An eye on novel anti-cancer agents: an evidence-based approach to external eye assessment

BY HELENA FAWDRY AND ANDREW COOMBES

Novel anti-cancer therapies have led to significant advancement in cancer treatment, however, they can be associated with external eye complications. It is important to be mindful of such adverse effects during assessment of patients enrolled in clinical trials.

Annually, approximately 330,000 individuals are diagnosed with cancer in the UK, with this number predicted to exceed 400,000 by 2030 due to an ageing and expanding population [1]. Despite an increasing burden of cancer diagnoses, mortality from cancer is, conversely, falling [1]. This is thanks in part to an emphasis on early diagnosis and early specialist input, but also due to revolutionary new treatment that has emerged over the last two decades [1,2]. Targeted anti-cancer treatments, which inhibit the growth, progression and spread of cancer through their action on specific molecular targets have contributed to huge leaps in survival rates [3]. These novel agents represent an important area of anti-cancer research [3]. Unfortunately, accompanying these significant gains is a plethora of ocular adverse effects, therefore, it is crucial that all eye specialists are equipped with the skills to identify and treat these complications.

What are targeted anti-cancer treatments?

Targeted anti-cancer treatments differ from conventional chemotherapy through their ability to act on specific targets associated with a cancer, rather than all rapidly dividing cells [3]. The National Cancer Institute broadly classifies these as [3]:

Hormone therapies

Breast, ovarian, endometrial and prostate cancer, amongst others, are dependent on hormones such as oestrogen and testosterone for proliferation and spread, with over 75% of breast cancers oestrogen-receptor positive [3]. Therapies that directly or indirectly target these include aromatase inhibitors, such as letrozole and selective oestrogen receptor modulators (SERMs), such as tamoxifen [2,3].

Monoclonal antibodies

Immune checkpoint inhibitors (ICIs), such as pembrolizumab and ipilimumab, are monoclonal antibodies whose action leads to an upregulated immune response against tumours [2]. Despite the eye's relative immune privilege, immune-related adverse events (irAEs) may occur in any ocular structure, affecting 1% of patients on ICIs [4]. Antibody-drug conjugates (ADCs) target specific antigens on a malignant cell, aiming to spare healthy cells from apoptosis [2].

Cancer growth inhibitors

Cellular growth and division are dependent on the action of growth factors and chemical messengers, such as tyrosine kinases [3,5]. Inhibition of these targets, as well as mTOR, BRAF and MEK proteins, has proven effective in treatment of a variety of cancers [5]. Dysregulated angiogenesis is a cornerstone of malignancy. Medications such as pazopanib and azitinib target vascular endothelial growth factor receptors (VEGFR), a key stimulant for new vessel growth [2].

PARP inhibitors

Inhibition of poly ADP-ribose polymerases (PARPs), which are responsible for repairing damaged DNA and thus evasion of apoptosis, is an important treatment for breast and ovarian cancer [2].

Apoptosis-inducers

Therapeutic agents such as everolimus and boretezomib target key points in the signalling pathway to induce apoptosis in a malignant cell [2].

What is the role of the ophthalmologist?

If ocular adverse events are not recognised and treated promptly, they can have a significant impact on quality of life and may contribute to patients discontinuing potentially lifesaving treatment [6].

Patients with baseline pathology or history of ocular symptoms, such as dry eyes, are at an increased risk of developing ocular complications over the course of treatment [6]. Incorporating a structured approach to assessment is crucial, as patients are significantly more likely to report symptoms with focused questioning [7]. Slit-lamp examination is important to identify severe pathology which may be asymptomatic or present non-specifically [2,6]. For example, during the DREAMM-2 trial, some patients with severe keratopathy or corneal ulcers were only detected on routine ocular assessment [7].

Structured slit-lamp examination

Adopting a systematic approach to examination is key to identifying common anti-cancer therapy-related adverse effects. Whilst this list is not exhaustive, it serves as a basis for eye specialists examining the external eye on novel therapeutic agents.

Conclusion

Targeted anti-cancer therapies have led to significant improvements in cancer-related mortality since their introduction. Many of these agents suppress cellular growth and stimulate apoptosis by targeting cell-signalling pathways or promoting an upregulated immune response. This can result in off-target adverse effects in all body systems, importantly including the eye. It is crucial that these patients are monitored regularly with a systematic structured ocular examination, and that eye specialists are equipped with the knowledge and skills to identify common treatment-related complications.

Table 1: A systematic approach to eye examination.	
External structures and adnexa	*1. Skin lesions* Frequent dermatological examinations are crucial for patients on BRAF-inhibitors, who are at increased risk of cutaneous squamous cell carcinoma and keratoacanthoma [8]. It is important to be alert for such periorbital lesions. *2. Steven Johnson Syndrome (SJS) / Toxic Epidermal Necrolysis (TEN)* Drugs such as efitinib, BRAF inhibitors and ICIs have infrequently been associated with TEN/SJS [2]. *3. Periorbital oedema* Up to 80% of patients on imatinib and nearly half of patients treated with avapritinib, a tyrosine kinase inhibitor, experienced periorbital oedema [2,9,10]. Periorbital oedema has also been described with evorolimus and rucaparib treatment [2]. Some report successful treatment with diuretics and dose reductions, whilst others required blepharoplasty [11,12]. *4. Giant cell arteritis (GCA)* GCA is the most common systemic vasculitis and a sight-threatening emergency. Several cases have been associated with ICI use [13]. *5. Orbital myositis / myasthenia gravis* Patients on ICIs presenting with ocular pain, proptosis, diplopia, eyelid oedema and restricted extraocular motility should be carefully worked up for orbital myositis. Recognition of this diagnosis is key given its association with potentially life-threatening myocarditis and diaphragmatic myositis [2]. This should be differentiated from myasthenia gravis, also present in <1% of patients on ICIs, which more commonly presents with fatigable ptosis and ophthalmoplegia and may be associated with acetylcholine receptor antibodies [14]. *6. Viral infections* 10% of patients on tofacitinib developed herpes zoster in one study, with further case reports of Ramsay-Hunt syndrome [15,16].
Lids and lashes	*1. Blepharitis* Blepharitis and meibomian gland dysfunction have been reported in three-quarters of patients on aromatase inhibitors in a small case-control study [17]. Less frequent association with ICIs and EGFR inhibitors has been reported [4,18]. It is also important to consider previous therapies; baseline assessment of patients enrolled to one trial showed a high burden of blepharitis [6]. Most of these patients had undergone previous treatment with steroids and bortezomib [6]. *2. Increased lacrimation* One-quarter of all patients treated with avapritinib, a tyrosine kinase inhibitor, experienced increased lacrimation in one trial [10]. *3. Trichomegaly* Excessively tortuous, thickened and hyperpigmented eyelash growth has been frequently reported with erlotinib use [18].
Conjunctiva and sclera	*1. Conjunctivitis* Inflammation, redness and swelling of the conjunctiva was reported in one-quarter of studies analysed in a retrospective review, affecting between 0.4-6% of patients on ICIs [4]. A 57-year-old woman receiving atezolizumab therapy developed bilateral cicatrising conjunctivitis, which resolved with steroids, scleral contact lenses and treatment discontinuation [19]. *2. Episcleritis* Inflammation of episcleral tissues may infrequently occur with drugs affecting cellular growth and immune response (0.5-2% patients on BRAF/MEK inhibitors; <1% of those on ICIs) [2,20]. *3. Conjunctival haemorrhage* Subconjunctival haemorrhage may be caused by tyrosine kinase inhibitors, with 4.4% of patients treated with pazopanib in a multicentre, randomized control trial developing this complication [21].
Cornea	*1. Dry eyes* Dry eye is one of the most frequently reported ocular surface irAEs, with between 1-24% of patients in half of the studies analysed reporting dry eyes [23]. This was also frequently reported amongst patients treated with aromatase inhibitors or ADCs such as belantamab mafodotin [6,17]. *2. Keratitis / keratopathy* A high index of suspicion for keratopathy should be considered for all novel agents. Nearly three-quarters of patients treated with any dose of belantamab mafodotin experience Grade 1-4 keratopathy [7]. A distinctive bilateral, white 'whorl-like' superficial keratopathy is noted in patients treated with tamoxifen (between two to ten percent of patients in one study) [22]. Use of erlotinib may cause keratitis, kerato-uveitis or corneal oedema [23]. *3. Corneal epithelial changes* Nearly half of all patients previously treated with bortezomib or steroids had corneal epithelial abnormalities [7]. Corneal microcyst-like epithelial changes (MECs) are frequently associated with antibody-drug conjugates which contain monomethyl auristatin F [24]. One patient in this study subsequently developed a corneal ulcer [24]. Reduced corneal wound healing has been reported in patients on erlotinib [23].

References

1. Creighton H, Beach B, Bamford SM. Rethinking cancer: The BigC: Quantifying the social and economic impact. International Longevity Centre. September 2015: https://ilcuk.org.uk/wp-content/uploads/2018/10/Rethinking-Cancer-The-big-C.pdf
2. Fortes BH, Tailor PD, Dalvin LA. Ocular Toxicity of Targeted Anticancer Agents. *Drugs* 2021;**81(7)**:771-823.
3. Targeted Cancer Therapies. National Cancer Institute. 2021: https://www.cancer.gov/about-cancer/treatment/types/targeted-therapies/targeted-therapies-fact-sheet
4. Park RB, Jain S, Han H, Park J. Ocular surface disease associated with immune checkpoint inhibitor therapy. *Ocul Surf* 2021;**20**:115-29.
5. Cancer Growth Blockers. Cancer Research UK. 2021 https://www.cancerresearchuk.org/about-cancer/cancer-in-general/treatment/targeted-cancer-drugs/types/cancer-growth-blockers
6. Wahab A, Rafae A, Mushtaq K, et al. Toxicity of Belantamab Mafodotin, an Oncological Perspective of Management in Relapsed and Refractory Multiple Myeloma. *Front Oncol* 2021;**11**:678634.
7. Kruft B, Nelson LA, Stewart JA, Stewart WC. Adverse event reporting. *Ophthalmology* 2007;**114(7)**:1420.
8. Anforth R, Fernandez-Peñas P, Long GV. Cutaneous toxicities of RAF inhibitors. *Lancet Oncology* 2013;**14(1)**:e11-e18.
9. Breccia M, Gentilini F, Cannella L, et al. Ocular side effects in chronic myeloid leukemia patients treated with imatinib. *Leukemia Research* 2008;**32(7)**:1022-5.
10. Heinrich MC, Jones RL, von Mehren M, et al. Avapritinib in advanced PDGFRA D842V-mutant gastrointestinal stromal tumour (NAVIGATOR): a multicentre, open-label, phase 1 trial. *Lancet Oncology* 2020;**21(7)**:935-46.
11. Pascual J, Marcén R, Ortuño J. Clinical experience with everolimus (Certican): optimizing dose and tolerability. *Transplantation* 2005;**79(9)**:S80-S84.
12. Schear MJ, Rodgers R. A case of everolimus-induced eyelid edema. *Ophthalmic Plast Reconstr Surg* 2018;**34(1)**:e21-e22.
13. Narala R, Reddy SA, Mruthyunjaya P. Giant cell arteritis manifesting as retinal arterial occlusion and paracentral acute middle maculopathy in a patient on pembrolizumab for metastatic uveal melanoma. *Am J Ophthalmol* Case Rep 2020;**20**:100891.
14. Caberry WY, Yau M, Mezey N, et al. Neuro-Ophthalmic complications of immune checkpoint inhibitors: a systematic review. *Eye and Brain* 2020;**12**:139.
15. Winthrop KL, Melmed GY, Vermeire S, et al. Herpes zoster infection in patients with ulcerative colitis receiving tofacitinib. *Inflamm Bowel Dis* 2018;**24(10)**:2258-65.
16. Kobak S. Tofacitinib-induced Ramsay-Hunt syndrome in a patient with rheumatoid arthritis. *Curr Drug Safety* 2021;**16(1)**:107-9.
17. Chatziralli I, Sergentanis T, Zagouri F, et al. Ocular surface disease in breast cancer patients using aromatase inhibitors. *Breast J* 2016;**22(5)**:561-3.
18. Zhang G, Basti S, Jampol LM. Acquired trichomegaly and symptomatic external ocular changes in patients receiving epidermal growth factor receptor inhibitors: case reports and a review of literature. *Cornea* 2007;**26(7)**:858-60.
19. An S, Raju I, Surenkhuu B, et al. Neutrophil extracellular traps (NETs) contribute to pathological changes of ocular graft-vs.-host disease (oGVHD) dry eye: Implications for novel biomarkers and therapeutic strategies. *Ocul Surf* 2019;**17(3)**:589-614.
20. Méndez-Martínez S, Calvo P, Ruiz-Moreno O, et al. Ocular adverse events associated with MEK inhibitors. *Retina* 2019;**39(8)**:1435-50.
21. Csaky KG, Dugel PU, Pierce AJ, et al. Clinical evaluation of pazopanib eye drops versus ranibizumab intravitreal injections in subjects with neovascular age-related macular degeneration. *Ophthalmology* 2015;**122(3)**:579-88.
22. Dulley P. (1999). Ocular adverse reactions to tamoxifen – a review. *Ophthalmic Physiol Opt* 1999;**19(Suppl1)**:S2-9.
23. Zhou Z, Sambhav K, Chalam KV. Erlotinib-associated severe bilateral recalcitrant keratouveitis after corneal EDTA chelation. *Am J Ophthalmol Case Rep* 2016;**4**:1-3.
24. Farooq AV, Degli Esposti, S, Popat R, et al. Corneal epithelial findings in patients with multiple myeloma treated with antibody–drug conjugate belantamab mafodotin in the pivotal, randomized, DREAMM-2 study. *Ophthalmol Ther* 2020;**9(4)**:889-911.

(All links accessed December 2021).

"Patients with baseline pathology or history of ocular symptoms are at an increased risk of developing ocular complications"

TAKE HOME MESSAGE

- If in doubt about the aetiology of external eye complications – consider current or previous anti-cancer therapy.
- Adopt a systematic approach to examination as some pathology may be asymptomatic.
- Most complications from targeted anti-cancer therapy can be managed without treatment cessation, however, prompt recognition and treatment are essential.

AUTHORS

Dr Helena Fawdry,
Senior House Officer,
Royal London Hospital, London, UK.

Mr Andrew Coombes,
Ophthalmology Consultant, Royal London Hospital, London, UK.

Declaration of competing interests: None declared.