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Adverse Events Associated With Novel Cancer Therapies

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Introduction

Advancements in novel anticancer therapeutics have enhanced the precision with which cancerous cells can be selectively identified and destroyed. Breakthroughs in adoptive cell therapy, checkpoint inhibitors, and anti-drug conjugates have been at the forefront of these advancements. The purpose of this review is to highlight the mechanisms of action underlying these novel anticancer therapeutics, provide an overview of their reported ocular adverse effects (AE), and where possible, provide a starting point for ocular AE prophylaxis and management.

Adoptive Cell Therapy (CAR T and TIL)

CAR T Therapy

Chimeric antigen receptor T-cell (CAR T) therapy is a novel therapeutic approach used to treat hematological malignancies, particularly those refractive to first-line therapies. Ongoing research is evaluating its utility within retinoblastoma, uveal melanoma, and neuromyelitis optica spectrum disorder.[1] First approved by the Food and Drug Administration (FDA) in 2017, CAR T therapy involves extracting T cells from the patient, then genetically engineering them to express chimeric antigen receptors specific for antigens on the surface of the malignant cells of interest. The engineered CAR T cells are clonally expanded and infused back into the patient's circulation, where they continue to expand and target cells expressing the chimeric antigen of interest. Despite its promise, CAR T therapy can be associated with serious ocular AEs, including conjunctivitis and keratitis, exudative retinal detachment, candida endophthalmitis, optic neuropathy, worsening ocular graft versus host disease, and acute retinal necrosis[1,2] **(Table 1)**. There have been case reports of intraocular recurrence of hematological malignancies following completion of CD19 CAR T therapy.[1] CAR T therapies can also be associated with life-threatening systemic complications induced by rapid immune activation, including cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome.[3] These syndromes can present with optic neuropathy, increased intracranial pressure with optic nerve edema, and intraocular inflammation.[1] The underlying mechanism of these AEs is hypothesized to be disruption of the blood-brain-barrier, causing immune cell invasion and neurotoxicity.[1] Due to a paucity of data, the outcomes of these AEs are limited to a few case reports that demonstrate variability in their treatment response and reversibility. Ongoing monitoring will be essential toward elucidating a more comprehensive pattern of ocular toxicities associated with CAR T therapies.

TIL Therapy

Tumour-infiltrating lymphocyte (TIL) therapy is another form of cell therapy showing promise for treating solid tumour malignancies. The process involves surgically excising a tumour sample from the patient, extracting TILs (primarily CD8+ cytotoxic T cells) that have already infiltrated the tumour, and then selecting the most potent TILs ex vivo for clonal expansion. Patients are preconditioned with lymphodepletion, and the expanded TILs are reinfused into the patient, where they circulate, infiltrate, and destroy cancer cells by recognizing tumour-associated antigens and neoantigens retained by the TIL. Although TIL therapy has not yet been approved for use by Health Canada, it was approved for use by the FDA in 2024 for treating unresectable or metastatic melanoma that has failed previous therapies. While early results show tremendous promise to induce early complete tumour regression and maintain remission up to 24 months after therapy, it has been associated with significant ocular autoimmune sequelae.[4]

Examples	Applications	Reported Ocular Toxicities	Reported Treatment/ Reversibility
CAR T Therapy			
Tisagenlecleucel (Kymriah®) Axicabtagene ciloleucel (Tescarta®) Brexucabtagene autoleucel (Tecartus®) Lisocabtagene maraleucel (Breyanzi®)	Acute lymphoblastic leukemia Non-Hodgkin lymphoma Mantle cell lymphoma Multiple myeloma Refractory hematological malignancies	Mydriasis Xerophthalmia Allergic conjunctivitis Retinal vein occlusion Vitreous hemorrhage Exudative retinal detachment Retinal hemorrhage Retinitis Blindness Ocular lymphoma Candida endophthalmitis Intraocular hematological relapse Worsening ocular graft versus host disease (persistent epithelial defects, symblepharon) Herpes zoster ophthalmicus Acute retinal necrosis Optic neuropathy Anisocoria Nystagmus Keratitis Conjunctivitis Visual field defect Diplopia Optic disc edema Metamorphopsia	Improvement with intravenous antiviral therapy (herpes zoster ophthalmicus, acute retinal necrosis) Aggressive lubrication, topical steroid, amniotic membrane corneal bandage contact lenses, topical cyclosporine, scleral lens for worsened ocular graft versus host disease patients with minimal improvements Improvement in cases of bilateral exudative retinal detachment with optic disc edema and intravitreal triamcinolone injections, bilateral orbital radiation
TIL Therapy			
Lifileucel (Amtagvi®)	Melanoma (unresectable, refractory, metastatic)	Ocular autoimmune sequelae Bilateral anterior uveitis Bilateral panuveitis Vogt-Koyanagi-Harada Bilateral cystoid macular edema	Persistently elevated proinflammatory cytokines in aqueous humor reported with cessation of treatment
Checkpoint Inhibitors			
Ipilimumab (Yervoy®) Nivolumab (Opdivo®) Pembrolizumab (Keytruda®) Atezolizumab (Tecentriq®) Avelumab (Bavencio®) Durvalumab (Imfinzi®)	Melanoma Renal cell carcinoma Small cell lung cancer Non-small cell lung cancer Colorectal cancer	Dry eye disease Uveitis Ocular myasthenia gravis Inflammatory orbitopathy Uveal effusion Optic neuritis Papillitis Vitritis Choroidopathy Ocular myositis Cerebellar ataxia with nystagmus Retinal vasculitis Vogt-Koyanagi-Harada-like syndrome Birdshot-like uveitis Corneal graft rejection Corneal perforation Fundus depigmentation Acute macular neuroretinopathy Extraocular muscle paresis Stevens-Johnsons syndrome Periorbital edema Glaucoma or elevated IOP	Consider suspension of treatment until normalization or improvement of ocular symptoms with moderate adverse effects Majority of inflammatory AEs improved with systemic corticosteroids, but rarely with observation alone Consider continuation of treatment if ocular adverse effect experienced is secondary to a paraneoplastic event

Examples	Applications	Reported Ocular Toxicities	Reported Treatment/ Reversibility
Antibody-Drug Conjugates Brentuximab vedotin (Adcetris®) Trastuzumab emtansine (Kadcyla®) Sacituzumab govitecan (Trodelvy®)	Acute lymphoblastic leukemia B-cell lymphoma Multiple lymphoma Hodgkin lymphoma Hairy cell lymphoma Breast cancer Cervical cancer Ovarian cancer Urothelial carcinoma Gastric cancer Non-small cell lung cancer Pleural mesothelioma Pancreatic adenocarcinoma	Foreign body sensation Blurred vision Dry eye disease Conjunctivitis Keratitis/keratopathy Xerophthalmia Cataract formation Ocular pain Photophobia Microcystic corneal disease Nyctalopia Purtscher-like retinopathy Retinal hemorrhage	Artificial tears and aggressive lubrication Topical ocular corticosteroids Consideration of vasoconstrictor drops prior to treatment initiation as prophylaxis Consideration of cooling eye pads during treatment infusion as prophylaxis
Molecularly Targeted Therapies Trametinib (Mekinist®) Cobimetinib (Cotellic®) Binimetinib (Mektovi®) Vemurafenib (Zelboraf®) Dabrafenib (Tafinlar®) Encorafenib (Braftovi®) Osimertinib (Tagrisso®) Neratinib (Nerlynx®) Cetuximab (Erbitux®) Alectinib (Alecensa®) Brigatinib (Alunbrig®)	Metastatic melanoma Leukemia Non-small cell lung cancer Breast cancer Ovarian cancer Colorectal cancer Renal cancer Esophageal cancer Mesothelioma Prostate cancer Glioblastoma Pancreatic cancer	MEK-associated retinopathy Retinal vein occlusion Periorbital edema Dyschromatopsia Glaucoma Eye pain Ocular inflammation (anterior uveitis) Epiphora Conjunctivitis Cataract development Tear film dysfunction/dry eye Central serous chorioretinopathy Blepharitis Trichomegaly Meibomitis Iridocyclitis Corneal epithelial lesions Corneal keratopathy Corneal ulcers Presbyopia Blurry vision Optic neuropathy Retinal hemorrhage Diplopia Macular edema Positive visual phenomena	The majority of long-term adverse events associated with MEK inhibitors had resolved without long-term consequences or interruption of therapy A minority of adverse events associated with BRAF inhibitors required short-term corticosteroids The incidence of ocular adverse events induced by EGFR inhibitors varied significantly with the agent of choice

Table 1. Range of reported ocular toxicities and their outcomes; *courtesy of Grace Yin, MD, MPhil and C. Maya Tong, MD, FRCSC*

Abbreviations: AEs: adverse events; **BRAF:** V-Raf murine sarcoma viral oncogene homolog B; **CAR-T Therapy:** Chimeric antigen receptor T-cell therapy; **CRS:** cytokine release syndrome; **EGFR:** Epidermal growth factor receptor; **IOP:** intraocular pressure; **MEK:** mitogen-activated protein kinase; **TIL Therapy:** Tumor-infiltrating lymphocyte therapy.

Early in the treatment course, TIL therapy has been associated with bilateral anterior uveitis.[5] Later in the treatment course, bilateral panuveitis with diffuse retinal pigment epithelium hypopigmentation concerning for Vogt-Koyanagi-Harada syndrome, and bilateral cystoid macular edema has been reported.[5] Even with cessation of treatment, persistently elevated proinflammatory cytokine levels have been demonstrated in the aqueous humour, suggesting strong ocular immune sequelae.[5] Given the novelty of TIL therapy and its recent introduction to the market in 2024, ongoing surveillance of its potential ocular AEs will be critical as more patients undergo TIL therapy.

Checkpoint Inhibitors

Checkpoint inhibitors are monoclonal antibodies that bind to specific T-cell receptors (programmed cell death protein 1 [PD-1], cytotoxic t-lymphocyte-associated protein 4 [CTLA-4], and programmed cell death ligand 1 ([PD-L1]) to override inhibition of T-cell activation by cancerous cells and reactivate programmed cell death signal pathways. This allows the patient's immune system to recognize and attack malignant cells more effectively. Checkpoint inhibitors have shown benefit in treating melanoma, renal cell carcinoma, lung cancer (small cell, and non-small cell), colorectal cancer, and more. Although ocular AEs are rare, approximately 15 toxicities have been reported in <1% of patients, with approximately 70% occurring within the first 2 months of starting treatment.[6] However, the degree of variability in toxicity is high and includes dry eye disease, uveitis, ocular myasthenia gravis, inflammatory orbitopathy, uveal effusion, optic neuritis, papillitis, vitritis, choroidopathy, ocular myositis, cerebellar ataxia with associated nystagmus, retinal vasculitis, Vogt-Koyanagi-Harada (VKH)-like syndrome, corneal graft rejection, and corneal perforation.[7] A key concern raised with checkpoint inhibitor therapy resides in the risk of unopposed immune reactivation with the potential to cause broad-spectrum toxicity to non-target systems such as the eye. It has been speculated that high-levels of PD-L1, PD-1, and CTLA-4 expressed within ocular tissues, including the retinal pigment epithelium, may provide an explanation for the mechanisms driving the ocular toxicities observed with checkpoint inhibitors.[8] Moderate ocular AEs may warrant suspending treatment until symptoms normalize or improve, with concurrent consideration for corticosteroids. For severe ocular reactions, both suspending therapy and initiating high-dose systemic corticosteroids are typically indicated. Notably, some ocular toxicities, particularly uveitis-like responses, have been observed to correlate with regression of tumour burden and are thus speculated to be a prognostic marker of therapeutic response.[7] Some ocular AEs observed with checkpoint inhibitor therapy may be confounded by the emergence of paraneoplastic events triggered by autoimmunity. As such, decisions regarding the discontinuation and re-introduction of checkpoint inhibitor therapies following severe ocular toxicities may require careful multidisciplinary risk-benefit discussions involving the ophthalmologist, the patient, and their oncologist. Further, in cancer patients presenting with uveitis-like symptoms, clinicians should consider ocular toxicities secondary to immune checkpoint inhibitor use, and exercise caution before considering such reactions to be solely inflammatory-driven.

Antibody-Drug Conjugates

Antibody-drug conjugates (ADC)s are typically comprised of an antibody (often IgG) covalently linked to a cytotoxic drug. The antibody component is specific for an intended antigen expressed by malignant cells. The ideal antigen target is exclusively or overly expressed on malignant cells of interest (e.g., human epidermal growth factor receptor 2 [HER2], epidermal growth factor receptor [EGFR], CD19, among others), and is internalized following antigen-antibody complex binding to facilitate an effective portal of entry for the linked cytotoxic drug. Thus, ADCs target tumour tissue while minimizing off target, or "bystander killing". ADCs have demonstrated greatest promise in treating acute lymphoblastic leukemia, multiple myeloma, and various lymphomas, including B-cell, Hodgkin, and hairy cell lymphoma subtypes, as well as breast cancers, cervical cancer, ovarian cancer, urothelial carcinoma, gastric cancer, and non-small cell lung cancer. The most commonly reported AEs associated with ADCs have involved the corneal surface, including dry eye symptoms, conjunctivitis, keratitis, xerophthalmia, cataract formation, ocular pain, night blindness, photophobia, and microcystic corneal disease.[9] Posterior-involving AEs including nyctalopia, retinal hemorrhage, and Purtscher-like retinopathy have also been reported.[10] It is speculated that the

mechanism by which ADCs cause ocular AEs may be secondary to uptake of ADCs by non-target cells (e.g., HER2 receptor expression on normal corneal epithelial cells), or through non-target uptake facilitated by endocytosis, and diffusion, among others.[10] Strategies for managing ADC-induced ocular AEs include artificial tears and lubrication, topical ocular corticosteroids, vasoconstrictor drops prior to infusions, and consideration for suspension, discontinuation, or dose-reduction of ADCs.[10] However, the effectiveness of each intervention is highly variable and ADC-specific. Due to limited available data, our ability to understand the precise rate and reversibility of identified ocular toxicities remains poorly understood.

Molecularly Targeted Therapies

MEK Inhibitors, BRAF Inhibitors

Molecularly targeted therapies encompass both monoclonal antibodies (mABs) and small molecule kinase inhibitors (SMKIs). Broadly, mABs exert their effects through inhibition of growth factor receptor signalling, while SMKIs suppress key protein kinases involved in the propagation of cancer cells. Among these, mitogen-activated protein kinase (MEK) inhibitors and V-Raf murine sarcoma viral oncogene homolog B (BRAF) inhibitors are two prominent classes, with promising effectiveness in treating metastatic melanomas, solid organ tumours, and some leukemias. BRAF inhibitors act by inhibiting cellular proliferation regulated by the Ras/Raf/MEK/ERK pathway, whereas MEK inhibitors target MEK1 and MEK2, which are critical components of this cascade. When used in combination, these inhibitors exert a synergistic effect. However, MEK inhibitors have been frequently implicated in the development of MEK-associated retinopathy (MEKAR). MEKAR primarily affects the outer retinal layers in a dose-response fashion and have been reported to be observed in up to 100% of patients receiving MEK-inhibitor therapy.[11] MEKAR is characterized by multifocal symmetrical central serous chorioretinopathy-like changes involving the fovea in the absence of altered choroidal thickness.[11] Additional cases of retinal vein occlusion, periorbital edema, dyschromatopsia, glaucoma, eye pain, ocular inflammation (especially anterior uveitis), epiphora, conjunctivitis, cataract development, and tear film dysfunction have been reported.[11] A recent review of MEK-inhibitor toxicities found that the majority of ocular AEs were resolved without long-term consequence or the need to interrupt therapy. Moreover, the overall incidence of serious, vision-threatening ocular AEs was found to be low. Patients may benefit from a baseline retinal examination before initiating treatment. Compared to MEK inhibitors, BRAF inhibitors have been more commonly associated with uveitis, dry eye, and central serous chorioretinopathy.[12,13] The majority of BRAF inhibitor toxicities were successfully managed without requiring discontinuation of therapy, and a minority required short-term corticosteroid treatment for resolution.[14]

Epidermal Growth Factor Receptor Inhibitors and Anaplastic Lymphoma Kinase Inhibitors

Epidermal growth factor receptor (EGFR) inhibitors are mABs that target the EGFR tyrosine kinase receptor to inhibit its phosphorylation and thereby prevent its subsequent ability to act as a docking site for key signalling molecules important for cellular proliferation. EGFR inhibitors have demonstrated clinical utility across a broad range of malignant solid tumours, including non-small cell lung cancer, breast and ovarian cancers, colorectal, renal, esophageal, mesothelioma, prostate, glioblastoma, and pancreatic cancers. Most reported ocular AEs involve the anterior segment and include blepharitis, trichomegaly, meibomitis, dysfunctional tear film, iridocyclitis, corneal epithelial lesions, cortex keratopathy, and corneal ulcers.[15,16] However, the incidence of these ocular AEs may differ significantly, with some agents being reported to have a low incidence rate (e.g., osimertinib at 0.5%) and others have shown a very high incidence of occurrence (e.g., ABT-414 has shown a 100% incidence of vortex keratopathy)[16] However, partial or complete recovery has been achieved with treatment discontinuation and/or treatment with topical steroids.[16]

Anaplastic lymphoma kinase (ALK) inhibitors function by targeting the ability of their corresponding receptor tyrosine kinase to autophosphorylate, thereby preventing activation of subsequent signal pathways involved in cellular proliferation. These agents have been shown to have excellent utility in treating non-small cell lung cancer and ALK-positive malignancy. Ocular AEs reported in association with ALK inhibitors include presbyopia, blurry vision, optic neuropathy, retinal hemorrhage, diplopia, macular edema, cataract

formation, and visual disturbances.[17,18] The majority of ocular AEs have not required discontinuation of therapy and have improved with conservative or medical management.

Summary and Future Directions

Oncology and cancer therapeutics represent a fast-growing area of research focused on precision medicine approaches such as small molecule inhibitors, therapeutic cancer vaccines, and T-cell receptor-based strategies. Although the eye is traditionally considered to be "immune privileged", this protection is not absolute. Patients on novel chemotherapeutic agents may benefit from timely access to care with ophthalmologists as an active part of the oncology care team to support co-management of treatment decisions when serious AEs occur. The rapid advancements in cancer therapeutics and the renewed hope that they offer to patients with malignancies is nevertheless exciting. The pace of innovation may re-shape the landscape of oncology, ocular immunity, and the boundaries of immune privilege.

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