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Acute keratoconjunctivitis associated with tisotumab vedotin-tftv for metastatic cervical cancer

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ABSTRACT

Purpose: Tisotumab vedotin-tftv, an antibody-drug conjugate, was recently FDA-approved for metastatic or treatment-resistant cervical cancer. A high rate of ocular comorbidities was seen in pivotal clinical trials. We present a case of a 46-year-old woman who experienced prolonged ocular surface adverse effects associated with use of the drug.

Observations: Our patient was initiated on tri-weekly 2mg/kg infusions of tisotumab for metastatic cervical cancer. Baseline ophthalmic exam was unremarkable. One week after the second infusion, she developed bilateral eyelid edema and chalazia managed with initiation of lid hygiene measures. Preceding the fourth infusion, she developed unilateral pseudomembranous conjunctivitis and bilateral meibomitis that improved with topical corticosteroids. The fifth infusion was subsequently given at a reduced dosage. Despite this, she experienced decreased vision, bilateral diffuse punctate epitheliopathy, and subepithelial haze. The patient was subsequently referred to the cornea service. Symptomatic and clinical improvement was initially achieved with the addition of bandage contact lenses (BCLs). As the keratitis improved, topical steroids were tapered and BCLs removed. She is currently maintained on a regimen that includes eyelid hygiene, preservative-free artificial tears, punctal plugs, autologous serum tears, and lifitegrast. Given the severity of the ophthalmic adverse effects, however, further tisotumab infusions were held.

Conclusions and importance: This is a report of a patient with prolonged ocular surface disease following the initiation of tisotumab, significant enough to lead to discontinuation. Antibody-drug conjugates are an emerging class of therapeutics across oncology, and ophthalmologists should be aware of their potential effects on ocular health.

Patient consent

The patient consented to publication of the following case in writing.

1. Introduction

In September 2021, tisotumab vedotin-tftv (hereafter referred to as tisotumab) received accelerated Food and Drug Administration (FDA) approval for the treatment of recurrent or metastatic cervical cancer with progression of disease during or after chemotherapy.[1] The drug belongs to a class of immunotherapy agents known as antibody-drug conjugates (ADCs), typically containing three parts: an antibody, a linker, and a cytotoxic component.[2,3] Tisotumab comprises a monoclonal antibody specific to tissue factor conjugated to a microtubule inhibitor known as monomethyl auristatin E (MMAE). The drug binds to cells expressing tissue factor and is then rapidly internalized. Upon lysosomal degradation, MMAE is released and binds to tubulin, interrupting microtubule polymerization. This process leads to cell cycle arrest during the G2/M phase and results in subsequent cellular apoptosis.[4] Other proposed indirect mechanisms contributing to tisotumab's efficacy include the bystander effect, where MMAE leaves target cells and subsequently destroys nearby tumor cells, and stimulation of host innate and adaptive immune response resulting in immunogenic cell death.[5] The therapy is an intravenous infusion administered every three weeks until disease progression suggestive of inadequate efficacy or until unacceptable toxicity.

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In the pivotal phase 2 study innovaTV 204, there was a 53 % rate of ocular adverse effects, including conjunctivitis (26 %), dry eye (23 %), and keratitis (11 %). Severe ulcerate keratitis occurred in 2 % of patients, one of whom required keratoplasty due to perforation.[5] As a result, the medication carries a "black box warning" from the FDA for potential ocular toxicity.[6] All patients initiated on tisotumab should undergo ophthalmic examinations at baseline and before each infusion. A specific set of mitigation measures has also been incorporated into the package administration instructions, including instillation of a topical corticosteroid and vasoconstrictor prior to infusion, use of cold packs over both eyes during the infusion, and continued use of corticosteroid drops for 72 hours following infusion.[6] Patients are instructed to avoid contact lens use during the entirety of treatment and use copious artificial lubrication as needed throughout treatment duration and for thirty days after the last dose.[6,7] Topical vasoconstrictors are hypothesized to reduce local blood flow, potentially reducing off-tumor delivery of tisotumab to the ocular surface.[7] Prophylactic use of topical corticosteroids has been shown to either reduce severity of ocular adverse effects or reduce rate of treatment dose reduction due to ocular adverse effects in other ADCs, including mirvetuximab soravtansine (ovarian cancer),[8] denintuzumab mafoditin (acute lymphoblastic leukemia),[3,9] and vorsetuzumab mafodotin (non-Hodgkin's lymphoma).[3,9] It is important to note that the prophylactic use of corticosteroids has not been shown to have a clear benefit in prevention of ocular toxicity in all cases of ADCs, most notably belantamab mafodotin (multiple myeloma).[10] Thus, the increased risk of cataract and glaucoma with such corticosteroid use must be weighed against the possibility of worsened ocular surface adverse effects without steroid use.

Despite the high rate of ocular adverse reactions in early clinical trials, there is an absence of reported cases in the ophthalmic literature. Herein, we present a case of ocular surface adverse effects associated with the use of tisotumab in a patient with metastatic cervical cancer.

2. Case report

A 46-year-old Caucasian female with a prior ophthalmic history of myopia presented for serial ophthalmic exams in conjunction with tisotumab infusions for metastatic cervical cancer. She was diagnosed with mucinous adenocarcinoma of the cervix in 2012, initially treated with radical hysterectomy and adjuvant chemoradiation. In the subsequent years, she sustained multiple recurrences treated with further chemotherapy. Due to the continued progression of disease following chemotherapy with 15 cycles of pembrolizumab between March and December 2021, in January 2022, the decision was made to initiate tisotumab infusions at the standard dose of 2 mg/kg every three weeks. Per the published protocol, she received an ophthalmic examination prior to her first infusion, which was unremarkable for ocular surface and anterior segment abnormalities, notably negative for the presence of blepharitis, meibomian gland dysfunction, conjunctivitis, keratitis, and anterior uveitis. No baseline slit lamp photos were obtained. The patient adhered to the described prophylactic measures to mitigate ocular side effects.

Her first ophthalmic symptoms began one week following her second infusion. She presented with bilateral mild upper eyelid edema and crusting. Best-corrected visual acuity (BCVA) remained 20/20 in both eyes (OU), and slit lamp examination revealed mild meibomian gland dysfunction OU and a left upper eyelid chalazion. She was advised to start warm compresses, increase artificial lubrication, and proceed with tisotumab infusions at the standard dosage. Days prior to her fourth tisotumab infusion, she experienced worsened bilateral eye irritation, redness, and mucous discharge. Slit-lamp examination revealed 2+ conjunctival injection and a pseudomembrane in the right cornea. The left eye demonstrated mild persistent upper eyelid edema and 1+ conjunctival injection. She began topical prednisolone acetate 1 % four times daily OU with prompt symptomatic and clinical improvement. After discussion with the treating oncology service, the decision was made to proceed with the fourth infusion of tisotumab at a reduced dose of 1.3 mg/kg.

Three weeks after her fifth infusion, the patient returned with bilateral pain, photophobia, and significant serous discharge. BCVA had decreased to 20/30 in both eyes. Slit-lamp examination revealed 2+ bilateral conjunctival injection, 3+ diffuse punctate epithelial erosions (PEE) with subepithelial haze in the right eye, and 2+ diffuse PEE of the left eye. At this point, she was referred to the cornea service. Matrix metalloproteinase 9 testing was negative in each eye. Tear osmolarity was 354 mOsm/L OD and above range (>400 mOsm/L) OS consistent with severe disease. Bandage contact lenses were placed OU, and she was maintained on topical moxifloxacin, prednisolone acetate 1 %, and artificial tears four times daily OU. Following discussion with the oncology service, further doses of tisotumab were held.

Nine weeks after her fifth and final infusion of tisotumab, she experienced persistent bilateral tearing, foreign body sensation, and photophobia. BCVA was 20/25 in the right and 20/40 in the left, and slit-lamp examination revealed diffuse PEE in both eyes with a new area of inferior subepithelial haze in the left eye (Fig. 1). Due to difficulty maintaining her bandage contact lenses, the patient underwent bilateral lower lid punctal plug placement. She was started on autologous serum tears four times daily and lifitegrast twice daily OU. Over the next four weeks, the bilateral anterior stromal haze improved, and BCVA returned to 20/20. Topical corticosteroids were tapered to an as needed basis. Despite the improvement, she continues to have moderate punctate staining OU nearly three months after her fifth infusion (Fig. 2). She is currently maintained on preservative-free artificial tears, lifitegrast, autologous serum tears, and a lid hygiene regimen.

3. Discussion

Antibody-drug conjugates (ADCs) show tremendous promise as a class of targeted oncologic treatment. Traditional chemotherapeutic agents are highly cytotoxic to tumor cells, but their relative lack of specificity leads to high rates of systemic side effects. ADCs combine the precision of their associated antibody with the cytotoxicity of the linked small-molecule drug. While circulating the bloodstream, the monoclonal antibody recognizes a specific tumor-associated antigen. The complex is then internalized by the tumor cell via a receptor-mediated endocytosis. Subsequently, the cytotoxic molecule is released, leading to apoptotic cancer cell death.

In particular, tisotumab targets tissue factor, also known as coagulation factor III, platelet tissue factor, and CD142. Tissue factor is a particularly attractive target in treating cervical cancer, as it is expressed in 94–100 % of cervical cancer cells and has only limited expression on the surface of healthy cells.[4] The specific mechanism of tisotumab's ocular toxicity is not fully understood, but it is plausible that tissue factor plays a role. Vergote and Kim performed in vitro human tissue cross-reactivity, revealing that tisotumab binds to ocular tissue, including conjunctival epithelial cells. In addition, this group performed toxicity studies in cynomolgus monkeys wherein evidence of conjunctivitis was present after five doses of tisotumab but absent when an unconjugated anti-tissue factor antibody was used (Vergote I et al. IJGC 2022, 32: IGCS E-poster EP064/#192). Additionally, tissue factor has been shown to be expressed in conjunctival pterygium cells and healthy conjunctival epithelial cells.[11]

Ocular adverse effects related to antibody-drug conjugates are variable, with the most common symptoms including blurred vision, conjunctivitis, punctate keratitis, dry eye, and microcystic corneal edema.[3] More rare but potentially more serious complications, such as corneal ulceration, uveitis, retinal vein occlusion, and optic neuropathy, have also been reported.[3] In 2015, Eaton et al. published a review article citing ocular or vision-impairing adverse events in 22 individual articles related to 13 unique ADCs.[3] Of the ADCs referenced, 12/13 contained cytotoxins that inhibit tubulin (8 with maytansinoids and 4 with auristatins), just as in the mechanism of Tisotumab against monomethyl

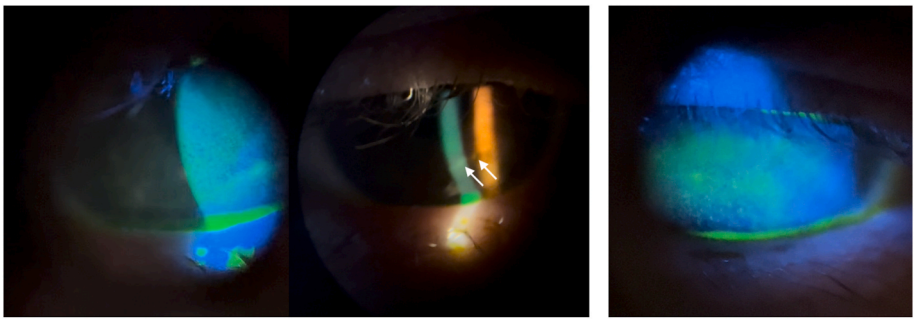

Fig. 1. Bilateral diffuse superficial punctate keratitis and subepithelial haze (white arrows) following the 5th Tisotumab infusion.

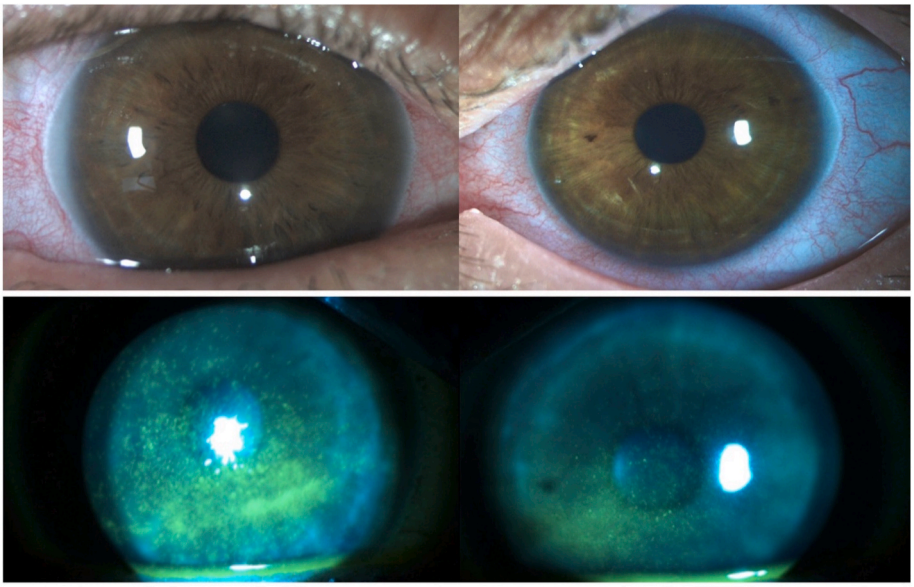

Fig. 2. Approximately 3 months following the 5th infusion of Tisotumab, sub-epithelial haze had resolved (upper panels). She experienced persistent pronounced bilateral superficial punctate keratitis (lower panels).

auristatin E. A high rate of ocular surface involvement as corneal toxicity has also been demonstrated in unconjugated tubulin-inhibiting drugs, such as Docetaxel and Paclitaxel.[12] Additionally, belantamab mafoditin, an ADC for refractory multiple myeloma, has a microtubule conjugate and has been notoriously associated with its high rate of ocular toxicity, occurring between 53 and 73 % in phase 1 and 2 clinical trials.[10] Though the exact mechanism has yet to be elucidated, possible hypotheses include off-target delivery of an unconjugated cytotoxin and creation of a toxic, cell membrane-permeable metabolite after on-target delivery of the ADC. Additionally, as microtubules are required for cell mitosis, structures with a higher baseline rate of cell turnover, such as the corneal and conjunctival epithelium, may be more susceptible to tubulin inhibition relative to those with a lower rate of turnover, such as the corneal stroma and endothelium.

Using the Common Terminology Criteria for Adverse Events (CTCAE) grading, our patient experienced Grade 2 conjunctivitis, dry eye, and keratitis through her treatment course with tisotumab.[7] Compared to the subjects in the pivotal innovaTV 204 trial, our patient's onset of eyelid disease, manifesting as blepharitis and a chalazion at week 4, was more rapid than the median of approximately 7 weeks seen in the study.[5] However, the patient's conjunctivitis at 9 weeks and corneal disease at 15 weeks both manifested later than the median 6 weeks and 8 weeks, respectively. This may be due to the early initiation of treatment for eyelid and surface disease and, following the development of conjunctivitis, the rapid initiation of corticosteroid therapy. Despite reported compliance with the recommended ocular mitigation measures as described previously, our patient continued to have decline in visual acuity and significant keratoconjunctivitis over two months after her last infusion. These adverse effects ultimately led to cessation of tisotumab and exploration of other treatment avenues for her relapsed metastatic cervical cancer. The ocular surface manifestations were only able to be controlled on an extensive surface medication regimen that included preservative-free artificial tears, a lid hygiene regimen, punctal plugs, lifitegrast, and autologous serum tears. Additionally, the time to symptom stabilization was demonstrably longer (approximately 2.3 months) than the median time to symptom resolution in the pivotal trials (0.7 months).[7] For all patients on tisotumab, this group stresses the necessity for close monitoring of ocular adverse events related to the drug itself, including conjunctivitis, dry eye and ulcerative keratitis, and potentially unintended side effects of prophylactic measures, such as elevated intraocular pressure and cataract formation.

Finally, it is important to mention that before the initiation of tisotumab, the patient underwent 15 cycles of chemotherapy with pembrolizumab between March and December of 2021. Pembrolizumab is an immune checkpoint inhibitor specifically targeting the programmed death protein 1 (PD-1). Ocular adverse events, including uveitis, dry eye, and ocular myasthenia, have been widely reported in this class of immunotherapy agents.[13] At the time of her first tisotumab infusion, the patient had been off pembrolizumab for approximately two months. It is certainly plausible that her course of pembrolizumab induced a subclinical but contributory effect to her ocular surface health, though reassuringly, her baseline ophthalmologic examination prior to

initiation of tisotumab was unremarkable for lid margin, ocular surface, or anterior segment abnormalities.

4. Conclusion

Tisotumab is indicated for recurrent or metastatic cervical cancer that has insufficiently responded to chemotherapy. Our case demonstrates a prolonged course of ocular surface disease following imitation of tri-weekly infusions of tisotumab. As new antibody-drug conjugates continue to enter the market, it will be important for ophthalmologists to be aware of their potential ophthalmologic effects. Baseline eye exams, proper mitigation efforts, and routine monitoring should be employed while patients are on treatment. Treatment cessation in coordination with the oncology service may be warranted in cases of prolonged keratitis to avoid corneal melt and perforation.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

CRediT authorship contribution statement

Ankur A. Parikh: Conceptualization, Writing – original draft, Writing – review & editing. **Jovana Hanna:** Conceptualization, Writing – original draft, Writing – review & editing. **Amar P. Shah:** Conceptualization, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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None.

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