Uveitis secondary to cancer therapeutics

Sruthi Arepalli, Arthi G. Venkat

Cole Eye Institute, Cleveland Clinic, Cleveland, OH, USA

Contributions: (I) Conception and design: All authors; (II) Administrative support: AG Venkat; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Arthi G. Venkat, MS, MD. Cleveland Clinic Foundation, Cole Eye Institute, Cleveland Clinic, 9500 Euclid Ave., i-30, Cleveland, OH 44115, USA. Email: venkata@ccf.org.

Abstract: Cancer cells provide a therapeutic challenge as they impede the immune system and its response to malignancy. Checkpoint inhibitors and targeted therapy provide novel methods for the treatment of these metastases. These use of immunotherapy and targeted therapy is widespread, with indications including metastatic melanoma, squamous cell carcinoma, non-small cell lung cancer, colon cancer, gastric cancer, renal cell carcinoma, Merkel cell carcinoma and urothelial cancer. Checkpoint inhibitors act upon three main receptors or ligands to achieve this goal: cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed death protein (PD-1) and programmed death ligand-1 (PD-L1). Additionally, targeted therapies counter the mutations leading to cancer cell proliferation, which include the mitogen-activated protein kinase (MEK) pathway and BRAF enzyme. However, they are known to cause ocular side effects in up to 1% of patients, with uveitis comprising a fraction of these patients. These secondary uveitis manifestations can present with severity ranging from solitary anterior uveitis to panuveitis, sometimes in concert with systemic manifestations such as Vogt-Koyanagi-Harada (VKH)-like syndrome. The uveitis caused by these medications can present both diagnostic and treatment challenges that can complicate patient care. Systemic steroids have demonstrated mixed data regarding the reduction of cancer therapeutic efficacy, and as a result, immunotherapy and targeted therapy are often held when systemic steroids are used for immune-related adverse event (irAE) treatment. Local steroids, although prone to their own set of adverse effects, may therefore be preferable to systemic steroids in the treatment of uveitis secondary to cancer therapeutics. In this review, we provide an overview of uveitis secondary to targeted therapy and immunotherapy, as well as treatment considerations.

Keywords: Immunotherapy; uveitis; checkpoint inhibitors; targeted therapy

Received: 17 November 2019; Accepted: 27 April 2020; Published: 15 June 2020.
doi: 10.21037/aes-19-108
View this article at: http://dx.doi.org/aes-19-108

Introduction

Immune checkpoint inhibitors and targeted therapy provide novel methods for the treatment of metastatic malignancy (1,2). Cancer cells can stimulate inhibitory T-cell receptors to down-regulate the immune system; checkpoint inhibitors combat this evasive method by stimulating T-cell activity, resulting in the detection and subsequent destruction of malignant cells (1,2). Checkpoint inhibitors achieve this by acting on cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed death protein (PD-1) and programmed death ligand-1 (PD-L1). Targeted therapies work by counteracting specific mutations that lead to unrestricted proliferation of cancer cells, the mitogen-activated protein kinase (MEK) pathway and BRAF enzyme (3-5).

These therapies have been approved for, but are not limited to, the treatment of metastatic melanoma, squamous cell carcinomas, non-small cell lung cancer, colon cancer, gastric cancer, renal cell carcinoma, Merkel cell carcinoma and urothelial cancer (6-8). While monumental in the management of malignancies, these medications often lead to adverse inflammatory side effects, including secondary uveitis (1-3). Here, we review the literature to date describing uveitic complications of checkpoint inhibitors and targeted therapies.

Immune checkpoint inhibitors

CTLA-4

The CTLA-4 receptor is present on T-cell membranes and is integral to down-regulating T-cell activity. T-cells express both the CTLA-4 and CD28 receptor. Initially, ligands on antigen presenting cells (APCs), namely, B7-1 and B7-2, attach to the CD28 receptor, causing T-cell activation. Once activated, these T-cells also express CTLA-4, which has a higher binding affinity than CD28 to APC ligands (9,10). The presence of both these receptors creates a feedback loop mechanism to prevent chronic immune activation (2,9,10). Malignant cells manipulate the CTLA-4 down-regulatory pathway to enable their spread throughout the immune system. Ipilimumab, a monoclonal antibody, binds to CTLA-4. Following this binding, the normal down-regulatory mechanism of CTLA-4, as well as CD28-B7 co-stimulation, is interrupted. Subsequent T-cell upregulation then leads to anti-tumor immunity (10,11).

PD-1 and PD-L1

PD-1, like CTLA-4, is a T-cell down-regulator that decreases immune response by binding to PD-L1 (2). However, unlike the CTLA-4 pathway, the ligand PD-L1 is expressed directly on cancer cells rather than APCs. The binding of PD-1 and PD-L1 therefore allows tumor cells to directly initiate apoptosis of immune cells (2). This mechanism is still utilized by malignant cells even when the CTLA-4 pathway is inhibited; consequently, monotherapy with ipilimumab may not be sufficient for certain malignancies (12). Both pembrolizumab and nivolumab are PD-1 inhibitors that prevent binding to PD-L1, up-regulating T-cell activity as a result (3). Atezolizumab, avelumab and durvalumab bind to PD-L1, preventing the interaction between PD-1 and PD-L1 and resulting in T-cell upregulation (3).

Targeted therapies

Targeted therapies include medications aimed at the MEK pathway (trametinib) and the BRAF enzyme (vemurafenib and dabrafenib) to inhibit the proliferation of malignant cells. Trametinib works in melanomas with the BRAF V600E or V600K mutation while dabrafenib inhibits the BRAF V600E kinase (13). Vemurafenib interferes with the serine/threonine protein kinase BRAF (14). These can be used in conjunction with or as sole agents with other immunotherapies.

Side effects

The side effects of checkpoint inhibitor and targeted therapy are widespread, with the most common findings including fatigue and skin rash occurring in up to 50% of individuals (2). Ocular side effects generally occur in 1% of patients, with a fraction of these patients experiencing uveitis (2). The cases of uveitis resulting from checkpoint inhibitor or targeted therapy range from isolated anterior uveitis to panuveitis, with some mimicking systemic disorders, such as Vogt-Koyanagi-Harada (VKH) syndrome.

Ipilimumab

Multiple reports detail the development of uveitis following the initiation of ipilimumab therapy. Anterior uveitis responsive to topical steroid therapy is well described (1,15-18). More recalcitrant cases of anterior uveitis secondary to ipilimumab have required treatment with either peri-ocular or oral steroids (17,19,20).

Secondary posterior uveitis and panuveitis treated systemic steroids has also been described (21,22). Tsui *et al.* report a case of retinal vasculitis and macular edema requiring oral steroids and an intravitreal steroid depot (23). Moreover, optic nerve involvement can occur with ipilimumab. Two reports document bilateral neuroretinitis; one of which improved on topical steroids alone while the other was treated with additional oral steroids (24,25). Wilson *et al.* describe a more devastating case of atypical optical neuritis resulting in a visual acuity of no light perception, unresponsive to systemic steroids (26). Additionally, severe uveitis with systemic findings such as VKH-like syndrome have been documented with ipilimumab, often treated with systemic steroids (27-29).

Pembrolizumab

Similarly, pembrolizumab has a range of uveitic manifestations. Multiple cases of anterior uveitis have been reported, some of which have required injectable or systemic steroid therapy in addition to topical therapy in order to achieve adequate control (30,31).

Other reports have detailed the development of panuveitis utilizing periocular and systemic steroids, and in one case hypotony requiring silicone oil placement (32-35). Interestingly, in a patient with metastatic uveal melanoma, which required enucleation of the eye and the initiation on pembrolizumab therapy, the unaffected eye subsequently developed panuveitis with vasculitis treated with intravitreal steroids (36). Systemic manifestations linked to the secondary uveitis are also well-described. Bricout *et al.* recount a case of VKH-like systemic manifestations (37). Lise *et al.* describe a case in which sarcoidosis was unmasked in a patient with panuveitis; the patient had hilar and mediastinal lymphadenopathy, elevated angiotensin converting enzyme levels, and bronchial biopsy showing noncaseating granulomas (38).

Nivolumab

Many reports discuss the development of anterior uveitis in patients treated with nivolumab (1,39-41). Aside from uveitis, corneal transplant rejection has also been described in conjunction with nivolumab therapy, with ultimate failure of the graft even after initiation of systemic steroids and cessation of the drug (42).

Posterior, panuveitis and systemic syndromes associated with uveitis have also been described. Gonzales *et al.* describe a case of posterior scleritis with anterior uveitis treated with nivolumab and cabiralizumab (43). Multifocal choroiditis after initiation of the drug has also been described (35), as have recalcitrant cases utilizing oral and injectable steroids (44). Multiple reports recount VKH-like syndromes as well (35,45,46).

Atezolizumab

A few reports exist linking atezolizumab to uveitis development. Conrady and colleagues report a case of a patient developing paracentral acute middle maculopathy and venous occlusions treated with oral steroids (35). Venkat *et al.* document a case of superior limbal keratitis and macular edema treated with topical steroids and intravitreal steroids (1).

Trametinib and dabrafenib

Anterior uveitis has been documented after initiation of dabrafenib (34), however there are many more reports of secondary uveitis in the setting of combination trametinib and dabrafenib therapy. Whist *et al.* report several patients on combination of trametinib and dabrafenib therapy that developed anterior uveitis (47). Intermediate and posterior uveitis have additionally been described with this combination therapy (48,49). Extensive uveitis, including panuveitis with serous retinal detachments and systemic VKH-like manifestations have also been reported (13,50,51). In two patients treated sequentially with nivolumab followed by trametinib/dabrafenib, both patients developed VKH-like symptoms treated with intravenous steroids (52).

Vemurafenib

Anterior uveitis with and without intermediate and posterior involvement have been described in the setting of vemurafenib (14,22,53). These patients were treated with topical, injectable, and systemic steroids. Panuveitis has been described, and in one case was severe enough to cause a serous retinal detachment requiring surgical intervention in addition to steroid therapy (53-55). Two patients have developed a VKH-like syndrome that was treated with systemic steroids (56,57).

Conclusions

Immunotherapy and targeted therapy provide crucial interventions for metastatic cancer patients. The uveitic manifestations of these medications are, in some cases, dramatic with visually significant consequences. The Common Terminology Criteria for Adverse Events (CTCAE) is used to grade immune-related adverse events (irAEs) secondary to cancer therapy, and are used as criteria at which cessation of therapy may be recommended based on irAE severity. The most updated version of the CTCAE was used to develop a consensus report on ocular irAEs that recommended permanent discontinuation of checkpoint inhibitors with grade 3 or 4 uveitis, which encompasses anterior uveitis with 3+ or more cells, intermediate uveitis, posterior uveitis, panuveitis, or 20/200 vision or worse (58). Therefore, withholding of cancer therapy is often recommended for these secondary uveitides (59). However, these cancer therapies have led to the extension of life expectancy in cases of terminal cancer by several months (1). In addition, due to concerns that systemic steroids could affect the efficacy of checkpoint inhibitors and targeted therapy, cessation of therapy is often also recommended by oncologists when uveitis is treated with systemic steroids. However, multiple cases in the literature have managed secondary uveitis with local therapy alone, allowing the continuation of cancer therapy and the avoidance of systemic corticosteroids (1). The management of the uveitic manifestations of these medications therefore requires interdisciplinary discussion between ophthalmology and oncology to determine the best course of action, and whether discontinuation of cancer therapy is absolutely necessary. In certain cases, such as those with associated systemic irAEs, discontinuation of cancer treatment in concert with steroid therapy may be the optimal course of action.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Steven Yeh) for the series "Innovations in the Diagnosis and Management of Uveitis" published in *Annals of Eye Science*. The article was sent for external peer review organized by the Guest Editor and the editorial office.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/aes-19-108). The series "Innovations in the Diagnosis and Management of Uveitis" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Venkat AG, Arepalli S, Sharma S, et al. Local therapy for cancer therapy-associated uveitis: a case series and review of the literature. Br J Ophthalmol 2020;104:703-11.
2. Dalvin LA, Shields CL, Orloff M, et al. Checkpoint inhibitor immune therapy: systemic indications and ophthalmic side effects. Retina 2018;38:1063-78.
3. Moorthy RS, Moorthy MS, Cunningham ET Jr. Drug-induced uveitis. Curr Opin Ophthalmol 2018;29:588-603.
4. Choe CH, McArthur GA, Caro I, et al. Ocular toxicity in BRAF mutant cutaneous melanoma patients treated with vemurafenib. Am J Ophthalmol 2014;158:831-7.e2.
5. Welsh SJ, Corrie PG. Management of BRAF and MEK inhibitor toxicities in patients with metastatic melanoma. Ther Adv Med Oncol 2015;7:122-36.
6. Company B-MS. Yervoy (Ipilimumab) Injection [Prescribing Information]. Princeton: Company B-MS, 2017.
7. Merck & Co, Inc. Keytruda (Pembrolizumab) for Injection [Prescribing Information]. Whitehouse Station: Merck & Co, Inc., 2017.
8. Nghiem PT, Bhatia S, Lipson EJ, et al. PD-1 Blockade with Pembrolizumab in Advanced Merkel-Cell Carcinoma. N Engl J Med 2016;374:2542-52.
9. Farkona S, Diamandis EP, Blasutig IM. Cancer immunotherapy: the beginning of the end of cancer? BMC Med 2016;14:73.
10. Wolchok JD, Saenger Y. The mechanism of anti-CTLA-4 activity and the negative regulation of T-cell activation. Oncologist 2008;13 Suppl 4:2-9.
11. Postow MA, Callahan MK, Wolchok JD. Immune Checkpoint Blockade in Cancer Therapy. J Clin Oncol 2015;33:1974-82.
12. Geng Q, Jiao P, Jin P, et al. PD-1/PD-L1 Inhibitors for Immuno-oncology: From Antibodies to Small Molecules. Curr Pharm Des 2018;23:6033-41.
13. Sarny S, Neumayer M, Kofler J, et al. Ocular toxicity due to Trametinib and Dabrafenib. BMC Ophthalmol 2017;17:146.
14. Fonollosa A, Mesquida M, Adan A. Uveitic macular oedema after treatment with vemurafenib. Acta Ophthalmol 2015;93:e686-7.
15. Miserocchi E, Cimminiello C, Mazzola M, et al. New-onset uveitis during CTLA-4 blockade therapy with ipilimumab in metastatic melanoma patient. Can J Ophthalmol 2015;50:e2-4.
16. Papavasileiou E, Prasad S, Freitag SK, et al. Ipilimumab-induced Ocular and Orbital Inflammation--A Case Series and Review of the Literature. Ocul Immunol Inflamm

2016;24:140-6.
17. Chang CJ, Chen SJ, Hwang DK, et al. Bilateral anterior uveitis after immunotherapy for malignant melanoma. Taiwan J Ophthalmol 2018;8:173-5.
18. Zimmer L, Goldinger SM, Hofmann L, et al. Neurological, respiratory, musculoskeletal, cardiac and ocular side-effects of anti-PD-1 therapy. Eur J Cancer 2016;60:210-25.
19. Nallapaneni NN, Mourya R, Bhatt VR, et al. Ipilimumab-induced hypophysitis and uveitis in a patient with metastatic melanoma and a history of ipilimumab-induced skin rash. J Natl Compr Canc Netw 2014;12:1077-81.
20. Numata S, Iwata Y, Okumura R, et al. Bilateral anterior uveitis and unilateral facial palsy due to ipilimumab for metastatic melanoma in an individual with human leukocyte antigen DR4: A case report. J Dermatol 2018;45:113-4.
21. Tan AX, Ang A, Campbell WG, et al. Bilateral ipilimumab-induced posterior uveitis following treatment for metastatic choroidal melanoma. Clin Exp Ophthalmol 2018;46:819-21.
22. Fierz FC, Meier F, Chaloupka K, et al. Intraocular Inflammation Associated with New Therapies for Cutaneous Melanoma - Case Series and Review. Klin Monbl Augenheilkd 2016;233:540-4.
23. Tsui E, Gonzales JA. Retinal Vasculitis Associated with Ipilimumab. Ocul Immunol Inflamm 2019:1-3. [Epub ahead of print].
24. Hahn L, Pepple KL. Bilateral neuroretinitis and anterior uveitis following ipilimumab treatment for metastatic melanoma. J Ophthalmic Inflamm Infect 2016;6:14.
25. Yeh OL, Francis CE. Ipilimumab-associated bilateral optic neuropathy. J Neuroophthalmol 2015;35:144-7.
26. Wilson MA, Guld K, Galetta S, et al. Acute visual loss after ipilimumab treatment for metastatic melanoma. J Immunother Cancer 2016;4:66.
27. Crosson JN, Laird PW, Debiec M, et al. Vogt-Koyanagi-Harada-like syndrome after CTLA-4 inhibition with ipilimumab for metastatic melanoma. J Immunother 2015;38:80-4.
28. Wong RK, Lee JK, Huang JJ. Bilateral drug (ipilimumab)-induced vitritis, choroiditis, and serous retinal detachments suggestive of vogt-koyanagi-harada syndrome. Retin Cases Brief Rep 2012;6:423-6.
29. Witmer MT. Treatment of Ipilimumab-Induced Vogt-Koyanagi-Harada Syndrome With Oral Dexamethasone. Ophthalmic Surg Lasers Imaging Retina 2017;48:928-31.
30. Basilious A, Lloyd JC. Posterior subcapsular cataracts and hypotony secondary to severe pembrolizumab induced uveitis: Case report. Can J Ophthalmol 2016;51:e4-6.
31. Abu Samra K, Valdes-Navarro M, Lee S, et al. A case of bilateral uveitis and papillitis in a patient treated with pembrolizumab. Eur J Ophthalmol 2016;26:e46-8.
32. Reid G, Lorigan P, Heimann H, et al. Management of Chronic Hypotony Following Bilateral Uveitis in a Patient Treated with Pembrolizumab for Cutaneous Metastatic Melanoma. Ocul Immunol Inflamm 2019;27:1012-5.
33. Hanna KS. A Rare Case of Pembrolizumab-Induced Uveitis in a Patient with Metastatic Melanoma. Pharmacotherapy 2016;36:e183-8.
34. Taylor SC, Hrisomalos F, Linette GP, et al. A case of recurrent bilateral uveitis independently associated with dabrafenib and pembrolizumab therapy. Am J Ophthalmol Case Rep 2016;2:23-5.
35. Conrady CD, Larochelle M, Pecen P, et al. Checkpoint inhibitor-induced uveitis: a case series. Graefes Arch Clin Exp Ophthalmol 2018;256:187-91.
36. Aaberg MT, Aaberg TM Jr. Pembrolizumab administration associated with posterior uveitis. Retin Cases Brief Rep 2017;11:348-51.
37. Bricout M, Petre A, Amini-Adle M, et al. Vogt-Koyanagi-Harada-like Syndrome Complicating Pembrolizumab Treatment for Metastatic Melanoma. J Immunother 2017;40:77-82.
38. Lise QK, Audrey AG. Multifocal choroiditis as the first sign of systemic sarcoidosis associated with pembrolizumab. Am J Ophthalmol Case Rep 2016;5:92-3.
39. Baughman DM, Lee CS, Snydsman BE, et al. Bilateral Uveitis and Keratitis Following Nivolumab Treatment for Metastatic Melanoma. Med Case Rep (Wilmington) 2017. doi: 10.21767/2471-8041.100044.
40. Karlin J, Gentzler R, Golen J. Bilateral Anterior Uveitis Associated with Nivolumab Therapy. Ocul Immunol Inflamm 2018;26:283-5.
41. Kanno H, Ishida K, Yamada W, et al. Uveitis induced by programmed cell death protein 1 inhibitor therapy with nivolumab in metastatic melanoma patient. J Infect Chemother 2017;23:774-7.
42. Le Fournis S, Gohier P, Urban T, et al. Corneal graft rejection in a patient treated with nivolumab for primary lung cancer. Lung Cancer 2016;102:28-9.
43. Gonzales JA, Shantha J, Acharya NR. Combination nivolumab- and cabiralizumab-associated acute bilateral anterior and posterior scleritis and anterior uveitis. Am J Ophthalmol Case Rep 2018;10:117-8.
44. Wang W, Lam WC, Chen L. Recurrent grade 4 panuveitis

with serous retinal detachment related to nivolumab treatment in a patient with metastatic renal cell carcinoma. Cancer Immunol Immunother 2019;68:85-95.
45. Arai T, Harada K, Usui Y, et al. Case of acute anterior uveitis and Vogt-Koyanagi-Harada syndrome-like eruptions induced by nivolumab in a melanoma patient. J Dermatol 2017;44:975-6.
46. Obata S, Saishin Y, Teramura K, et al. Vogt-Koyanagi-Harada Disease-Like Uveitis during Nivolumab (Anti-PD-1 Antibody) Treatment for Metastatic Cutaneous Malignant Melanoma. Case Rep Ophthalmol 2019;10:67-74.
47. Whist E, Symes RJ, Chang JH, et al. Uveitis caused by treatment for malignant melanoma: a case series. Retin Cases Brief Rep 2019. [Epub ahead of print].
48. Joshi L, Karydis A, Gemenetzi M, et al. Uveitis as a Result of MAP Kinase Pathway Inhibition. Case Rep Ophthalmol 2013;4:279-82.
49. Lim J, Lomax AJ, McNeil C, et al. Uveitis and Papillitis in the Setting of Dabrafenib and Trametinib Therapy for Metastatic Melanoma: A Case Report. Ocul Immunol Inflamm 2018;26:628-31.
50. Draganova D, Kerger J, Caspers L, et al. Severe bilateral panuveitis during melanoma treatment by Dabrafenib and Trametinib. J Ophthalmic Inflamm Infect 2015;5:17.
51. Rueda-Rueda T, Sánchez-Vicente JL, Moruno-Rodríguez A, et al. Uveitis and serous retinal detachment secondary to systemic dabrafenib and trametinib. Arch Soc Esp Oftalmol 2018;93:458-62.
52. Fujimura T, Kambayashi Y, Tanita K, et al. HLA-DRB1*04:05 in two cases of Vogt-Koyanagi-Harada disease-like uveitis developing from an advanced melanoma patient treated by sequential administration of nivolumab and dabrafenib/trametinib therapy. J Dermatol 2018;45:735-7.
53. Guedj M, Quéant A, Funck-Brentano E, et al. Uveitis in patients with late-stage cutaneous melanoma treated with vemurafenib. JAMA Ophthalmol 2014;132:1421-5.
54. Wolf SE, Meenken C, Moll AC, et al. Severe pan-uveitis in a patient treated with vemurafenib for metastatic melanoma. BMC Cancer 2013;13:561.
55. Agemy SA, Mehta AN, Pachydaki SI, et al. Bilateral panuveitis in a patient on vemurafenib BRAF inhibitor therapy for stage IV melanoma. Eur J Ophthalmol 2014;24:629-32.
56. Matsuo T, Yamasaki O. Vogt-Koyanagi-Harada disease-like posterior uveitis in the course of nivolumab (anti-PD-1 antibody), interposed by vemurafenib (BRAF inhibitor), for metastatic cutaneous malignant melanoma. Clin Case Rep 2017;5:694-700.
57. Apivatthakakul A, Kunavisarut P, Rothova A, et al. Development of Acute Vogt-Koyanagi-Harada-like Syndrome during the Treatment Course with Vemurafenib for Metastatic Melanoma. Ocul Immunol Inflamm 2020;28:505-8.
58. National Institutes of Health. Common Terminology Criteria for Adverse Events (CTCAE). 2017.
59. Puzanov I, Diab A, Abdallah K, et al. 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;5:95.

doi: 10.21037/aes-19-108
Cite this article as: Arepalli S, Venkat AG. Uveitis secondary to cancer therapeutics. Ann Eye Sci 2020;5:19.