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Short communication

Ocular toxicity and mitigation strategies for antibody drug conjugates in gynecologic oncology

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A B S T R A C T

Recently, two antibody drug conjugates were FDA approved for the treatment of recurrent gynecologic malignancies. Both of these new agents are associated with ocular toxicity. Ocular toxicity can be prevented and mitigated by utilizing recommended eye care strategies.

1. Introduction

Brief Commentary: There are 2 FDA-approved antibody drug conjugates (ADCs) for the management of recurrent gynecologic malignancies. Antibody-drug conjugates have 3 parts: an antibody, a linker, and a potent cytotoxic agent. Ocular toxicity occurs most commonly with ADCs that use either the payload monomethyl auristatin F (MMAF) or the maytansinoid DM4 (Eaton et al., 2015). Tisotumab vedotin, which targets tissue factor and has the payload MMAE, is approved for the treatment of second line and beyond metastatic or persistent/recurrent cervical cancer. Mirvetuximab soravtansine, DM4 payload, is approved for the treatment of folate receptor (FRα) positive platinum-resistant ovarian cancer. Both of these ADCs are associated with ocular adverse events, which are not commonly caused by other treatments for gynecologic cancers. The labels for these new treatments include boxed warnings regarding ocular toxicity. The ocular toxicities seen with mirvetuximab are off-target effects on the cornea, as a study demonstrated no FRα expression in human corneal tissues (Matulonis et al., 2019).

In the innovaTV 204 study, a phase 2 trial of tisotumab which enrolled 102 patients with recurrent or metastatic cervical cancer, 53 % of patients experienced ocular adverse events, mostly low grade; conjunctivitis (26 %), dry eye (23 %), and keratitis (11 %). Grade 3 ulcerative keratitis occurred in 2 patients (2 %). The median time to onset was 1.4 months (IQR 0.7–2) with median time to resolution 0.7 months (0.3–1.6). The majority (86 %) of these events resolved within 30 days after the last dose. 22 % of patients were dose reduced due to ocular toxicity, and both patients (2 %) who developed ulcerative keratitis were discontinued from study drug. (Coleman et al., 2021) 1/158 patients with recurrent or metastatic cervical cancer treated with tisotumab 2 mg/kg on all trials required a corneal transplant due to ulcerative keratitis with perforation (https://www.tivdakhcp.com/eye-care/ accessed on 12/2922).

Mirvetuximab has been studied in two phase 3 trials, FORWARD 1 and SORAYA. In FORWARD 1, 243 patients were treated with mirvetuximab, compared to 106 in SORAYA. About 40 % of patients developed blurred vision, most commonly during *C*2, about 1.5 months after the first dose. However, grade $\geq$ 3 blurred vision is uncommon, with rates of 2.5–5.7 %. Keratopathy occurs in about one-third of patients treated with mirvetuximab, with grade $\geq$ 3 in $<$ 10 % of patients in these two trials. One patient did have grade 4 keratopathy in Soraya- and it resolved completely within 15 days, though this did lead to treatment discontinuation. Ocular toxicity led to dose reduction or delays in about 20 % of patients (Moore et al., 2021; Matulonis, Lorusso, Oaknin, Pignata, Denys, et al., 2022).

A baseline ophthalmic exam is required for both of these ADCs, including slit lamp exam and visual acuity. This can be performed by an optometrist or an ophthalmologist. The eye care provider evaluating a patient treating with tisotumab can be directed to the website https://www.tivdakhcp.com/eye-care/ and read the portion under the heading "What you need to know as an eye care provider." (https://www.tivdakhcp.com/eye-care/ accessed on 12/2922). This website is also very useful for physicians and other healthcare providers in regards to comprehensive eye care guidelines when prescribing tisotumab. Similarly, there are helpful mitigation strategies and an ocular assessment form available on the company website for mirvetuximab under the eye care tab: https://www.elaherehcp.com/eye-care https://www.elaherehcp.com/eye-care accessed on 12/29/22. If a patient is diagnosed.

with an ocular toxicity, follow up for improvement and/or resolution should be done by either the eye care specialist or oncologist, as

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Table 1
Recommended eye mitigation strategies.

Drug	Eye Exam	Lubricating eye drops	Corticosteroid eye drops[a]	Vasoconstrictor eye drops[b]	Cold Packs	Contact lenses
Tisotumab	Baseline and prior to each cycle	Daily and as needed and for 30 days after last infusion	1 drop each eye tid- 1st about 10 min prior to infusion D1-3	3 drops per eye immediately prior to infusion or as prescribed	Cover eyes with cold packs for 60 min- start prior to infusion, continue about 20 min after infusion complete	Avoid use
Mirvetuximab	Baseline and every other cycle for first 8 cycles	At least qid (wait 10 min after applying steroid drop)	1 drop each eye 6 times/ day −1 to Day 4, 1 drop each eye qid D5-8	Not recommended	Not recommended	Avoid use

[a]For example dexamethasone 0.1%.
[b]For example brimonidine 0.2%.

Table 2
Dose modification for tisotumab for ocular adverse events (AE). Modified from https://www.tivdakhcp.com/eye-care/. Starting dose 2 mg/kg (max 200 mg), 1st dose reduction 1.3 mg/kg (max 130 mg), 2nd dose reduction 0.9 mg/kg (max 90 mg).

Severity	Occurrence	Dose Modification
Keratitis		
Superficial punctate (SPK)	Any	Monitor
Confluent superficial	First	Hold dose until SPK or resolved, then dose reduce 1 level
	Second	Permanently discontinue
Ulcerative or perforation	Any	Permanently discontinue
Conjunctival ulceration	First	Hold dose until complete conjunctival re-epithelialization, then dose reduce 1 level
	Second	Permanently discontinue
Conjunctival or corneal scarring or symblepharon	Any	Permanently discontinue
Conjunctivitis and other AE		
Grade 1	Any	Monitor
2	First	Hold dose until Grade ≤ 1, then resume same dose
	Second	Hold dose until Grade ≤ 1, then dose reduce 1 level
	Third	Permanently discontinue
3 or 4	Any	Permanently discontinue

Table 3
Dose modification for mirvetuximab for ocular adverse events (AE). Modified from https://www.elaherehcp.com/dosing#modifications. Starting dose 6 mg/kg adjusted body weight (ABW). 1st dose reduction 5 mg/kg ABW, 2nd dose reduction 4 mg/kg ABW.

Severity	Dose Modification
Keratitis	
Nonconfluent superficial	Monitor
Confluent superficial, cornea epithelial defect or 3-line or more loss in corrected VA[1]	Hold dose until improved or resolved, maintain same dose or consider dose reduce 1 level
Corneal ulcer, stromal opacity, corrected VA 20/200 or worse	Hold dose until improved or resolved, dose reduce 1 level
Corneal perforation	Permanently discontinue
Uveitis	
Grade 1: rare cell in anterior chamber	Monitor
2: 1–2 + cell or flare in anterior chamber	Hold dose until Grade ≤ 1, then resume same dose
3: 3 + cell or flare in anterior chamber	Hold dose until Grade ≤ 1, dose reduce 1 level
4: Hypopyon	Permanently discontinue

[1]VA visual acuity.

appropriate.

Because of the potential for ocular toxicity, mitigation plans have been developed to reduce the incidence and severity of these adverse events. Please see Table 1 for a summary of recommended eye care for both tisotumab and mirvetuximab. Refer to Table 2 for dose modification and discontinuation recommendations for tisotumab and ocular toxicity, and Table 3 for mirvetuximab. Either drug should be discontinued for any grade 4 ocular adverse events.

In conclusion, while ocular toxicities from these ADCs are common, most are low grade and reversible, and mitigation strategies are effective at preventing severe ocular toxicity. Dose interruptions and reductions should also be utilized per guidelines.

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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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