Review Article

Uveitis secondary to cancer therapeutics

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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

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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.

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