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Complications of Treatment

Emerging toxicities in the treatment of non-small cell lung cancer: Ocular disorders ☆

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ABSTRACT

The treatment of advanced disease (stage IIIb and IV) of non-small cell lung cancer (NSCLC) is based on systemic treatment with platinum-based chemotherapy or biological compounds depending on the disease molecular profile. In the last few years, intensive investigational efforts in anticancer therapy have led to the registration of new active chemotherapeutic agents, combination regimens, and biological drugs, expanding choices for customizing individual treatment. However, the introduction of new drugs in the clinical setting has led to several new toxicities, creating some difficulties in daily management. Among these, ocular toxicity is generally overlooked as more common toxicities such as myelosuppression, stomatitis, diarrhea, vomiting, "hand–foot syndrome", and neurological alterations attract greater attention. Ophthalmic complications from cytotoxic chemotherapeutics are rare, transient, and of mild/moderate intensity but irreversible acute disorders are possible. The best way to prevent potential irreversible visual complications is an awareness of the potential for ocular toxicity because dose reductions or early drug cessation can prevent serious ocular complications in the majority of cases. However, given the novelty of many therapeutic agents and the complexity of ocular pathology, oncologists may be unfamiliar with these adverse effects of anticancer therapy. Although toxicities from chemotherapy are generally intense but short lasting, toxicities related to targeted drugs are often milder but longer lasting and can persist throughout treatment. Here we review the principal clinical presentations of ocular toxicity arising from chemotherapy [1–3], target therapies [4], and newly developed drugs and provide some recommendations for monitoring and management of ocular toxicity.

Introduction

The treatment of non-small cell lung cancer (NSCLC) is challenging, but several new targeted agents are emerging from the pipeline. At the same time, oncologists face the prospect of new types of adverse events, among them ocular toxicity. Although targeted agents are directed against aberrations in tumor cells, they are associated with toxicities affecting multiple organs, including the eye, as a result of target expression in ocular and eyelid tissue.

Ocular toxicity (Table 1) is generally underestimated and considered minor. Nevertheless, oncologists must be challenged to recognize clinical cases and understand how to manage them; it is also important that oncologists refer to the ophthalmologist when the complexity of clinical status require a specialistic evaluation. Some ocular toxicity (e.g., conjunctivitis) may be diagnosed during a normal physical examination whereas retinal damage requires a specialist ophthalmologic examination.

Ocular toxicities are grouped in the CTC-AE [5] for ocular toxicity, which mainly takes into account interference with the activities of daily living, as for other adverse events. However, while for chemotherapeutics, toxicities are generally short lived and the intensity can be considered a good marker for intervention, toxicities for targeting agents can be long lasting albeit of relatively mild intensity, and the existing systems for recording are not adequate for measuring patient unease.

At present, with new investigational agents with known preclinical ocular toxicity observed in animal models, clinical trials include specialist ophthalmologic visits; this is mandatory as part of many study protocol procedures.

Ophthalmological toxicities arising from chemotherapy

The ocular complications associated with cancer chemotherapeutics have been described in three major systematic reviews

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Table 1
Definitions of common ocular toxicity.

Toxicity	Definition
Blepharitis	Inflammation of the eyelids, mainly at the margin; main signs are redness and flaking of skin on the lids and crusting worse on waking
Central serous retinopathy	Localized serous retinal detachment observable only on fundoscopy; manifests as slightly blurry vision and the perception of objects smaller than they really are (micropsia)
Conjunctivitis	Inflammation and redness of the conjunctiva
Cystoid macular edema	Chronic inflammation of the macular area only observable on fundoscopy and confirmed by fluorescein angiography
Epiphora	Excessive tear production usually caused by eye irritation
Hemianopia	Visual field defect that respects the vertical midline in both eyes; it can be homonymous or bitemporal
Keratitis	Inflammation of the cornea, usually referring to the corneal surface (epithelium); manifests as pain, photophobia, and increased lacrimation, more evident in slit lamp examination with the aid of a dye
Periorbital edema	Inflammation and increased fluid accumulation of the interstitial tissues from the eyelid into the orbital septum; manifests as a hard swelling of the eyelids
Photopsia/ photophobia	Ocular pain and sensitivity to light
Trichomegaly	Pathologically long eyelashes that can get misdirected and cause ocular surface abrasions
Uveitis	Inflammation of the uveal tract; it can be anterior (involving the anterior chamber and iris) or posterior (involving the vitreous and choroid)

[1–3], but none has specifically focused on NSCLC patients. Here we review only toxicities related to approved chemotherapeutics for NSCLC and that are commonly used by oncologists in their daily clinical practice, referring both to the adjuvant and to the metastatic setting.

Cisplatin is a heavy metal compound and the cornerstone of several antitumor therapies. All the main clinical guidelines (American Society of Clinical Oncology (ASCO) [6] and European Society of Medical Oncology (ESMO) [7]) recommend a first-line cisplatin-based chemotherapy as the treatment of choice in the advanced and adjuvant setting. Drugs that may be combined with platinum include the third-generation cytotoxic drugs docetaxel, gemcitabine, irinotecan, paclitaxel, pemetrexed, vinorelbine and etoposide (just for small-cell lung cancer). Neurotoxicity represents the major dose-limiting toxicity of cisplatin. The neuropathy is uncommon below a cumulative cisplatin dose of 400 mg/m^2 but nearly universal in the cumulative-dose range of 600–800 mg/m^2. The cumulative dose that causes peripheral neuropathy tends to be higher in children and younger patients than in the elderly and the risk of neurotoxicity is higher in patients with renal dysfunction [8–10]. Visual impairment has been considered an infrequent form of cisplatin neurotoxicity. Case reports have attributed visual alterations to optic neuritis and cortical blindness, which have sometimes been accompanied by seizure activity [11–14]. Ocular toxicity has generally been reported after the use of regimens with higher doses or greater dose frequencies than those recommended by the manufacturer. Improvement and/or total recovery usually occurs after discontinuation of cisplatin [15]. An alert of possibly cisplatin-induced retinal ischemia was reported by Kwan in 2006 [16].

Intravenous administration of **carboplatin** is less frequently associated with ocular disturbances, and a few cases of maculopathy, optic neuropathy, cortical blindness, sore eyes, blurred vision, and chorioretinitis to optic neuritis have been reported [17–19]. In any case, visual disturbances were reversible after drug cessation.

Pemetrexed is an antifolate chemotherapeutic agent. The antitumor activity of this agent likely derives from inhibition of several key folate-requiring enzymes, including thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyltransferase. The drug is currently approved for the treatment of pleural mesothelioma combined with a platinum compound and for first- and second-line therapy in advanced NSCLC with non-squamous histology. The only well-known drug-related ocular adverse event is conjunctivitis, also a common adverse effect of other antimetabolite antineoplastic agents such as cytosine arabinoside, 5-fluorouracil, and methotrexate [20,1,21]. This disturbance is generally associated with hyperemia, irritation, and serous secretions. It has been reported in less than 5% of mesothelioma-naïve patients who were randomly assigned to receive cisplatin in combination with pemetrexed or single-agent cisplatin, with the same incidence in the two arms. Another case has been documented in which a patient received pemetrexed as third-line therapy for NSCLC advanced disease and developed conjunctivitis; this was a cutaneous adverse event that consisted of the simultaneous occurrence of periorbital edema, conjunctivitis, and inflammatory edema of the upper and lower limbs [22].

Several prophylactic approaches have been investigated in the prevention of antimetabolite-induced conjunctivitis. Matteucci et al., [23] investigated in a randomized trial the efficacy of dexamethasone in combination with diclofenac eye drops as prophylaxis for conjunctivitis induced by high-dose cytosine arabinoside. They concluded that the combination of dexamethasone/diclofenac therapy compared with dexamethasone alone significantly prevented drug-induced conjunctivitis (incidence 13% *vs.* 45% respectively; $p \leqslant 0.09$). Treatment of drug-induced conjunctivitis usually involves the use of artificial tears, withdrawal of the agent wich determined the toxicity, and a short course of topical steroids, and is typically curative [1,21], even though, most of the time, the conjunctivitis is recurrent despite symptomatic treatment. Steroideal therapy (topical or systemical) should be administered only if a possible infectious has been eliminated.

Gemcitabine has structural similarities to the other antimetabolite chemotherapeutic drugs so that ocular toxicities cannot be completely excluded. The drug is currently approved for the treatment of advanced disease and commonly used in the locally advanced and metastatic settings. Only one case of a drug-related visual serious adverse event has been reported,identified as a Purtscher retinopathy [24]. This is a rare syndrome characterized by the appearance of a vaso-occlusive retinal injury and concomitant presence of cutaneous vasculitis; this retinopathy was associated with digital necrosis and antinuclear antibody elevation. Another case report [25] of gemcitabine-induced retinopathy in a diabetic patient presented with retinal changes that included aneurysms, cotton-wool spots, intraretinal hemorrhages, and vascular leakage on fluorescein angiogram; clinical improvement after gemcitabine withdrawal and relapse of retinopathy from re-exposure strongly suggested gemcitabine to be causative of the disorder.

Docetaxel is an effective chemotherapeutic agent that is widely used in the treatment of locally advanced and metastatic NSCLC. Canalicular and nasolacrimal duct obstruction possibly due to stromal fibrosis are well-known ocular side effects of docetaxel [26]. Epiphora due to canalicular stenosis in patients treated with weekly docetaxel was first reported by Esmaeli et al., [27]. Nasolacrimal duct obstruction secondary to treatment with docetaxel may be partly due to stromal fibrosis in the mucosal lining of the lacrimal