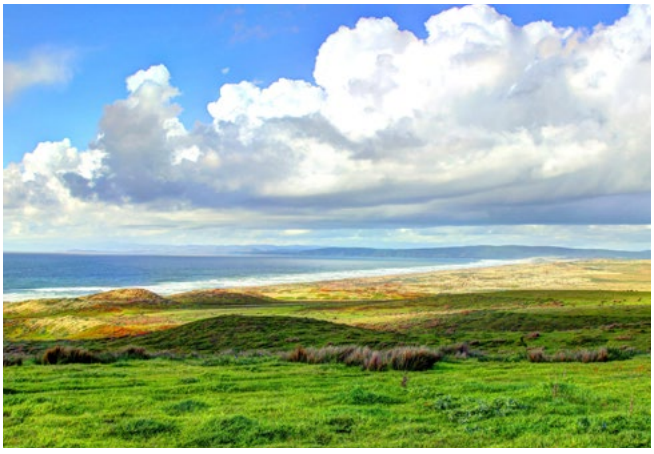

Photo courtesy of Lynn E. Harman, MD. *Point Reyes Beach North.*

Recognizing ocular complications of chemotherapy before they result in irreversible injury involves taking a clinical history and performing a basic eye examination.

Ophthalmic Complications Related to Chemotherapy in Medically Complex Patients

Lynn E. Harman, MD

Background: *Systemic cancer therapies cause a variety of ophthalmic complications. Mitigating harmful adverse events involves screening patients at risk for ocular injury and vision loss.*
Methods: *A review of the relevant literature on the ophthalmic complications of cancer therapy was used to formulate an approach to screening patients for serious complications presenting at a nonophthalmic specialty center.*
Results: *Rarely, ocular complications of cancer therapy can occur. Establishing a causal association for any given agent is complicated because many treatment-related adverse events result in symptoms and ocular findings indistinguishable from primary eye disorders.*
Conclusions: *Recognizing potentially serious ocular complications of cancer therapy before they result in irreversible injury starts with taking a relevant clinical history and performing a basic eye examination, including assessments of visual acuity and fields. Given the wide range of treatment-related adverse events and the challenges of diagnosis, the screening process plays an important role in expediting referral to an ophthalmologic specialist.*

Introduction

The majority of published research about the ocular complications of cancer therapy reviews the adverse events of individual chemotherapies and targeted therapies.[1-7] Cataloging these adverse events can be approached in several ways. One method is anatomical, in which the therapeutic agents are listed according to the parts of the eye or ocular adnexa they affect (eg, conjunctiva, lens, retina),[1] whereas another method lists therapies according to the type of injury they cause (eg, punctate keratitis, sterile uveitis, macular edema).[4] It is also possible to describe ocular toxicities and adverse events by pharmacological group (eg, plant alkaloids, antimetabolites, nitrosoureas) or by individual agent.[2,3] Such surveys are invaluable when attempting to establish whether causal links exist between a particular ocular condition and a therapeutic agent; however, these inventories do not address clinical questions about how to manage the onset of a suspected event.

Uncertainty sometimes exists about the seriousness of an ocular symptom or a new finding on an eye examination if it occurs in patients receiving chemotherapy. For those who are hospitalized or too ill to be seen at an ophthalmology center, the situation can be disconcerting. Few adverse drug reactions are characteristic enough to diagnose with absolute certainty on

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an abbreviated examination, and confirming whether an adverse event is drug related with a drug rechallenge is usually not an option. Consultative input is desirable even when it may be logistically difficult.

In this article, the term *ocular* is inclusively used to describe the eye, visual pathway, and ocular adnexa. More than 60 distinct ocular-related adverse events have been associated with systemic chemotherapies and targeted cancer therapies.[1-7] These events vary from finding asymptomatic deposits in the retina to cataracts, cranial nerve palsies, to keratoconjunctivitis sicca. Most of these complications have clinical features that overlap with acquired diseases.[1,4,5] Treatment-related adverse events range from being self-limited conditions to permanent vision loss.[1,4,5] The diversity of these complications speaks to the variety of molecular and cellular mechanisms involved. Thus, this review will focus on evaluating ocular complaints occurring in the context of medically complex treatment and when it is difficult for patients to be seen at a specialty eye clinic.

This paper will also provide a general approach for screening patients outside the setting of an eye clinic in order to expedite consultation with an eye specialist and reduce unnecessary referrals. It will also address when to anticipate, and possibly preemptively reduce, some common ocular-related adverse events associated with select chemotherapy agents. Given the vastness of the topic, this paper will not include complications of radiotherapy, therapies for primary cancers of the eye and ocular adnexa, or the ocular manifestations of graft-vs-host disease. Although selected examples of adverse events are cited to emphasize elements of the ocular history and eye examination, they are not meant to represent a comprehensive directory of complications.

Table 1. — Somewhat Commonly Occurring Adverse Events of Cytotoxic Chemotherapies

Adverse Event	Drug	Route of Administration
Arteriovenous shunts (central nervous system)	Carmustine	Intra-arterial
Blurred vision	Busulfan	Intravenous
	5-fluorouracil	Intravenous
Conjunctivitis	5-fluorouracil	Intravenous
	Deoxycoformycin	Intravenous
Corneal opacity	Cytosine arabinoside	Intravenous
Cranial nerve palsies	Plant alkaloids	Intravenous
Epiphora	5-fluorouracil[a]	Intravenous
Eye pain	5-fluorouracil	Intravenous
Focal demyelination of the optic nerve	Carmustine/cisplatin	Intra-arterial
Foreign body sensation	Cytosine arabinoside	Intravenous
	5-fluorouracil	Intravenous
Keratitis	Cytosine arabinoside[a]	Intravenous
	5-fluorouracil	Intravenous
Keratoconjunctivitis sicca	Cyclophosphamide	Intravenous
	Busulfan	Intravenous
Macular pigment	Cisplatin	Intravenous
Papilledema	Carmustine	Intra-arterial
Periorbital edema	5-fluorouracil	Intravenous
	Methotrexate	Intravenous
Photophobia	5-fluorouracil	Intravenous
Ptosis	Plant alkaloids	Intravenous
Retinal arterial narrowing	Carmustine	Intra-arterial
Retinal hemorrhages	Carmustine	Intra-arterial

[a]Considered common.

Adapted from Schmid KE, Kornek GV, Scheithauer W, et al. Update on ocular complications of systemic cancer chemotherapy. *Surv Ophthalmol.* 2006;51(1):19-40, with permission from Elsevier.

Incidence

The proportion of patients who experience a serious adverse event from chemotherapy is low. Most of these complications are considered rare or reported only as single case reports.[1-7] A 2006 comprehensive review found that 57 different ocular-related (ie, eye, visual pathway, ocular adnexal) complications could be attributed to cytotoxic chemotherapies (Table 1).[4] A total of 38% of drug-specific complications were deemed to be rare and another 46% were identified through case reports.[4] A total of 15% of drug-specific complications were considered to be somewhat common and 1.4% were noted to be common.[4]

The low overall proportion of adverse events comes with a clinical caveat[1-7]: The event rate is probably lower than anticipated for "incidental" (or unrelated) findings on routine eye examinations. Common conditions such as uncorrected presbyopia, refractive errors, dry eyes, chronic blepharitis, and age-related cataracts can all cause symptoms that could be mistakenly attributed to chemotherapy if the clinician has not taken a careful clinical history and performed a basic eye examination. Clinicians who do not specialize in ophthalmology are not typically expected to perform a complete eye examination, nor are they usually familiar with the nuances of minor, pre-existing eye conditions. This emphasizes the importance of a clinical history and basic tests of visual function (with corrective lenses) to screen for potentially serious problems.

Attributing an ocular complication to a therapeutic agent is a process of exclusion. Some of the most challenging diagnoses in ophthalmology arise in the context of cancer treatment; for example, the distinction between sterile drug-related uveitis and infectious endophthalmitis (typically when a patient is immunocompromised), as well as the distinction between

drug-related cranial nerve palsy and metastatic cancer or an age-related vascular event.

Complaints

The ophthalmic complications of systemic cancer therapy can cause some of the same symptoms seen with primary eye diseases. They can include vision loss (central, peripheral [or both], night blindness), abnormal visual perceptions (distorted vision, smoky vision, double vision, floaters), and all degrees of eye and periocular pain, among other issues.[1-7] The close temporal relationship of new-onset eye complaints with the initiation of cancer therapy provides presumptive evidence of a causal link. This chronological correlation, along with the cessation of symptoms after stopping the offending agent, may be the most compelling evidence of causation.

Vision Loss/Impairment

Patients who have difficulty describing their visual loss should be queried as to whether the loss is unilateral or bilateral, whether it occurs with or without pain, and whether it was preceded by or associated with other symptoms. If it was transient, then the clinician should ask the patient how long it lasted. Asking the patient to describe the visual experience that surrounded the sensory phenomenon of vision loss may also be helpful in sorting through diagnostic possibilities.

Table 2 lists clinical inferences typically correlated with different types of complaints associated with vision loss or impairment.

Double Vision

Acute onset of binocular diplopia requires a neurological evaluation, whereas monocular diplopia does not. Monocular diplopia is typically caused by an underlying refractive problem. Patients may report double vision as being a shadowing or ghosting of images due to improperly corrected refractive error. Patients may not be aware whether they can see 2 images with both eyes open or with a single eye. Because such a distinction is critical, the clinician must directly question the patient to confirm and test for true binocular diplopia in all fields of gaze. If diplopia disappears when either eye is occluded (ensuring vision is tested in the direction of symptomatic double vision), then double vision is binocular. New-onset binocular diplopia necessitates a neurological evaluation.[8-15]

Examples of chemotherapy agents associated with cranial nerve palsies or double vision are listed in Table 3.[4,5,8-18]

Pain

Characteristics of ocular and periocular pain can provide clues to an underlying disease process. Dry eyes and mild forms of keratitis may be described as producing a "sandy feeling" or foreign-body sensation. Generalized mild eye discomfort, heavy eyelids, and brow ache associated with near visual tasks are features of asthenopia, which may be secondary to use of outdated prescription glasses or need for reading glasses or bifocals. Onset of sudden, sharp, stabbing pain with intense sensitivity to light suggests a corneal epithelial erosion or corneal abrasion. Typically, 1 drop of topical anesthetic quickly relieves such pain. A deep boring pain exacerbated by eye movements is suggestive of scleritis. Optic neuritis can also produce pain or discomfort with eye movements, but it is usually not as severe as scleritis. Severe, unilateral, ocular and periocular pain progressing for minutes to hours and associated with ipsilateral blurred vision or halos around lights is a typical presentation of acute glaucoma. Two symptoms of acute

Table 2. — Clinical Inferences Associated With Symptoms or Features of Visual Loss

Symptom	Clinical Inference
Colored halos around lights	Corneal edema from elevated intraocular pressure
Decreased vision in dim illumination	Impaired dark adaption Vitamin A deficiency
Distortion of straight lines	Macular dysfunction due to edema or blood beneath or within the retina
Floaters, unilateral or bilateral	Blood or inflammatory cells in vitreous Age-related collapse, condensation of vitreous gel; with photophobia and eye pain suggests inflammation
Loss of side or peripheral vision	Branch artery occlusion Cerebrovascular accident Retinal detachment
Pain on eye movement	Optic neuritis Orbital inflammation Scleritis
Painless "spot" in center of vision	Macular dysfunction Optic neuropathy
Photophobia, tender eye	Acute glaucoma Keratitis Uveitis
Severe lancet-like pain, blurred vision	Corneal abrasion Corneal erosion Keratitis
Sudden, catastrophic vision loss	Vascular occlusion of retina or optic nerve
Transient obscurations of vision lasting seconds, usually bilateral	Increased intracranial pressure
Transient visual loss lasting minutes, binocular	Cardiac arrhythmia Posterior circulation event Orthostatic hypotension
Transient visual loss lasting minutes, monocular	Anterior circulation event Amaurosis fugax

glaucoma, periocular pain and headache, are sometimes associated with nausea and vomiting.

Terms and phrases frequently used to characterize pain associated with specific ocular conditions are listed in Table 4.

Table 3. — Chemotherapeutic Agents Associated With Cranial Nerve Palsies or Diplopia[a]

Complication	Select Example	Route of Administration
Bilateral lateral rectus palsy	Cytosine arabinoside and mitoxantrone[15]	Intravenous
Cavernous sinus syndrome	Cisplatin[14]	Intra-arterial
Cranial nerve palsy	Vinca alkaloids[10,11]	Intravenous
Diplopia	Chlorambucil[5]	Intravenous
Disturbance in oculomotor function	5-fluorouracil[12]	Intravenous
Fibrosis of extraocular muscles	Carmustine Nitrosoureas[8,13]	Intra-arterial Intravenous
Internuclear ophthalmoplegia	Methotrexate Nitrosoureas[8,9]	Intra-arterial Intrathecal
Oculomotor nerve palsy	Interferon α[5]	Intravenous

Also refer to references 4 and 16 to 18 for a more thorough discussion on neuro-ophthalmological complications of chemotherapy.

Table 4. — Descriptions of Ocular and Periocular Pain

Description	Clinical Inference[a]
Deep boring eye pain worse with eye movement	Scleritis
Foreign body sensation Grit or sand in eyes	Dry eyes Mild keratitis
Mild to moderate pain with eye movement and vision loss	Optic neuritis
Moderate to severe eye pain worse with light exposure	Uveitis
Ocular and periocular discomfort associated with near visual tasks Lid heaviness Tired eyes Brow ache	Asthenopia Eye strain Does not suggest serious underlying disease
Ocular and periocular pain severity increasing minutes to hours with progressive vision loss	Acute glaucoma
Ocular pain in presence of bright light (photophobia)	After exclusion of known causes (eg, keratitis, uveitis) consider "essential" or idiopathic photophobia
Sudden severe stabbing in 1 eye, relieved when eye is shut	Recurrent erosion or corneal abrasion Pain relief with topical anesthetic Erosions more common in dry eyes or eyes with corneal edema

[a]Clinical conditions do not always produce stereotypic pain complaints.

Other Symptoms

Excessive tearing is a common complaint among middle-aged and older individuals with dry eyes (and dry eye with chronic blepharitis) due to reflex tearing, and it is often associated with a mild foreign body sensation. Exacerbations can be triggered by air conditioning, low humidity, or use of over-the-counter medications (eg, antihistamines). If the symptoms are not relieved by treatment with artificial tears, then other causes of epiphora should be considered. A variety of chemotherapy agents has been associated with excessive tearing, although the mechanisms triggering excessive or overflow lacrimation differ (Table 5).[4,5,7,19-27] Excessive tearing also accompanies disorders of the ocular surface such as conjunctivitis and keratitis. In these situations, findings on an eye examination will usually indicate that the corneal surface lacks its normal luster or that the eye is inflamed.

Because mild photophobia is a common chronic problem, particularly in certain environmental settings, it is important for the clinician to exclude the possibility of a pre-existing condition through a careful history. Keratitis and uveitis also commonly cause photophobia, and these diagnoses must be excluded before idiopathic (or drug-related) photophobia is a considered. Doing so requires a slit lamp inspection of

Table 5. — Clinical Inferences Associated With Excessive Tearing

Relevant History and Finding	Clinical Inference	Potential Drug Implication
Excessive tearing associated with mass in medial canthal region	Consider mechanical obstruction of nasal-lacrimal outflow Swelling in medial canthal region may or may not show signs of inflammation	No drug implications In context of cancer treatment, consider infection or metastatic tumor
New-onset tearing associated with mild red eyes, ocular discomfort, or photophobia	Consider secondary to ocular surface disorder (keratitis or conjunctivitis) Diagnosis of drug-related keratitis or conjunctivitis is process of exclusion	5-fluorouracil[19,20] Capecitabine[5,21] Cytosine arabinoside[23-25] Deoxycoformycin[4] Chorambucil[4] Docetaxel[26,27]
Pre-existing symptoms associated with itching, or past "problems" with eyelids	Consider ocular allergies, trichiasis, or abnormalities of eyelid position	Same medications that exacerbate dry eyes can worsen pre-existing allergy symptoms
Pre-existing symptoms worse in certain environments like air-conditioned rooms or under fans Mild foreign body sensation	Reflex tearing due to dry eyes	Often exacerbated by antihistamines and other common medications

the corneal surface (with fluorescein stain) and a magnified examination of the aqueous humor and vitreous cavity for cells and protein transudate. Presence of photophobia associated with ocular inflammation typically requires referral to an eye specialist.

Eye Examination

Patients unable to be promptly evaluated in a specialty ophthalmology clinic or onsite by an ophthalmologist should have a reliable assessment of visual function (central and peripheral vision) and a basic eye examination, which involves a modicum of basic equipment (Fig).

Central vision can be tested using a near visual acuity card held at 40 cm. If patients are older than 40 years of age, near vision usually requires bifocals (for persons using distance correction) or separate near-reading glasses (unless near sighted). The clinician must individually test each eye. If prescription glasses are unavailable, then the patient's uncorrected vision should be obtained and then tested again using over-the-counter readers (+1.25 to +3.00 D). For lens powers greater than +2.50 D, the near visual acuity card may need to be held closer than 40 cm for best focus.

Confrontation visual field testing is designed to detect gross field defects. The patient should be situated approximately 1 m from the clinician at equal eye level. The clinician then presents 1 or 2 fingers in each quadrant of the visual field. While the patient occludes 1 eye and maintains central fixation with the other, the clinician asks the patient to count the clinician's fingers, randomly shifting his or her fingers to include each sector of the visual field.

In patients complaining of diplopia, the clinician must confirm their visual experience as binocular (ie, with both eyes open in each field of gaze). Testing should then be repeated, with the patient closing each eye so that the clinician can document diplopia that abates. Typically, moderate and large deviations in ocular alignment can be detected on casual inspection; however, small misalignments are difficult to identify, and they may require special examination techniques.

The Amsler grid is used to screen for macular disease, and standard color plates (Hardy–Rand–Ritter or Ishihara) are valuable for the screening of optic neuropathies. These sensory tests are available in physical prints but are also available online (Amsler grid: http://development.aao.org/eyecare/conditions/macular-degeneration/amsler.cfm; color testing: http://colorvisiontesting.com). Both tests are presented individually to each eye and take less than 1 minute to complete.

Inspection of periocular tissues, eyelids, and the front surface of the eyes with good illumination are often sufficient to detect clinically important inflammation during a basic eye examination. Abnormalities of

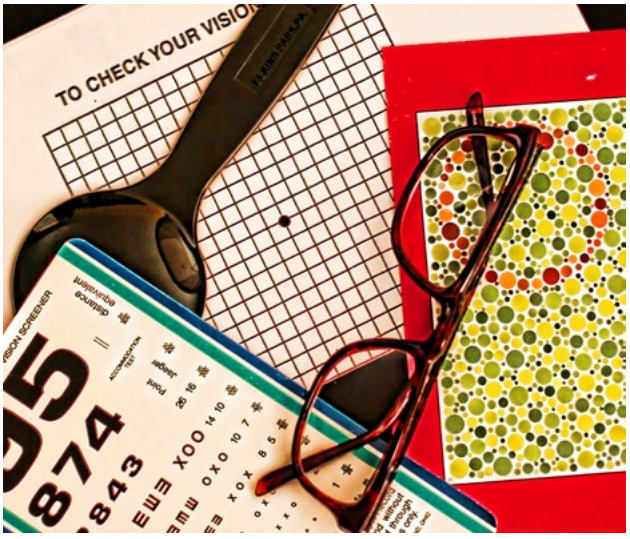

Fig. — Basic equipment for visual sensory testing includes an Amsler grid (top left), Ishihara color plates (bottom right), and a near vision card (bottom left). Visual stimuli are separately presented to each eye, making sure 1 eye is occluded. Over-the-counter +2.50 glasses (focal length 40 cm) may be needed for patients older than 40 years who have no reading glasses or bifocals without myopia.

the cornea can often be appreciated without magnification because the tissue lacks its normal luster and transparency. If available, 1 drop of sterile fluorescein dye will stain epithelial defects and enhance them when using a cobalt blue light filter.

A penlight can detect aberrations in the normal red light reflex seen through the pupil. Deviations are easier for the clinician to appreciate when they are unilateral and the patient's opposite eye serves as a control. Although fundamentals of a pupil examination (eg, size, shape, reactivity to light, presence or absence of a relative afferent pupillary defect) are beyond the scope of this article, characterizing pupil function is helpful when localizing injury to the visual pathway and for prioritizing special studies.

A penlight may also be useful for detecting small lesions of the eyelid such as petechial hemorrhages or abnormal position, but gross swelling or erythema of the eyelids can often be seen best under general illumination. New-onset proptosis is a rare complication of chemotherapy.[4,14] In a patient with cancer who is receiving chemotherapy, new-onset proptosis is more likely to be secondary to hemorrhage (bleeding diathesis or infection) or a rapidly expanding tumor.[28-30] Regardless of the cause, new-onset proptosis requires prompt evaluation. Subtle displacement of the eye in the orbit can be appreciated by viewing the patient from several feet away, looking for differences in symmetry and the relative amounts of visible sclera. Proptosis can be mimicked by enophthalmos of the opposite eye (eg, due to metastatic scirrhous breast carcinoma) or by lid ptosis.

An exception to the penlight detection of important

ocular inflammation can occur with uveitis, in which signs of external inflammation may be subtle. In this situation, symptoms of pain and photophobia, new-onset floaters, or evidence of decreased vision may be clues to more serious problems.

Clinicians not specializing in ophthalmology are not typically expected to pursue an eye examination beyond these tests because doing so usually requires use of special equipment (slit lamp, tonometer, ophthalmoscope).

Anticipated Complications

Few complications occur with sufficient regularity that some authorities recommend preventive measures to mitigate their occurrence (Table 6).[4,5,7,19-27,31-37] Examples of such complications include keratitis caused by cytarabine, ocular irritation from high-dose methotrexate, and canalicular and nasolacrimal duct stenosis after taking docetaxel.[19-25,27] Optimal strategies are not universally agreed upon, but most offer some benefit.[31,33,35,37]

Logistical Dilemma

Onset of new visual symptoms or other ocular complaints in patients receiving cancer treatment could represent an opportunistic infection, metastatic disease, or the coincidental occurrence or exacerbation of an unrelated eye disease. Some ocular or visual complaints arising in medically complex cases or in high-intensity medical care settings are neither vision-threatening nor have long-term adverse consequences. Most ocular-related complications of chemotherapy are rare,[1-7] so a clinical history and eye examination are usually required to distinguish treatment-related adverse events from common disorders of the eye, as well as to differentiate potentially serious from relatively unimportant problems. However, when patients cannot be examined at an eye clinic in a timely manner because of extenuating circumstances, screening for serious eye complications must be performed by their primary care physicians and oncologists.

Table 6. — Preemptive Strategies for Common Ocular-Related Adverse Events of Chemotherapy

Agent	Adverse Event	Strategy[a]
5-fluorouracil	Conjunctivitis (noninfectious)	Cool compresses Topical methylcellulose drops Topical corticosteroids[4,37]
Cyclophosphamide	Dry eyes	Artificial tear treatment[4,7]
Cytosine arabinoside	Keratitis	Topical corticosteroid drops started prior to treatment and tapered[33-36] Topical artificial tears[33-36] Topical 2-deoxycytine drops prior to therapy[33,36]
Docetaxel	Canalicular fibrosis Secondary epiphora	Temporary intubation of lacrimal puncta in patients with early symptoms[31]
Methotrexate	Keratitis Photophobia	Artificial tear treatment[32]

[a]The references cited discuss the relative merits of therapy and alternative strategies.

Conclusions

The potential ocular complications with the greatest likelihood of causing adverse outcomes present with demonstrable declines in visual function (eg, loss of central vision, loss of peripheral vision), symptoms and/or signs of oculomotor nerve palsy (eg, diplopia, loss of ocular alignment related to cranial nerves III, IV, or VI), or abnormalities detectable on penlight examination (eg, loss of red reflex; inflammation or swelling of the eyelids, conjunctiva, sclera; proptosis).[1-7,16-18] Correlating symptoms and basic clinical findings with previously reported treatment-related adverse events is the first step in identifying possible causative drugs.[1-7,16-18] Because causal associations with drug exposures usually involve the exclusion of other disease processes, it is likely that an ophthalmologic specialist will need to be involved in the diagnostic evaluation; however, the urgency of the consultation will be dictated by the results of screening.

For patients with suspected ocular complications related to cancer therapy who cannot be quickly seen at a specialty eye clinic, care must be expedited through communication with an ophthalmologist and include relevant ocular history findings, results of vision tests, and findings from the external eye examination.

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