible after discussion with oncologist Ensure outpatient follow
2	Moderate; minimal, local or noninvasive intervention indicated Limiting age appropriate instrumental ADL	Glucocorticoids (initial dose of 0.5–1 mg/kg/d of prednisone or equivalent)	Consider hospitalization versus discharge May consider observation status if short stay is anticipated Discuss disposition with oncologist
3	Severe or medically significant but not immediately life-threatening Hospitalization indicated Disabling; limiting self-care ADL	High-dose glucocorticoids (prednisone 1–2 mg/kg/d or equivalent) Glucocorticoids should be tapered over 4–6 weeks	Admission to the hospital
4	Life-threatening consequences with urgent intervention indicated	Same as Grade 3	Admission with ICU level care if indicated

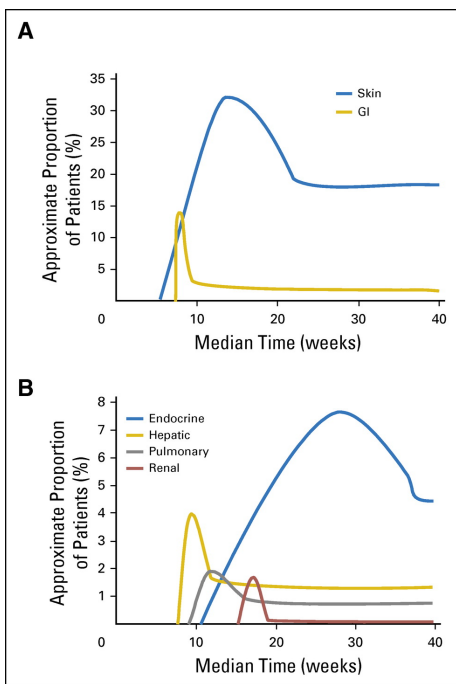
ASCO: American Society of Clinical Oncology; ICU: intensive care unit. \*Definitions follow the Common Terminology Criteria for Adverse Events (Version 5).

✓ Examples of grading for three specific adverse effects (Source: Cancer Care Ontario)

DERMATITIS	
Grade	Description
GRADE 1	Macules/papules covering <10% BSA with or without associated symptoms <sup>a</sup> .
GRADE 2	Macules/papules covering 10-30% BSA with or without associated symptoms <sup>a</sup> ; limiting ADL.
GRADE 3	Macules/papules covering >30% BSA with or without associated symptoms <sup>a</sup> ; limiting self care ADL; local superinfection.
GRADE 4	SJS <sup>b</sup> or widespread mucosal ulcerations: complicated rash with full-thickness dermal ulceration or necrosis; life-threatening.

DIARRHEA/COLITIS	
Grade	Description
GRADE 1	<4 stools/day above baseline.
GRADE 2	4-6 stools/day above baseline; abdominal pain, mucus or blood in stool.
GRADE 3	≥7 stools/day above baseline; incontinence, need for hospitalization for IV fluids ≥24hrs.
GRADE 4	Grade 3 plus fever, or peritoneal signs consistent with bowel perforation, or ileus; life-threatening.

PNEUMONITIS	
Grade	Description
GRADE 1	Asymptomatic; diagnostic radiological observations only; no intervention needed.
GRADE 2	Symptomatic; medical intervention indicated; limiting instrumental ADL.
GRADE 3	Severe symptoms; limiting self care ADL; oxygen indicated.
GRADE 4	Life-threatening respiratory compromise; urgent intervention indicated (e.g. intubation and ventilation).



Source: Weber et al, J Clin Onc 2017, 35(7):785-792



Example Rash. Source: NCCN Immunotherapy Side Effects Handout

### Timing of Toxicity

- ✓ Toxicity can occur months to years after exposure, making a detailed history of all chemotherapeutics taken during treatment paramount in identifying potential immune checkpoint inhibitor toxicity
- ✓ Generally, dermatologic, hepatic and intestinal toxicity occurs earlier following treatment compared to pulmonary, renal, neurologic and endocrine toxicity
- ✓ However, toxicity can occur at any time

### See Part 3: Management of Toxicity for management tips and case resolution in subsequent Pearls of the Week

The Calgary Clinical Pharmacology physician consultation service is available Mon-Fri, 8am-5pm. The on-call physician is listed in ROCA. Clinical Pharmacology consultation service is also available through the Netcare e-referral process and through Calgary Zone Specialist Link. Click [HERE](#) for more details.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414 (AB and NWT) or 1-866-454-1212 (SK)

## References :

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9. [NCCN Guidelines for Patients Immune Checkpoint Inhibitors https://www.nccn.org/patients/guidelines/content/PDF/immunotherapy-se-ici-patient.pdf](https://www.nccn.org/patients/guidelines/content/PDF/immunotherapy-se-ici-patient.pdf)