Management of Immune Related Adverse Events

anti-PD-1 and PD-L1: nivolumab, pembrolizumab, atezolizumab, durvalumab, avelumab, cemiplimab

anti-CTLA-4: ipilimumab

Horvat TZ, Adel NG, Dang TO, Momtaz P, Postow MA, Callahan MK, Carvajal RD, Dickson MA, D'Angelo SP, Woo KM, Panageas KS, Wolchok JD, Chapman. Immune-Related Adverse Events, Need for Systemic Immunosuppression, and Effects on Survival and Time to Treatment Failure in Patients With Melanoma Treated With Ipilimumab at Memorial Sloan Kettering Cancer Center. J Clin Oncol. 2015;33(28):3193. Epub 2015 Aug 17. PUBMED.

Dermatologic

- Most common.
- Rash and/or pruritis in 50% of patients treated with ipilimumab, 30/40% with nivolumab and pembrolizumab. Vitiligo can be seen as well.

- G1/2: topical steroids and management of pruritus (diphenhydramine, hydroxyzine hcl)
- G3/4: hold immunotherapy, oral steroids

Naidoo J, Page DB, Li BT, Connell LC. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. Schindler K, Lacouture ME, Postow MA, Wolchok JD. Annals of Oncology. 2015;26(12):2375. Epub 2015 Sep 14. PUBMED

Colitis

- R/o infectious diarrhea.
- diarrhea >3 days, pain/cramping, e/o colonic inflammation on imaging

G1: <4 stools a day over baseline.
- Loperamide, diphenoxylate/atropine.
- GI consult if not improving.

G2: 4-6 stools over baseline.
- Hold immunotherapy.
- Oral steroids, loperamide, diphenoxylate/atropine.
- R/o infectious diarrhea, CBC, CMP + magnesium. Correct any electrolyte imbalance.
- Test for HIV, Hep A&B, TB in preparation for possible future infliximab.

Colitis

G3/4:

- 7+ stools over baseline, blood, pain.
- Discontinue immunotherapy permanently.
- Hospitalization for IV glucocorticoid, hydration, possible infliximab.

Abu-Sbeih H, Ali FS, Naqash AR, Owen DH, Patel S, Otterson GA, Kendra K, Ricciuti B, Chiari R, De Giglio A, Sleiman J, Funchain P, Wills B, Zhang J, Naidoo J, Philpott J, Gao J, Subudhi SK, Wang Y, Resumption of Immune Checkpoint Inhibitor Therapy After Immune-Mediated Colitis. Journal Clinical Oncology. 2019;37(30):2738. Epub 2019 Jun 4.

Hepatotoxicity

- More likely with nivo/ipi combination.
- Elevated transaminases, occasionally elevated total bilirubin.
- Often no findings on liver/abdominal imaging.
- Med review for all hepatotoxic OTC, prescription, herbals.

Hepatotoxicity

G2: AST or ALT >2.5 times the upper limit of normal, or total bilirubin >1.5 times the ULN.

- Hold immunotherapy.
- Abdominal imaging to r/o disease progression or new liver mets.
- Glucocorticoids (minimum of 3wks, often requires prolonged or multiple tapers).

G3: AST or ALT >5 times the ULN, or total bilirubin >3 times the ULN.

- Immunotherapy permanently discontinued.
- Abdominal imaging to r/o disease progression or new liver mets.
- Glucocorticoids (minimum of 3wks, often requires prolonged or multiple tapers)

Hepatotoxicity

- Rarely, elevated AST and ALT are refractory to glucocorticoid therapy, may require immunosuppression with mycophenolate mofetil.
- DO NOT GIVE Infliximab (hepatotoxic)
- Often requires prolonged or multiple tapers – Careful with DM

Pneumonitis

- Presents with dyspnea and cough, sometimes asymptomatic and found on imaging
- Most events are low grade, though can progress despite immunosuppression and cessation of IO.
- Incidence similar in lung cancer and melanoma

Naidoo J, Wang X, Woo KM, Iyriboz T, Halpenny D, Cunningham J, Chaft JE, Segal NH, Callahan MK, Lesokhin AM, Rosenberg J, Voss MH, Rudin CM, Rizvi H, Hou X, Rodriguez K, Albano M, Gordon RA, Leduc C, Rekhtman N, Harris B, Menzies AM, Guminski AD, Carlino MS, Kong BY, Wolchok JD, Postow MA, Long GV, Hellmann MD. Pneumonitis in Patients Treated With Anti-Programmed Death-1/Programmed Death Ligand 1 Therapy. J Clinical Oncology. 2017;35(7):709. Epub 2016 Sep 30.

Pneumonitis

G1: clinical or imaging only. Asymptomatic.

- Can continue therapy and monitor.
- Consider short interval CT. Consider
- PFTs.

G2: Symptomatic, Affecting ADLs.

- Hold immunotherapy until improvement to G1 or less.
- Prednisone 1-2 mg/kg/day, taper by 5 to 10 mg/week over four to six weeks.
- Consider bronchoscopy with BAL.
- Consider empiric antibiotics.
- If improvement not seen after 3 days of steroids = G3

Endocrinopathies

Is fatigue just an expected AE of immunotherapy or something else?

Primary hypothyroidism

- Full TFTs to ensure primary hypothyroidism.
- Levothyroxine.
- Can consider prednisone 1mg/kg/day for acute thyroiditis.

Primary hyperthyroidism

- Endocrinology consult.
- Severe cases/thyroid storm - hospitalization

Adrenal Insufficiency

- Rare irAE but can present severely with adrenal crisis: ED
- Consider in patient with unexplained nausea/fatigue/failure to thrive that doesn’t appear related to cancer
- **Also consider in patient with other IO related AE who has recently tapered off steroids.**

Hypophysitis

- Clinical presentation is usually fatigue and HA.
- Low adrenocorticotropic hormone [ACTH], TSH, follicle-stimulating hormone [FSH], luteinizing hormone [LH], growth hormone [GH], prolactin.
- CMP
- Check TFTs and cortisol to differentiate from primary hypothyroidism and primary hypoadrenalism
- MRI
- If suspected, give high dose glucocorticoids as it may prevent the need for long term hormone replacement, however most cases will advance and lead to secondary hypothyroidism and secondary hypoadrenalism and the patient will need thyroid hormone and hydrocortisone replacement.

Solinas C, Porcu M, De Silva P, Musi M, Aseslagh S, Scartozzi M, Willard-Gallo K, Mariotti S, Saba L. Cancer immunotherapy-associated hypophysitis. Seminars in Oncology. Volume 45, Issue 3, June 2018, Pages 181-186

Type I Diabetes Mellitus

- glucocorticoids or infliximab will not help
- Insulin
- Endocrine for management

Pancreatitis

- Routine monitoring of lipase/amylase not usually done (asymptomatic elevations can be present on immunotherapy)
- If symptomatic, likely will require hospitalization
- Long steroid taper
- GI consultation

Kohlmann J, Wagenknecht D, Simon JC, Ziemer M. Immune-related pancreatitis associated with checkpoint blockade in melanoma. Melanoma Res. 2019 Oct;29(5):549-552. doi: 10.1097/CMR.0000000000000611. PMID: 30964768.

Nephritis

- Discontinue immunotherapy.
- Prednisone taper. Supportive care with IV hydration and electrolyte monitoring.
- Some continue to recover, some recover initially, then worsen.
- Nephrology for consultation and long term monitoring

Musculoskeletal

- Consider imaging to r/o mets, autoimmune labs
- Symptomatic treatment, pain relief
- In cases of more significant myositis, assess also for myocarditis
- Consider short treatment break to improve QOL and then resume if able.
- If synovitis or symptoms/arthralgia persist >4wks consider referral to Rheumatology

Myositis

Muscle pain and weakness, CPK elevation.

G1: Mild weakness with or without pain.
- H&P with neuro exam.
- Continue immunotherapy.

G2: Moderate weakness with or without pain; limiting age-appropriate instrumental ADL.
- Hold immunotherapy.
- Check CK, if elevated 3x or more initiate prednisone at 0.5-1mg/kg/day.
- NSAIDs (if patient can take). Consider Neurology/Rheumatology consults.
- Consider restarting immunotherapy when symptoms resolve or if CK is normal and if prednisone is <10mg/day.

G3 to 4: Severe weakness with or without pain; limiting self-care ADL.
- Hold immunotherapy. Neurology/Rheumatology consults. Hospitalization if necessary.
- Immunosuppression.
- Possibly consider restarting immunotherapy when off of immunosuppression, if symptoms are G1.
- Any e/o myocardial involvement, discontinue immunotherapy permanently.

Myositis/myocarditis

Hospitalization

Inflammatory Arthritis

G1: Mild pain with inflammation.

- Continue immunotherapy.
- Symptom management with acetaminophen or NSAIDs (if patient can take).

G2: Moderate pain with inflammation, limiting instrumental ADL.

- Hold immunotherapy.
- If pain is not controlled, start prednisone 10-20mg/day for 4-6wks.
- Consider restarting therapy when pain/symptoms are controlled and prednisone tapered down to <10mg/day

G3/4: Severe pain with inflammation limiting self-care ADLs, erythema; irreversible joint damage.

- Rheumatology referral
- Could consider restarting immunotherapy if resolves to G1 and not on immunosuppression (in consultation with Rheumatology)
- May need admission for pain control

Polymyalgia-like Syndrome

G1: Mild stiffness and pain.

- Continue immunotherapy.
- NSAIDs or acetaminophen if patient can take.

G2: Moderate stiffness and pain; limiting some ADLs.

- Consider hold of immunotherapy and prednisone 20mg/day (taper after 3-4wks if symptoms are improving.)

G3 to 4: Severe stiffness and pain.

- Severely limiting ADLs. Hold immunotherapy.
- Consult Rheumatology.
- Admission for pain control if indicated.

Brahmer JR, et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clinical Oncology 2018.

Neurologic

- Monitor for HA, peripheral sensory neuropathy, Guillain-Barre syndrome.
- Neurology consultation or admission for work up (imaging, lumbar puncture)

Eye

Ipilimumab: episcleritis, conjunctivitis, uveitis, orbital inflammation

Nivolumab, pembrolizumab: uveitis

- Ophthalmology consult
- Topical glucocorticoids
- G3/4 oral glucocorticoids

Mucositis

- R/o thrush
- Glucocorticoid rinse
- Lidocaine

Special Considerations

- Pneumocystis pneumonia prophylaxis: underlying lung conditions/glucocorticoids >6wks/continuing on chemotherapy

- Patient and family goals of care reassessment after irAE

References

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Time to irAE: https://www.uptodate.com/contents/image?imageKey=ONC%2F96620~ONC%2F115276&topicKey=ONC%2F96368&search=immune%20mediate&source=see_link

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