CLINICAL VIGNETTE

Steroid Refractory Immune Colitis Following CTLA-4 Checkpoint Inhibition

Joshua D. Rosenberg, MD and Mahshid Mosallaei-Benjamin, MD

Case Report

A 63-year-old woman presented with post-coital bleeding and was found to have an abnormal appearing cutaneous lesion on the vulva. A shave biopsy confirmed a vulvar melanoma. She underwent a radical, partial vulvectomy that revealed a Stage IIIC, nodular, malignant melanoma. The tumor was 4.2 mm thick and ulcerated with evidence of peri-neural invasion but no lymph-vascular space invasion. The mitotic index was 7/mm2. There were no microsatellite lesions and her margins were negative. Following her surgery, a PET/CT documented hyper-metabolic, right inguinal lymphadenopathy up to 3.3 cm. There was no evidence for distant metastatic disease. She subsequently underwent right inguinal, pelvic and deep femoral lymphadenectomies. She had metastatic melanoma in three of five inguinal nodes and one of three pelvic nodes. All twelve femoral nodes removed were negative for metastatic melano-ma. The patient's melanoma was both PD-L1 and BRAF mutation negative.

The patient initiated adjuvant Ipilimumab at 10 mg/kg 2 months post-op. Two days following her second cycle, she presented to a local Emergency Room for nausea, vomiting, and fatigue. She improved following fluids and intravenous anti-emetics and was discharged home. The patient was seen in clinic the following morning and started on prednisone at 2 mg/kg. Five days later, the patient returned to the Emergency Room for worsening nausea and vomiting. At this time, she was also complaining of near explosive, watery diarrhea of about eight episodes per day. The patient was admitted to the hospital for aggressive supportive care, transitioned to intravenous cortico-steroids and underwent a thorough infectious disease evaluation, which was entirely negative.

The patient continued to clinically decline in the hospital, and was recommended to start infliximab. Before starting, she underwent diagnostic colonoscopy that revealed pan-colitis with exceedingly edematous folds and spontaneous oozing. Multiple random biopsies were taken, revealing active colitis, negative for dysplasia, malignancy and micro-organisms. Following her endoscopy, the patient received Infliximab at 5 mg/kg IV, which she tolerated well.

Within 48 hours, the patient's diarrhea markedly improved, down to 3 stools per day. Her nausea was well controlled and she started tolerating nutrition by mouth. She was able to increase her diet to regular items within 72 hours of Infliximab, and was transitioned back to oral corticosteroids, with predni-sone dosed at 1 mg/kg. Expecting a slow and prolonged steroid taper, Trimethoprim-sulfamethoxazole prophylaxis and a daily proton pump inhibitor was started.

The patient's oral steroids were slowly tapered over 8 weeks. She had no recurrent bouts of nausea, vomiting or diarrhea during her taper. She is now completely asymptomatic and has an excellent performance status. She is back to work full time. We have to monitor her as opposed to attempting a different systemic, adjuvant regimen. She remains clinically without evidence for disease recurrence at this time.

Discussion

Checkpoint inhibitors are immunomodulatory antibodies utilized to stimulate and enhance the immune system and have been determined to improve both the prognosis and survival of patients with multiple advanced cancer diagnoses. This form of immunotherapy is felt to increase anti-tumor immunity via blockade of immunologic down-regulation through inhibition of cytotoxic T-lymphocyte antigen 4 (CTLA-4) and pro-grammed cell death protein 1 (PD-1) or its ligand (PD-L1). Ipilimumab, a CTLA-4 inhibitor, is approved for use in advanced melanoma. There are multiple PD-1 and PD-L1 checkpoint inhibitors including Nivolumab, Pembrolizumab, Atezolizumab, Avelumab and Durvalumab that have been effective in varying conditions including advanced non-small cell lung cancer, melanoma, renal cell carcinoma, head and neck squamous cell carcinoma, urothelial carcinoma, classic Hodgkin's lymphoma, Merkel cell carcinoma and solid tumors with high micro-satellite instability or mismatch repair deficiency.

Given the unique mechanism of action of checkpoint inhibition, adverse events can be unique and distinct from classically identified toxicities from standard cytotoxic chemothera-peutics. Although the precise pathophysiology of these immune related adverse events (irAEs) are largely unknown, the unique spectrum of side effects including dermatologic, gastrointestinal, renal, hepatic, endocrine and musculoskeletal are well described[1] and essentially result from excessive immunity against normal tissue. Most commonly, irAEs develop within the first few months of treatment initiation, though these events can develop at any time. Interestingly, studies do not show an increased cumulative incidence of irAEs in those patients receiving prolonged checkpoint inhibition,

though later term toxicity is still largely unknown given the relative infancy of this treatment paradigm.[2]

The irAEs are generally treated by delaying checkpoint inhibitor administration and/or initiating immunosuppressive agents, with oral glucocorticoids being the most common first line agent. The American Society of Clinical Oncology has general guidelines and organ-system-specific recommendations for irAEs associated with checkpoint inhibition.[3] Most commonly, patients with mild to moderate irAEs, prednisone 0.5 mg/kg/day is initiated while checkpoint inhibition is held until the irAE is grade 1 or less. For those patients with severe or life threatening irAEs, checkpoint inhibition is permanently discontinued and prednisone at 1-2 mg/mg/day is initiated. When symptoms improve to grade 1 or less, prednisone is slowly tapered off, usually over at least one month. As noted in our report, patients who do not respond to glucocorticoids are usually recommended to receive infliximab[4] which has high salvage rates. The question must be raised of whether we should be using infliximab earlier in the treatment of irAEs to provide both a quicker response and minimize the exposure to glucocorticoids.

Currently, there are no data to suggest that irAEs can be viewed as a favorable biomarker to establish higher anti-tumor efficacy. There are conflicting reports regarding the tumor response rates in patients with and without irAEs, and the general opinion is that patients can benefit from checkpoint inhibition even in the absence of irAEs.[5,6] Finally, there are no studies suggesting that immunosuppressive agents reduce the anti-tumor efficacy of checkpoint blockade, which has been of clinical concern for treating oncologists. Outcomes for patients treated with immunosuppressive agents following irAEs to checkpoint blockade appear no worse overall than for those patients who did not suffer from irAEs in a retrospective analysis. This continues to be a topic that should be investigated prospectively.[7]

REFERENCES

1. **Naidoo J, Page DB, Li BT, Connell LC, Schindler K, Lacouture ME, Postow MA, Wolchok JD**. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. *Ann Oncol*. 2015 Dec;26(12):2375-91. doi: 10.1093/annonc/mdv383. Epub 2015 Sep 14. Review. Erratum in: Ann Oncol. 2016 Jul;27(7):1362. PubMed PMID:26371282.
2. **Topalian SL, Sznol M, McDermott DF, Kluger HM, Carvajal RD, Sharfman WH, Brahmer JR, Lawrence DP, Atkins MB, Powderly JD, Leming PD, Lipson EJ, Puzanov I, Smith DC, Taube JM, Wigginton JM, Kollia GD, Gupta A, Pardoll DM, Sosman JA, Hodi FS**. Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. *J Clin Oncol*. 2014 Apr 1;32(10):1020-30. doi: 10.1200/JCO.2013.53.0105. Epub 2014 Mar 3. PubMed PMID: 24590637; PubMed Central PMCID: PMC4811023.
3. Management of Immune-Related Adverse Events in Patients Treated with Immune Checkpoint Inhibitor Therapy: *American Society of Clinical Oncology Clinical Practice Guideline*.
4. **Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, Chau I, Ernstoff MS, Gardner JM, Ginex P, Hallmeyer S, Holter Chakrabarty J, Leighl NB, Mammen JS, McDermott DF, Naing A, Nastoupil LJ, Phillips T, Porter LD, Puzanov I, Reichner CA, Santomasso BD, Seigel C, Spira A, Suarez-Almazor ME, Wang Y, Weber JS, Wolchok JD, Thompson JA**. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*. 2018 Feb 14:JCO2017776385. doi: 10.1200/JCO.2017.77.6385. [Epub ahead of print] PubMed PMID: 29442540.
5. **Michot JM, Bigenwald C, Champiat S, Collins M, Carbonnel F, Postel-Vinay S, Berdelou A, Varga A, Bahleda R, Hollebecque A, Massard C, Fuerea A, Ribrag V, Gazzah A, Armand JP, Amellal N, Angevin E, Noel N, Boutros C, Mateus C, Robert C, Soria JC, Marabelle A, Lambotte O**. Immune-related adverse events with immune checkpoint blockade: a comprehendsive review. *Eur J Cancer*. 2016 Feb;54:139-148. doi: 10.1016/j.ejca.2015.11.016. Epub 2016 Jan 5. Review. PubMed PMID: 26765102.
6. **Attia P, Phan GQ, Maker AV, Robinson MR, Quezado MM, Yang JC, Sherry RM, Topalian SL, Kammula US, Royal RE, Restifo NP, Haworth LR, Levy C, Mavroukakis SA, Nichol G, Yellin MJ, Rosenberg SA**. Autoimmunity correlates with tumor regression in patients with metastatic melanoma treated with anti-cytotoxic T-lymphocyte antigen-4. *J Clin Oncol*. 2005 Sep 1;23(25): 6043-53. Epub 2005 Aug 8. PubMed PMID: 16087944; PubMed Central PMCID: PMC1473965.
7. **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 PB**. 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 Oct 1;33(28):3193-8. doi: 10.1200/JCO.2015.60.8448. Epub 2015 Aug 17. PubMed PMID:26282644; PubMed Central PMCID: PMC5087335.

Submitted April 27, 2018