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Complications of Treatment

Emergence of ocular toxicities associated with novel anticancer therapeutics: What the oncologist needs to know

Azka Ali [a,b,*], Ankit A. Shah [d], Lauren J. Jeang [d], Kyle S. Fallgatter [d], Thomas J. George [a,b], David L. DeRemer [b,c]

[a] Division of Hematology and Oncology, Department of Medicine, University of Florida, Gainesville, FL
[b] University of Florida Health Cancer Center, Gainesville, FL
[c] Department of Pharmacotherapy and Translational Research, College of Pharmacy, University of Florida, Gainesville, FL
[d] Department of Ophthalmology, College of Medicine, University of Florida, Gainesville, FL

A B S T R A C T

As cancer treatment evolves in the era of precision oncology, molecularly targeted agents (MTAs) have become frontline therapy for many cancers. MTAs are biologically targeted and thought to have less off-target toxicity; however, the eye is particularly susceptible to off-target toxicities given its unique microenvironment. In this review, we present commonly used FDA-approved MTAs, any associated ocular toxicities and review the mechanisms, frequency, severity, and management. Increased awareness and communication between clinicians caring for cancer patients is needed for individualized risk assessment, earlier diagnosis, and mitigation of ocular toxicities.

Implications for Practice.

- While targeted agents have less off-target toxicity relative to traditional chemotherapy, there is notable overlapping toxicity in several organs, including the eye, due to expression of the common receptors.
- Accelerated pace of MTA approvals with associated ocular toxicities provides clinical challenges.
- With increased number and diversity of targeted anti-cancer agent approvals, it is important for care providers to be aware of these ocular adverse events.
- In this review, we present a succinct, yet updated clinical overview of ocular adverse events and treatments related to MTAs such as: small molecule inhibitors, monoclonal antibodies, and antibody drug conjugates.

Introduction

As an organ, the eye is particularly susceptible to toxicity given its high vessel density, abundant cell surface receptors, dependency on cellular signaling cascades, and populations of rapidly dividing cells [1]. Conventional cytotoxic chemotherapy such as cytarabine, cyclophosphamide, 5-fluorouracil, methotrexate and busulfan have long been associated with ocular toxicities such as conjunctivitis, keratitis, optic neuritis, and blurred vision [2]. These treatment-induced ocular adverse events (OAEs) are diverse and present with complications that range from minor sequelae to permanent vision loss [3]. While the toxicity profiles of traditional cytotoxic agents are well defined, the toxicity profiles of molecular targeted agents (MTAs) are not as well-defined and frequently include various OAEs [4]. Small molecule tyrosine kinase inhibitors (TKIs), monoclonal antibodies (MoAbs), and antibody drug conjugates (ADCs) can induce both on– and off-target toxicity notably OAEs, which are also among some of the most common toxicities associated with MTAs. These OAEs may range from mild annoyances to significant and potentially blinding dose limiting toxicities [5]. With the rapid pace of FDA approvals in the cancer setting, which now includes multiple MTAs, and an active drug development pipeline, clinicians providing care for patients with cancer should remain vigilant in monitoring for ocular toxicities. This review is intended to provide a clinical summary of ocular complications associated with recently approved and emerging anti-cancer MTAs. We also provide a concise overview of eye pathology along with management recommendations in a separate appendix (**Appendix**).

* Corresponding author at: Division of Hematology and Oncology, Department of Medicine, University of Florida, University of Florida Cancer Center, 1600 SW Archer Road, M401, Gainesville, FL 32610.
E-mail addresses: azka.ali@medicine.ufl.edu (A. Ali), ankit999@ufl.edu (A.A. Shah), ljeang@ufl.edu (L.J. Jeang), Kyle.Fallgatter@ufl.edu (K.S. Fallgatter), Thom.George@medicine.ufl.edu (T.J. George), dderemer@cop.ufl.edu (D.L. DeRemer).

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While a comprehensive review of all oncologic agents that could lead to ocular toxicity is beyond the scope of this clinical review, the agents included here represent more contemporary anti-neoplastic MTAs where clinical experience continues to evolve. In most situations, the OAE represents a direct consequence of the drug on the off-target physiology of the eye. Where indicated, class effects of agents are highlighted rather than individual compounds. As some OAEs can be non-specific and treatments redundant, detailed management is described either the first time OAEs appear in the manuscript or when MTAs have a significant association of said OAEs. For more information on OAEs associated with traditional cytotoxic oncology agents, we would refer readers to other well written reviews [3]. We summarize the drug classes and individual drugs based on the Food and Drug Administration (FDA) and European Medicines Agency (EMA) approval label, indication by tumor type, common OAEs, source and strength of evidence, and lastly, we highlight where special monitoring is recommended (Table 1). Where available, frequency of OAEs is reported as percent of patients affected. The data obtained for this review includes clinical trials, systematic reviews, meta-analyses, FDA package insert, retrospective reviews, and case reports.

Small molecule inhibitors

EGFR inhibitors

Mechanism: The epidermal growth factor receptor (EGFR) is a transmembrane glycoprotein in the tyrosine kinase receptor family and is expressed in many epithelial tissues including skin, glands, hair, conjunctiva, and cornea [6]. Thus, OAEs related to EGFR pathway inhibitors tend to be associated with the conjunctiva, sclera and cornea. EGFR inhibition is thought to decrease corneal epithelial cell proliferation and that can delay corneal wound healing [5]. Ocular complications have been associated with both reversible (e.g., erlotinib/gefitinib) and irreversible (e.g., osimertinib) EGFR inhibitors.

OAE frequency and severity: Erlotinib is associated with dry eye, blepharitis, trichomegaly (17–23%) [7], eyelid rash, hyperemia, keratitis, trichiasis (20%), severe conjunctivitis (33%), and severe keratitis (33%) [5,6,8,9]. Gefitinib is associated with mild conjunctivitis, dry eye (6.7%), keratitis (0.1%), corneal abrasion, aberrant eyelid growth (0.2%), visual disturbance, and blepharitis [10,11]. Incidence of grade 3 ocular disorders with gefitinib was 0.1% in clinical trials [11]. Osimertinib is associated with keratitis (0.7%) in a clinical trial, and VK (0.5%) and corneal epithelial changes (0.5%) in retrospective studies [12,13].

Management: Patients with conjunctivitis usually present with eye redness, and foreign body sensation, and symptoms are easily managed with artificial tears and often do not require cancer treatment discontinuation [14]. Patients with severe conjunctivitis, whose symptoms are not improved by supportive care, should be referred to ophthalmology. Conjunctivitis and periorbital rash is completely reversible with cessation of erlotinib within 6 weeks of stopping therapy [15]. Trichiasis or inward rotation of the eyelashes can be managed temporarily by eye lubricants, contact lenses and mechanical epilation but lashes tend to regrow and recurrences are frequent [16]. Definitive treatments of trichiasis include radiofrequency ablation, cryotherapy, bipolar electrolysis, laser ablation, and surgical procedures [16]. Trichomegaly, in contrast, refers to increase in length, curling or thickness of eyelashes [17]. Erlotinib associated trichomegaly can be managed with eyelash trimming [17]. Dry eye syndrome is a multifactorial disease characterized by altered tear film, inflammation, and damage to the corneal epithelium [18,19]. Treatment of mild dry eye is supportive with artificial tear lubrication, or warm compresses [19]. Treatment of moderate disease includes the addition of topical anti-inflammatory agents (cyclosporine, or lifitegrast), temporary topical corticosteroids, or punctal occlusion [19]. Severe disease management may need ophthalmology referral and management may include compounded serum tears, bandage contact lenses, scleral contact lenses, or tarsorrhaphy [20].

FGFR inhibitors

Mechanism: Similar to EGFR, the fibroblast growth factor receptor (FGFR) pathway is involved in the maintenance of epithelium health. In addition to several overlapping OAEs with the EGFR inhibitors, FGFR inhibitors are also associated with retinal OAEs [13,21].

OAE frequency and severity: In a retrospective review of over 6000 patients treated with EGFR and FGFR inhibitors, the most common reason for referral for eye exams included dry eye syndrome (6.9%), meibomian gland dysfunction (2.7%), keratitis (2%), conjunctivitis (1.4%), and blepharitis (1.2%) [13]. Erdafitinib was associated with dry eyes (19%), blurry vision (17%), and keratitis (5%) in the BLC2001 trial [22]. Central serous retinopathy/retinal pigment epithelial detachment (CSR/RPED) was reported in 25% of patients treated with erdafitinib, with median time to onset of 50 days [22,23].

CSR is a disorder characterized by serous retinal detachment with or without RPED, is confined to the macula, and associated with leakage of fluid through the retinal pigment epithelium (RPE) into the subretinal space [24]. Grade 3 CSR/RPED was reported in 3% of patients. CSA/RPED resolved in 13% of patients and was ongoing in 13% of patients at the study cutoff. CSR/RPED led to dose interruptions in 9% of patients, dose reductions in 14% of patients, and dose discontinuation in 3% of patients [23]. We present an example of erdafitinib induced CSR in Fig. 1**A-F**.

Pemigatinib is commonly associated with dry eye (27%) but RPED has been reported in 6% of patients, including grade 3–4 RPED in 0.6% [25]. RPED led to dose interruption in 1.7% of patients, dose reduction in 0.4% and dose discontinuation in 0.4% of patients.

Management: Most OAEs were mild and easily mitigated with dose reduction or therapy interruption [22]. Acute CSR can be self-limited and recovery of visual acuity may occur within 1–4 months [24]. If CSR/RPED is suspected, patients should be referred to ophthalmology for further management. FGFR-inhibitor related RPED is manageable by dose adjustment. RPED resolved or improved to grade 1 in 87.5% of patients who required dose adjustment of drug due to RPED [25,26]. Routine ophthalmologic exams before starting and while on therapy are recommended for all patients receiving erdafitinib and pemigatinib [23,25].

BRAF/MEK/ERK inhibitors

Mechanism: The mitogen-activated protein kinase (MEK) pathway is an intracellular signal transduction pathway that regulates multiple essential physiological processes, such as gene expression, cell cycle control, cell division, and proliferation. Retinal OAEs appear to be a class effect of all MEK inhibitors [27]. Trametinib is a MEK inhibitor and is approved for use with dabrafenib, which is a specific inhibitor of BRAF (v-raf murine sarcoma viral oncogene homolog B1) kinase. Although the mechanism of ocular toxicity remains incompletely characterized, animal models have suggested that MEK inhibitors induce a combination of oxidative stress and pro-thrombotic state, which increases the risk for retinal vein occlusion [28]. MEK associated retinopathy (MEKAR) is thought to be related to direct action of these drugs in non-dividing cells of the eye, such as photoreceptors and retinal pigment epithelial RPE cells, causing toxic retinopathy [29].

OAE frequency and severity: Trametinib has been associated with dose-limiting CSR and uveitis in phase I/II trials [5]. Associated OAEs in clinical trials have been reported in up to 15% with monotherapy and 10% as combination therapy, but only<1% of patients receiving therapy developed MEKAR [29]. OAEs of trametinib include dry eye, retinal vein occlusion (up to 14.5% of patients receiving trametinib and another agent) [30], MEKAR (<2% with trametinib and dabrafenib), and pigment epithelial detachment [29]. Vemurafenib, a potent BRAF V600

Table 1

Drug Class	Agent	Label	Indication	Ocular Adverse Events (OAEs) (%)	Strength of evidence	Recommendation
EGFR inhibitors	Erlotinib	**FDA/ EMA**	**NSCLC, Pancreatic cancer**	Dry eye Blepharitis Trichomegaly 17–23% Eyelid rash Hyperemia Trichiasis 20% Conjunctivitis 33% Keratitis 33%	**Clinical trials, Meta-analyses, Reviews**	NA
	Gefitinib	**FDA/ EMA**	**NSCLC**	Dry eye 6.7% Keratitis 0.1% Corneal abrasion Aberrant eyelid growth 0.2% Blepharitis	**Clinical trials**	NA
	Osimertinib	**FDA/ EMA**	**NSCLC**	Keratitis 0.7% Vortex keratopathy 0.5% Corneal epithelial changes 0.5%	**Clinical trials, Retrospective reviews**	NA
FGFR inhibitors	Erdafitinib	**FDA**	**Urothelial carcinoma**	Dry eye 19% Blurry vision 17% Keratitis 5% CSR/RPED 25%	**Clinical trials, Retrospective reviews**	Dry eye prophylaxis Perform monthly ophthalmological examinations during the first 4 months and every 3 months after
	Pemigatinib	**FDA/ EMA**	**Cholangiocarcinoma**	Dry eye 27% RPED 6%	**Clinical trials, Retrospective reviews**	Perform ophthalmologic exam at baseline, then every 2 months for 6 months and every 3 months thereafter during treatment
BRAF/MEK/ ERK inhibitors	Trametinib/ Dabrafenib	**FDA/ EMA**	**Melanoma, NSCLC**	Dry eye MEKAR 2% Retinal vein occlusion 14.5% Pigment epithelial detachment	**Clinical trials**	NA
	Vemurafenib/ Cobimetinib	**FDA/ EMA**	**Melanoma**	Conjunctivitis 2% Uveitis 4% Dry eye 2% CSR 26%	**Clinical trials**	NA
	Ulixertinib	**EAP FDA**	**MAPK pathway-altered solid tumors**	Combined OAEs* 13%	**Phase 1 study**	NA
ALK inhibitors	Crizotinib	**FDA/ EMA**	**NSCLC** **ALCL**	Combined OAEs** 62% Grade 4 visual field defect 0.2% Optic neuropathy	**Clinical trials, Case report**	Patients with ALCL: Perform ophthalmologic exam at baseline, then follow up retinal examination within 1 month of starting and then every 3 months and upon any new visual symptoms
	Ceritinib	**FDA/ EMA**	**NSCLC**	Vision disorder 9%	**Clinical trial**	NA
	Brigatinib	**FDA/ EMA**	**NSCLC**	Visual disturbance 7.4%	**Clinical trial**	NA
Multi-receptor kinases	Imatinib	**FDA/ EMA**	**CML** **ALL** **ASM** **HES** **DFSP** **GIST**	Periorbital edema 15% Eyelid edema 19% Epiphora 18% Macular edema 0.1–1% Conjunctival hemorrhage 1–10% Papilledema 0.01–0.1% Glaucoma 0.01–0.1%	**Clinical trial Retrospective reviews**	NA
	Dasatinib	**FDA/ EMA**	**CML** **ALL**	Visual disorders 1–10% Conjunctivitis 0.1–1% Visual impairment 0.1–1% Increased lacrimation 0.1–1% Photophobia < 0.1%	**Clinical trial**	NA
	Nilotinib	**FDA/ EMA**	**CML**	Eyelid edema 1% Periorbital edema < 1%	**Clinical trial**	NA
	Sunitinib	**FDA/ EMA**	**GIST** **RCC** **pNET**	Localized edema*** 18% Retinal detachments	**Clinical trial, Case reports**	NA
	Sorafenib	**FDA/ EMA**	**HCC** **RCC** **DTC**	Squamoproliferative lesions Retinal detachments Retinal tear	**Case reports**	NA

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Table 1 (*continued*)

Drug Class	Agent	Label	Indication	Ocular Adverse Events (OAEs) (%)	Strength of evidence	Recommendation
Monoclonal antibodies	Cetuximab	**FDA/ EMA**	**Head and neck cancer** **Colorectal cancer**	Dry eye 67% Blepharitis 63% Conjunctivitis 10–18% Eyelid rash 38% Foreign body sensation	**Clinical trial, Retrospective reviews, Case reports**	NA
	Panitumumab	**FDA/ EMA**	**Colorectal cancer**	Growth of eyelashes 6% Conjunctivitis 5% Corneal melt and perforation	**Clinical trial, Case report**	NA
	Trastuzumab	**FDA/ EMA**	**Breast cancer** **Gastric cancer**	Dry eye Conjunctivitis 2.5% Increased lacrimation 21% Blurry vision Corneal ulcers	**Clinical trial** **Case reports**	NA
	Bevacizumab	**FDA/ EMA**	**Colorectal cancer** **NSCLC** **Breast cancer** **Glioblastoma** **RCC** **Ovarian** **Cervical** **HCC**	Epiphora Optic nerve dysfunction Photopsias	**Case reports**	NA
	Nivolumab	**FDA**	**Melanoma** **NSCLC** **Malignant pleural mesothelioma** **RCC** **Classical Hodgkin lymphoma** **Head and neck cancer** **Urothelial carcinoma** **Colorectal cancer** **HCC** **Esophageal cancer** **Gastric, and gastroesophageal cancer**	Opthalmoplegia (40.5%) Uveitis (20.3%) Dry eye (17.7%) Retinopathy (5.1%) Conjunctivitis (5.1%) Optic neuritis (2.8%) Orbital inflammation (2.5%) Amaurosis fugax (1.3%) Giant cell arteritis (1.3%) Corneal graft rejection (1.3%) Corneal perforation (1.3%)	**Systematic reviews**	NA
	Ipilimumab	**FDA/ EMA**	**Melanoma** **RCC**			
	Pembrolizumab	**FDA/ EMA**	**Melanoma** **NSCLC** **SCLC** **Head and neck cancer** **Classical hodgkin's lymphoma** **Primary mediastinal large B-cell lymphoma** **Urothelial carcinoma** **Microsatellite instability-high cancer** **Gastric cancer** **Esophageal cancer** **Cervical cancer** **HCC** **Merkel cell carcinoma** **RCC** **Endometrial carcinoma**			
Antibody Drug Conjugates	ado-trastuzumab emtansine	**FDA/ EMA**	**Her2 + breast cancer**	Increased lacrimation (3.3–6%) Dry eye (3.9–4.5%) Blurry vision (3.9–4.5%)	**Clinical trials**	NA
	fam-trastuzumab deruxtecan-nxki	**FDA/ EMA**	**Her 2 + breast cancer**	Dry eye 11%	**Clinical trials**	NA
	Enfortumab vedotin-ejfv	**FDA**	**Urothelial cancer**	Dry eye 23% Blurry vision 15% Increased lacrimation 14%	**Clinical trials**	NA
	Tisotumab vedotin-tftv	**FDA**	**Cervical cancer**	Conjunctival AEs 40% Dry eye 29% Corneal AEs 21% Blepharitis 8%	**Clinical trials**	Premedication and required eye care during treatment. Preventive treatment includes corticosteroid eye drops, ocular vasoconstrictor drops, cold packs during infusion, and lubricating eye drops.

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Table 1 (*continued*)

Drug Class	Agent	Label	Indication	Ocular Adverse Events (OAEs) (%)	Strength of evidence	Recommendation
				Severe ulcerative keratitis 3.2%		Perform ophthalmological exam at baseline, then follow up exams prior to each dose, and as clinically indicated
	Belantamab mafodotin-blmf	**FDA/ EMA**	**Multiple myeloma**	Keratopathy 54% Blurry vision 18–28% Dry eye 13–23%	**Clinical trials**	**REMS required:** prescriber education, patient counseling, monitoring of symptoms via ophthalmologic exams at baseline, prior to each dose, and as clinically indicated

ALCL, Anaplastic large cell lymphoma; NCSLC, Non-small cell lung cancer; CML, Chronic myeloid leukemia; ALL, Acute lymphoblastic leukemia; ASM, Aggressive systemic mastocytosis; HES, Hypereosinophilic syndrome; DFSP, Dermatofibrosarcoma protuberans; GIST, Gastrointestinal stromal tumors; RCC, Renal cell carcinoma; pNET, Pancreatic neuroendocrine tumor; HCC, Hepatocellular carcinoma; DTC, Differentiated thyroid carcinoma; ROR, Reported Odd's Ratio with a 95% Confidence Interval; NA, Not Applicable, CSA/RPED, Central Serous Retinopathy/Retinal Pigment Epithelial Detachment; MEKAR, MEK Associated Retinopathy; REMS, Risk Evaluation and Mitigation Strategy; FDA, The Food and Drug Administration; EMA, European Medicines Agency; EAP, Expanded Access Program; OAE, Ocular Adverse Events; VKH, Vogt-Koyanagi-Harada syndrome.

[*] Combined OAEs included halo vision, photopsia, blurry vision, visual impairment, vitreous floaters, retinal detachment, retinal vein occlusion, retinopathy.

[**] Combined OAEs included visual impairment, photopsia, blurry vision, vitreous floaters, photopobia, diplopia.

[***] Localized edema included facial edema and eye/eyelid edema.

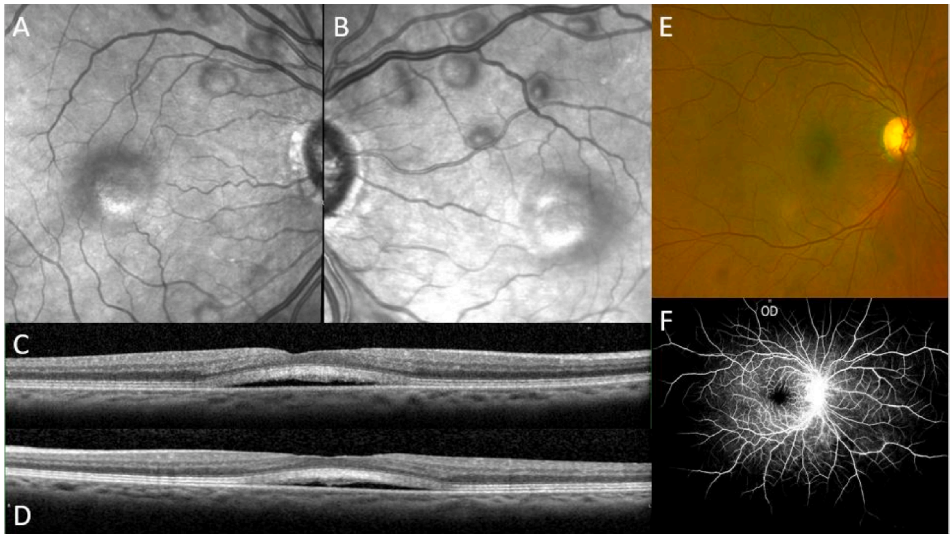

Fig. 1. Erdatfinib-induced central serous chorioretinopathy. A and C: Optical coherence tomography of the right eye demonstrating a large area of sub-retinal fluid through the fovea and multiple areas of circular elevation in the vessel arcades. B and D: Similar changes are noted in the left eye. E: Fundus color photo of the right eye 5 weeks after discontinuation and re-initiation of erdatfinib at a lower dose. Residual areas of depigmentation are noted in the superior macula. F: Fluorescein angiography of the right eye performed at the same time point as E demonstrates absence of fluid leakage in the fovea.

inhibitor [14], is approved for use with cobimetinib, a potent and specific inhibitor of MEK1 and MEK2 [31]. Vemurafenib monotherapy has also been associated with uveitis (4%), conjunctivitis (2%), and dry eye (2%) in clinical trials [14]. CSR was reported in 26% of the patients taking vemurafenib and cobimetinib in the coBRIM study compared with 3% of patients taking vemurafenib alone [32]. Ulixertinib (BVD-423) is a highly potent, reversible, ERK1/2 inhibitor that has shown clinical activity and was granted expanded access program (EAP) by the FDA for patients with MAPK pathway aberrant cancer [33]. As the terminal kinase of the MAPK pathway, ERK 1/2 (extracellular signal-regulated kinase) influences oncogenesis through multiple mechanisms involving cell proliferation and differentiation [33]. In a first-in-human phase I dose escalation study, ulixertinib was associated with 13% (18 out of 135) combined OAEs (halo vision, photopsia, blurry vision, visual impairment, vitreous floaters). Among the combined OAEs, serious events included retinal detachment (1 patient), retinal vein occlusion (1 patient), and retinopathy (1 patient) [33].

Management: Most patients receiving vemurafenib/cobimetinib had no or mild symptoms (grade 1), and resolved spontaneously in 38% of patients without dose modification [23]. MEKAR is usually mild, self-limited, and may resolve after continuous use of drug over time, or discontinuation of the drug, and vision may be completely restored with some exceptions [29]. In patients with grade 2 CSR, doses were reduced and 92% of patients had symptom resolution. Grade 3–4 CSR was managed by dose interruption of cobimetinib and 1 patient (out of 63 patients) needed surgical treatment [32]. Retinal vein occlusion presents as sudden painless vision loss, and can be treated with corticosteroids, anti-vascular endothelial growth factor (VEGF), and laser therapies [34,35]. Suspicion of any retinal vasculature pathology causing acute vision changes requires emergent ophthalmology evaluation and retinal vein occlusion requires long term follow up. Ulixertinib related grade 3 retinal vein occlusion occurred after $>$ 10 months on therapy and resolved with drug cessation [33].

ALK inhibitors

Mechanism: The exact mechanism of anaplastic lymphoma kinase (ALK)-induced ocular toxicity is unclear but it has been theorized that ALK inhibitors induce ocular toxicity by affecting the signal processing of retinal ganglion cells [36]. Crizotinib is associated with the highest frequency of OAEs among ALK inhibitors and several studies have tried to explain the discrepancy between the rates of visual disorders [36,37]. Electroretinograms (ERG) on various ALK inhibitors have suggested that the OAEs from crizotinib may not be from direct ALK inihibition as ERGs showed a significant reduction in b-wave amplitude (which is a representation of transmitted signals from inner layers of retina) in rats treated with crizotinib but not in rats treated with ceritinib (another ALK inhibitor) [37]. As crizotinib inhibits mesenchymal-epithelial transition

(MET) and receptor tyrosine kinase (ROS1), and ceritinib only inihibits ROS1, it was theorized that the OAEs may be from MET inhibition in the retina [37]. However, alectinib, ALK inhibitor with high selectivity over MET, was associated with less visual symptoms than crizotinib, so MET inhibition can also not explain a higher OAE frequency noted with crizotinib [37]. It is, however, possible that the degree of effect on retinal ganglion cells may predict the severity of OAEs. For instance, crizotinib can inhibit MET and ROS1 at nanomolar concentrations, whereas alectinib inhibits MET and ROS1 at micromolar concentrations or higher [37].

OAE frequency and Severity: Crizotinib is associated with visual impairment, photopsia (presence of perceived lights in visual fields), blurry vision, vitreous floaters, photophobia, and diplopia in phase I and II clinical trials in 62% of patients treated with crizotinib [38-40]. Across all clinical trials in patients with NSCLC, the incidence of Grade 4 visual field defect with visual loss was 0.2% [41]. Optic neuropathy has been case reported with crizotinib and this was followed by progressive vision loss 3 months after starting therapy, and ocular symptoms persisted despite interruption of therapy worsened after resuming therapy [42]. Ceritinib has been associated with photopsia, accommodation disorders (eye-focusing problems), presbyopia (far-sightedness), and reduced visual acuity in 9% of patients [4,43]. Visual disturbances (all grades) occurred in 7.3% of patients who received brigatinib, which included diplopia, photophobia, blurred vision, reduced visual acuity, visual impairment, vitreous floaters, visual field defect, macular edema, and vitreous detachment [37,44]. Grade 3 macular edema and cataract occurred in one patient in the dose escalation group [44,45].

Management: Most OAEs with crizotinib were grade 1, improved over time, and no patients required dose modifications [38-40].

Multi-receptor tyrosine kinase inhibitors

Mechanism: As their name implies, multi-receptor TKIs have diverse inhibitory properties that can generate a number of off-target ocular toxicities. The mechanism of edema is likely explained by an abundance of dermal dendrocytes in periocular skin, and expression of c-kit and platelet-derived growth factor receptor (PDGFR) tyrosine kinases, which are targeted by these agents. Targeting PDGFR may also result in decreased interstitial fluid pressure leading to localized edema. Since the orbit is a closed-in space with a relative lack of lymphatic channels, periorbital fluid may not be readily transported out of the orbital space [46].

OAE frequency and severity: Imatinib is associated with periorbital edema (15%), eyelid edema (19%), epiphora or excessive eye watering (18%), macular edema (0.1–1%), conjunctival hemorrhage (1–10%), papilledema (0.01–0.1% imatinib), and glaucoma (0.01–0.1%) [2,46-50]. Dasatinib is associated with visual disorders including visual disturbance, blurry vision, reduced visual acuity, and dry eye (1–10%), conjunctivitis, visual impairment, increased lacrimation (0.1–1%), and photophobia (<0.1%) [51]. Nilotinib is associated with any grade eyelid edema (1%) and periorbital edema (<1%) [52]. Sunitinib is associated with periorbital and eyelid edema described under the composite AE of localized edema, which included facial edema in addition to eye/eyelid edema with an incidence of 18% [47,53]. Sunitinib has been associated with retinal detachments (at least 24 cases) [54]. Sorafenib is associated with squamoproliferative lesions, such as keratoacanthomas, and squamous cell carcinoma affecting the eyelid [55], retinal detachments (at least 7 reported cases), and retinal tears (at least 2 reported cases) in case reports [54,56].

Management: Periorbital edema from imatinib is typically mild and can be managed conservatively. Severe cases have been treated with low-salt diet, topical 1% hydrocortisone, 0.25% topical phenylephrine, or oral diuretic [57]. Severe periorbital edema is not an indication for cessation of imatinib and many cases can be adequately managed. For cases of visual impairment that are refractory to medical management, surgery is a viable option [57]. Holding therapy may be appropriate for macular edema related to these therapies [48] while more significant findings may require intravitreal anti-VEGF or steroid injections, laser therapy, or surgery [58].

Targeted monoclonal antibodies

EGFR inhibitors

Mechanism: Cetuximab and panitumumab are MoAbs targeting the EGFR, with overall OAEs similar to the EGFR TKIs. Although considered largely interchangeable from a therapeutic standpoint, there are structural differences between these MoAbs. Cetuximab is an IgG1 isotype MoAb, and can elicit antibody dependent cell mediated cytotoxicity (ADCC), whereas panitumumab is an IgG2 isotype that does not possess these immune functions [59].

OAE frequency and severity: Cetuximab has been associated with dry eye (67%), blepharitis (63%), conjunctivitis (10–18%), and eyelid rash or hyperemia (38%) [6,60]. Other cetuximab associated OAEs in case reports include eye discomfort, foreign body sensation, tearing, and redness [61]. Overall class OAEs are mild and more common AEs include conjunctivitis (5%), growth of eyelashes (6%), blepharitis with increased lacrimation and eyelid irritation reported in 15% of patients [2,62]. Panitumumab has also been associated with corneal melt and eye perforation in a case report [63].

Management: Blepharitis or inflammation of lid margin results from meibomian gland dysfunction, which contains EGFR-expressing cells. Patients present with itching, watering of eyes and lids, and crusting of lashes [62]. Treatment of blepharitis includes warm compresses, eyelid scrubs, and topic antibiotics. Eyelid cultures should be considered if blepharitis does not improve with supportive measures. While there are no clear dose modification recommendations for EGFR inhibitors, Dranko et al suggest following dose modification recommendations for maculopapular rash [60,62].

HER2 inhibitors

Mechanism: HER2 is a member of the EGFR family and as such, the mechanism of OAE is likely similar to EGFR TKI. Trastuzumab is a fully humanized IgG1 MoAb that targets HER2. *In vivo*, trastuzumab was found to inhibit corneal neovascularization [64].

OAE frequency and severity: Trastuzumab is associated with dry eye, increased lacrimation (21%) conjunctivitis (2.5%), blurry vision, and corneal ulcers [5,65-67]. However, it has also been associated with more serious but rarer reported OAEs including macular edema, papilledema, serous retinal detachment, retinal hemorrhage, retinal artery occlusion, and retinal vein occlusion [5,68]. It should be noted that in major clinical trials reporting OAEs, trastruzumab was combined with docetaxel, which has been independently associated with OAEs [5,69]. Pertuzumab does not have widely reported OAEs, although the package insert notes increased lacrimation [4].

Management: Treatment is similar to EGFR toxicities. Topical treatment with autologous serum has been reported as an effective strategy to manage trastuzumab related corneal ulceration [65].

VEGF inhibitors

Mechanism: Bevacizumab is a humanized monoclonal anti-VEGF antibody commonly used systemically in combination with other anticancer therapies. Direct ocular administration of bevacizumab is effective in treating diabetic retinopathy, age-related macular degeneration, retinopathy of prematurity, and retinal vein complications [2]. Bevacizumab binds to the receptor binding domain of all VEGF-A isoforms and prevents the interaction between VEGF-A and its receptors on the surface of endothelial cells, and ultimately prevents cell proliferation and new blood vessel formation [70].

OAE frequency and severity: While there are reports of direct ocular

toxicity from ocular inflammation, retinal pigment epithelium tear, retinal detachment, and vitreous hemorrhage [71], systemic use of anti-VEGF antibody has reported to show minimal direct ocular toxicity [2]. Reported OAEs from bevacizumab include mild epiphora and optic nerve dysfunction [71], and photopsias during systemic bevacizumab therapy [71]. Endophthalmitis (inflammation of tissues inside the eye), iritis, vitritis, retinal detachment, increased intraocular pressure, and ocular hyperemia have all been reported from the postmarketing experience [72]. Preclinical studies have shown that intravitreal administration of ramicuramab [73] and Ziv-aflibercept [74] are safe and non-toxic to the retina.

Immune checkpoint inhibitors

Mechanism: ICIs work by inducing the body's inflammatory response and by preventing the body's ability to block autoimmunity. Commonly used agents include inhibitors to immune checkpoint proteins including cytotoxic T-lymphocyte associated antigen-4 (CTLA-4; ipilumumab, tremelimumab), programmed death-1 (PD-1; pembrolizumab, nivolumab, cemiplimab) and the ligand to PD-1 (PD-L1; atezolizumab, avelumab, durvalumab) [75]. The exact mechanism of OAE is unclear but it has been postulated that ICI related OAEs are related to autoimmune mediated mechanisms [75]. CTLA-4 inhibitors impair survival and functional of T regulatory cells but PD-1 inhibitors, in addition to that produce pathological autoantibodies. It is believed that the production of autoantibodies gives rise to an increased rate of inflammatory AEs seen with PD-1 inhibitors [75]. All currently approved ICIs are MoAbs, but oral small molecule inhibitors are in development.

OAE frequency and severity: ICI-related OAEs are caused by nonspecific over-activation of the host's immune response, and while OAEs are less frequent, they can have significant visual morbidity if not identified and managed early [75,76]. About 2.8–4.3% of the patients treated with ICIs have been reported to experience OAEs, based on the FDA Adverse Events Reporting System (FAERS) database [76]. Fang et al. provide an excellent report of review of ICI OAEs from the FAERS database from 2003 to 2018 with most common OAEs including uveitis, dry eye, ocular myasthenia, eye inflammation (data not shown as it is reported in reporting odds ratio) [75]. Most commonly reported OAEs with ICIs are ophthalmolplegia (40.5%), uveitis (20.3%), dry eye (17.7%), retinopathy (5.1%), conjunctivitis (5.1%), optic neuritis (3.8%), orbital inflammation (2.5%), amaurosis fugax (1.3%), giant cell arteritis (1.3%), corneal graft rejection (1.3%), corneal perforation (1.3%) [76].

As we know, CTLA-4 inhibitors are typically associated with a higher frequency of immune related AEs compared to PD-L1 inhibitors. Interestingly, due to an unclear discrepancy, it has been identified that OAEs occur more frequently with PD-1 inhibitors [76]. 44.3% of the patients with lung cancer treated with ICIs with OAEs were treated with PD-L1 inhibitors, whereas 36.7% were treated with PD-1, and 11.4% treated with PD-L1 plus CTLA-4 inhibitors. No significant difference in OAEs was noted between PD-L1 and PD-1 inhibitors, but significant differences were noted between monotherapy (PD-L1/PD-1 inhibitors) and combined therapy (PD-L1 plus CTLA-4 inhibitors) [76]. Average onset time of OAE was shorter with combined therapy (6.9 weeks) versus PD-1 (8.9 weeks) and PD-L1 inhibitor (17.5 weeks) [76].

Intra-ocular inflammation has been detected after a median of 9 weeks, 84–92% of patients were diagnosed with uveitis at 6 months. Median time to diagnosis of uveitis has been reported as 32.2 days, ophthalmoplagia 35–38 days, and and dry eye 6.5 months [76]. Ophthalmoplegia is the weakness or paralysis of one of the eye muscles and ptosis is the earliest and most common manifestation, followed by diplopia and strabismus [76]. Ptosis or eyelid droop is a key symptom of myasthenia gravis (MG) (75%), and is reported as a life-threatening AE. Other manifestations of MG include dyspnea (62%), limb weakness (55%), dysphagia (48%), and diplopia (42%) [76]. Uveitis represents a group of inflammatory disease that destroy the uveal tract, which consists of high vascular fibrous tissue susceptible to immune disorders. Uveitis symptoms include pain, redness, photophobia, and floaters. Moreover, Vogt-Koyanagi-Harada disease (bilateral granulomatous uveitis associated with exudative retinal detachment) has been reported with ICIs [76,77]. Pembrolizumab can induce orbital myositis with proptosis, ptosis, and restricted extraocular movements.[78]. Peripheral ulcerative keratitis has been reported with nivolumab [79]. Ipilimumab has been reported to cause bilateral vitritis, choroiditis, and serous retinal detachment [80].

Management: Treatment includes therapeutics aimed directly at the infectious source or at decreasing inflammation with topical, periocular, or intraocular medications. Given the risk of autoimmune uveitis with these agents, clinicians should seek an ophthalmology consult for slit lamp and fundus evaluation with photophobia as a sentinel symptom [81]. Discontinuation of ICIs must be considered if there is no improvement despite appropriate treatment, which may include systemic steroids and other means to mitigate severe ICI-induced autoimmune conditions [77,82].

Antibody drug conjugates

Mechanism: ADCs represent one of the newest classes of targeted cancer therapies, which are comprised of a MoAb linked to a cytotoxin through a linker molecule resulting in the functional delivery of a biologic toxic payload to a targeted cellular location. When it comes to ocular toxicity associated with ADCs, the pathophysiology is likely diverse owing to the complexity of molecular structure and pharmacology [1]. Available evidence suggests a strong association of microtubule targeting cytotoxic payloads consisting of maytansinoids (DM1 and DM4) or auristatins (MMAF) and the development of ocular toxicities [83]. The mechanism of this adverse event is not fully understood but is proposed to be an off-target delivery of unconjugated cytotoxin. Both non-cleavable and cleavable molecular linkers have been associated with ocular toxicity [1]. For a comprehensive review specifically on ADC related ocular toxicity, we direct the readers to an excellent summary of OAEs by Eaton, et al [1]. Here, we present OAEs from a representative group of ADCs increasingly relevant to clinical practice.

OAE frequency and severity: Aldo-trastuzumab emtansine (T-DM1) is a conjugate of HER2-binding antibody trastuzumab linked to DM, a maytansinoid. OAEs associated with T-DM1 include increased lacrimation (3.3–6%), dry eye (3.9–4.5%), blurry vision (3.9–4.5%) [1,84,85]. Fam-trastuzumab deruxtecan (T-DXd) is composed to a MoAb backbone of trastuzumab and has a cytotoxic payload derived from exatecan, a potent topoisomerase I inhibitor rather than a microtubule inhibitor [86]. Dry eye has been reported in clinical trials with T-DXd (11%, grades 3–4 0.4%) [87]. Thus, it appears most OAEs related to these ADCs are representative of their HER2 targeting backbone molecules.

Enfortumab vedotin-ejfv is comprised of a fully human MoAb targeting Nectin-4 conjugated to monomethyl auristatin E (MMAE) via protease-cleavable linker [88]. It is associated with dry eye (23%), blurry vision (15%), and increased lacrimation (14%) [88]. MMAE is also a component of tisotumab vedotin-tftv which uses a protease-cleavable linker to the targeting tissue factor specific MoAb [89]. OAEs in 60% of patients treated across trials; most common OAEs were conjunctival AEs (40%), dry eye (29%), corneal AEs (21%), and blepharitis (8%). Grade 3 OAEs occurred in 3.4% of patients and severe ulcerative keratitis occurred in 3.2% of patients. Median time to onset of first OAE was 1.2 months. Of the patients who had OAEs, 55% had complete resolution and 30% had decrease in severity by one or more grades. OAE led to tisotumab discontinuation in 6% of patients [90]. Tistotumab carries a boxed warning and it is recommended that patients are referred to ophthalmology for a baseline examination, prior to each dose, and as clinically indicated. It is also recommended that there is adherence to premedication and required eye care to reduce the risk of OAEs [90]. We present an example of severe keratitis from a patient on tisotumab (Fig. 2).

Belantamab mafodotin-blmf is an anti B-cell maturation antigen

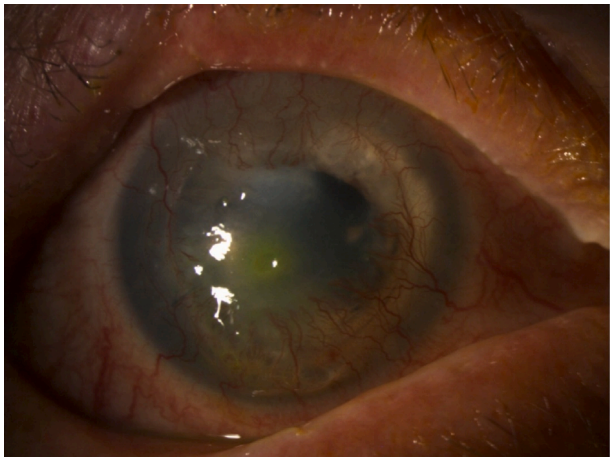

Fig. 2. Slit lamp photo showing severe keratitis in a patient with the use of tisotumab vedotin for 6 months. Note the heavy peripheral corneal neovascularization, central epithelial defect as highlighted by fluorescein staining, and the mild corneal haze indicative of previous stromal ulceration.

(BCMA) immunoconjugate with a humanized IgG1 anti-BCMA MoAb conjugated to an MMAF by a protease-resistant maleimidocaproyl linker [82]. OAEs occurred in 77% of the patients, and of those included keratopathy (76%), changes in visual acuity (55%), blurry vision (27%), dry eye (19%) in the DREAMM-2 study [82,91]. Grade 3 or more keratopathy occurred in 45.5% of patients. Of the patients with grades 2 to 4 keratopathy, 39% patients recovered to grade 1 after median follow up of 6.2 months. Of the 61% with ongoing keratopathy, 28% were still on treatment, 9% on follow up, and 24% were off study due to death, withdrawal or lost to follow up. In those who had keratopathy resolution, time to resolution was 2 months [91].

Management: Tisotumab OAEs improved with mitigation measures, which included use of preservative-free lubricating eye drops for the duration of study treatment, use of local ocular vasoconstrictor eye drops prior to infusion, cooling eye pads during the infusion and use of steroid eye drops for 3 days starting the day of infusion [89]. Belantamab associated keratopathy resolved after treatment adjustment. The median time to resolution was 21 days and permanent loss of vision was not reported [82]. Because of the ocular toxicity noted in the DREAMM-2 study, the FDA requires a risk evaluation and mitigation strategy (REMS) program for this agent, which includes prescriber education, counseling of patient on the risk of ocular toxicity, and requirement of monitoring of symptoms via ophthalmic exams at baseline, prior to each dose and at worsening of symptoms [91].

Summary

Given the pace of development and diversity of new MTAs, cancer patient care providers should be aware of the potential for ocular toxicities. EGFR inhibitors have ocular toxicity largely related to off-target effects on the epithelial layers of the eye. FGFR inhibitors additional have some retinal OAEs with a risk of central serous retinopathy and retinal pigment epithelial detachment, and for this reason, routine ophthalmological exams prior to and during treatment are recommended. MEK inhibitors have dose limiting OAEs, and care providers must be aware of MEKAR and retinal occlusion and should refer patients to ophthalmology if there is concern for retinal involvement. ICIs are commonly associated with eye inflammation with common OAEs including uveitis, ocular myasthenia and eye inflammation with ophthalmology referral suggested for any patients with photophobia. ADCs such as tistoumab are associated with severe keratitis and requires routine ophthalmological exams as well as preventative drug strategies and cooling packs during infusions. Belantamab mafodotin can also cause severe keratopathy and routine ophthalmological exams and REMS are required by the FDA.

By appreciating the incidence, frequency, and expected symptomology of OAEs from MTAs, cancer care providers improve their awareness of and intervene appropriately in the clinic. Close working relationships with ophthalmologists can ensure cancer patients are receiving optimal care to mitigate or manage OAEs associated with MTAs, especially those that that require baseline and routine eye exam surveillance.

CRediT authorship contribution statement

Azka Ali: Conceptualization, Writing – review & editing. **Ankit A. Shah:** Writing – review & editing. **Lauren J. Jeang:** Writing – review & editing. **Kyle S. Fallgatter:** Writing – review & editing. **Thomas J. George:** Conceptualization, Writing – review & editing. **David L. DeRemer:** Conceptualization, 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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Appendix A. Supplementary data

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