Clinical Pharmacology & Toxicology Pearl of the Week

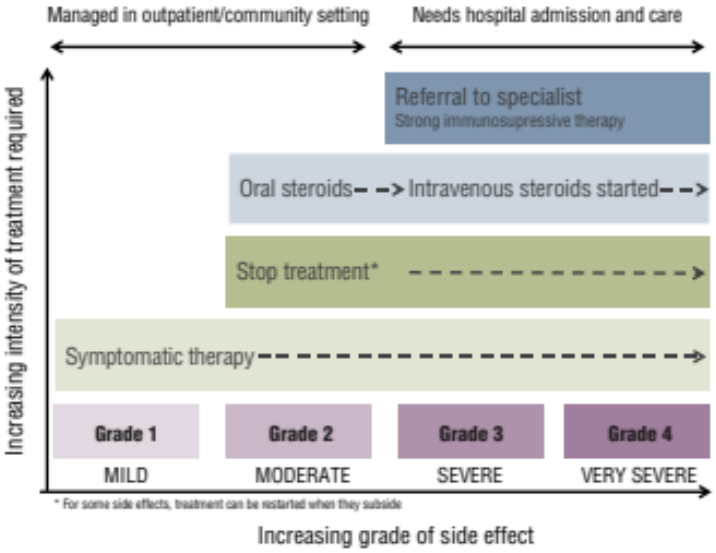
~Immune Checkpoint Inhibitors Part 3: Management of Toxicity~

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 possible adrenal insufficiency and neurology is consulted.
- ✓ How do we proceed to manage this patient?

Management

- ✓ A thorough history and high index of suspicion is required to identify potential immune checkpoint inhibitor toxicity
- ✓ Any previous exposure to immune checkpoint inhibitors needs to be ascertained regardless of time since exposure
- ✓ A thorough workup to rule out other potential causes of the presentation should be performed
- ✓ Early involvement of the patient's oncologist is generally recommended



Source: ESMO.org Patient

Treatment

- ✓ Treatment is specific to the organ system involved
  - 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)
  - These guidelines have specific recommendations for each clinical presentation of toxicity, broken down by severity of side effect

- ✓ General Treatment Considerations

I. **First line treatment is corticosteroids**
   a. Mild toxicity can often be managed supportively
      i. Consider topical steroids in isolated mild dermatologic involvement
   b. Moderate toxicity is treated with 1-2 mg/kg/day prednisone orally
   c. Severe toxicity is treated with IV steroids
      i. May also include immunosuppressants (infliximab, mycophenolate, IVIG, azathioprine, cyclosporine, etc.)

II. Treatment duration is often 4-6 weeks, with a minimum 30-day steroid taper at the end

III. Due to high dose steroid treatment, monitor for adverse effects:
   a. Monitor blood glucose, creatinine kinase, and for muscle weakness
   b. Consider PJP/Fungal prophylaxis

c. Consider PPIs and avoid NSAIDs.

IV. Involve the patient's oncologist early in care to explore the possibility of immune checkpoint inhibitor toxicity while ruling out other causes

Table 2 General guidance for corticosteroid management of immune-related adverse events

Grade of immune-related AE (CTCAE/equivalent)	Corticosteroid management	Additional notes
1	• Corticosteroids not usually indicated	• Continue immunotherapy
2	• If indicated, start oral prednisone 0.5-1 mg/kg/day if patient can take oral medication. • If IV required, start methylprednisolone 0.5-1 mg/kg/day IV • If no improvement in 2–3 days, increase corticosteroid dose to 2 mg/kg/day • Once improved to ≤grade 1 AE, start 4–6 week steroid taper	• Hold immunotherapy during corticosteroid use • Continue immunotherapy once resolved to ≤grade 1 and off corticosteroids • Start proton pump inhibitor for GI prophylaxis
3	• Start prednisone 1-2 mg/kg/day (or equivalent dose of methylprednisolone) • If no improvement in 2–3 days, add additional/alternative immune suppressant • Once improved to ≤ grade 1, start 4–6-week steroid taper • Provide supportive treatment as needed	• Hold immunotherapy; if symptoms do not improve in 4–6 weeks, discontinue immunotherapy • Consider intravenous corticosteroids • Start proton pump inhibitor for GI prophylaxis • Add PCP prophylaxis if more than 3 weeks of immunosuppression expected (>30 mg prednisone or equivalent/day)
4	• Start prednisone 1-2 mg/kg/day (or equivalent dose of methylprednisolone) • If no improvement in 2–3 days, add additional/alternative immune suppressant, e.g., infliximab • Provide supportive care as needed	• Discontinue immunotherapy • Continue intravenous corticosteroids • Start proton pump inhibitor for GI prophylaxis • Add PCP prophylaxis if more than 3 weeks of immunosuppression expected (>30 mg prednisone or equivalent/day)

Note: For steroid-refractory cases and/or when steroid sparing is desirable, management should be coordinated with disease specialists. AE, adverse event

Source: Puzanob et al. J Immunother Cancer 2017

Case Resolution

- The patient is admitted by his oncology team with neurology and endocrinology consulting.
- Cortisol, ACTH, and pituitary hormone levels are sent
- An MRI brain with sellar cuts is performed demonstrating pituitary enlargement and heterogeneous enhancement.
- Methylprednisolone 1-2 mg/kg/day IV is started, and hormone replacement is started as necessary.

References:

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5. Puzanov I, Diab A, Abdallah K, Bingham CO 3rd, Brogdon C, Dadu R, Hamad L, Kim S, Lacouture ME, LeBoeuf NR, Lenihan D, Onofrei C, Shannon V, Sharma R, Silk AW, Skondra D, Suarez-Almazor ME, Wang Y, Wiley K, Kaufman HL, Ernstoff MS; Society for Immunotherapy of Cancer Toxicity Management Working Group. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. J Immunother Cancer. 2017 Nov 21;5(1):95. doi: 10.1186/s40425-017-0300-z. PMID: 29162153; PMCID: PMC5697162.
6. https://www.esmo.org/content/download/124130/2352601/1/ESMO-Patient-Guide-on-Immunotherapy-Side-Effects.pdf
7. https://www.cancercareontario.ca/sites/ccocancercare/files/guidelines/full/ImmuneCheckpointInhibitor.pdf

The Clinical Pharmacology (CP) physician consultation service is available Mon-Fri, 8am-5pm. The on-call physician is listed in ROCA on the AHS Insite page. CP consultations are also available through Netcare e-referral and Specialist Link. You can also find us in the Alberta Referral Directory (ARD) by searching "Pharmacology" from the ARD home page. Click HERE for more details about the service.

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). Information about our outpatient Medical Toxicology Clinic can be found in Alberta Referral Directory (ARD) by searching "Toxicology" from the ARD home page.

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