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The Evaluation of Ocular Toxicity of Chemotherapy Drugs

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Abstract

Cancer continues to pose a substantial global health burden and remains one of the leading causes of mortality worldwide. Encouragingly, survival rates have consistently improved, largely due to advancements in diagnosis and treatment. The development of anticancer drugs, including cytotoxic chemotherapy, hormonal agents, and targeted therapies, has significantly enhanced the efficacy of cancer treatments.

Chemotherapy-induced ocular toxicity encompasses a wide range of disorders, influenced by the eye's unique anatomical and physiological characteristics. The mechanisms of these drugs can lead to systemic and ocular side effects, including cytotoxicity, inflammation, and neurotoxicity. While ocular side effects from targeted therapies are less common, they can be severe, disabling, and potentially irreversible. In some cases, immediate discontinuation of the drug may be necessary to prevent vision-threatening complications.

Understanding these ocular side effects is crucial for early recognition and intervention by ophthalmologists and oncologists to prevent blindness. Additionally, anticipating treatment-related toxicities enables pharmacists to develop strategies that minimize or mitigate these side effects.

This review focuses on the ocular toxicity associated with the most significant anticancer chemotherapeutic agents.

Keywords: Chemotherapy, Cyclophosphamide, Ocular, Tamoxifen, Toxicity

Introduction

Cancer is a class of disorders defined by the body's aberrant and uncontrollably dividing cells. These cancerous cells have the capacity to spread to different tissues or organs from their original location (1-4). An estimated 38.4% of people are expected to receive a cancer diagnosis at some point in their lives, according to the US National Cancer Institute (5). Patients and their families bear severe financial and psychological costs as a result (6). Despite these obstacles, improvements in diagnosis and treatment have led to a noteworthy 20% increase in survival rates over the past three decades (5- 7). Cancer treatment commonly involves a combination of approaches, including tumor-removal surgery, hormonal agents, anticancer medications, and radiation therapy. Tumors can be removed surgically, whereas radiotherapy uses ionizing radiation to shrink tumors and kill cancer cells. Anticancer medications either increase the cytotoxicity of cancer cells or block specific pathways necessary for cancer progression. These medications are integral to cancer therapy, either as standalone treatments or in combination. However, cytotoxic anticancer drugs target rapidly dividing cancer cells, and they can also damage healthy cells, particularly in the vascular, neurological, immune, and muscular systems. Additionally, the delicate balance of the ocular surface is vulnerable to chemotoxicity, leading to inflammatory, neurological, and cytotoxic effects (7).

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Although some studies have reviewed the ocular surface side effects, understanding the underlying mechanisms remains limited. In addition, due to high prevalence of cancer in our country (3), it is necessary to review such a study, therefore, this study aims to investigate ocular toxicity of chemotherapy drugs.

Anticancer drug

Cancer therapies can be broadly divided into three categories: (1) hormonal agents; (2) conventional cytotoxic chemotherapy, which causes cell death and reduces tumor burden by interfering with DNA synthesis and cellular division; and (3) the more recent molecularly targeted therapies, which are more precisely designed to target specific cellular functions in cancer cells rather than normal cells. Molecularly targeted therapies have become integral in systemic treatments across various cancer types, operating through mechanisms distinct from traditional cytotoxic chemotherapy by targeting cellular signaling and angiogenesis pathways crucial for tumor growth (7). In this article, we aim to explain the ocular side effects of the most important chemotherapy drugs.

Cyclophosphamide

Cyclophosphamide is used alone or in combination with other anticancer drugs to treat leukemias, malignant lymphomas, and various solid tumors, including breast cancer, testicular cancer, small cell lung carcinoma, neuroblastoma, and Ewing's sarcoma. Patients receiving cyclophosphamide, particularly those with breast cancer, may experience ocular symptoms such as dry eyes (keratoconjunctivitis sicca), inflammation of the eyelids and conjunctiva (blepharoconjunctivitis), and reversible excessive tearing (8, 9).

Ifosfamide

Ifosfamide is a chemotherapy medication utilized to treat various cancers such as bladder cancer, ovarian cancer, small cell lung cancer, and osteosarcoma. Certain patients have noted occurrences of visual disturbances and conjunctivitis as side effects (8).

Busulfan

Busulfan, an alkylating agent with myeloablative properties, inhibits DNA replication by inducing DNA crosslinking, leading to cell apoptosis. It is employed as a preparative regimen before hematopoietic stem cell transplantation due to its cytotoxic effects on host hematopoietic stem and progenitor cells. Busulfan infusion has been linked to dry eyes (keratoconjunctivitis sicca) in patients undergoing treatment for chronic myeloid leukemia and other myeloproliferative disorders (9, 10).

5-Fluorouracil (5-FU)

5-Fluorouracil, also known as 5-FU, is a chemotherapy drug used to treat various cancers. It is FDA-approved for gastric adenocarcinoma, pancreatic adenocarcinoma, breast adenocarcinoma, and colorectal adenocarcinoma. 5-FU functions by inflicting damage to DNA, especially the p53 gene, which is essential for controlling the course of the cell cycle and the response to DNA damage. More than 50% of colorectal cancers, the p53 gene is overexpressed. Ocular side effects associated with 5-FU include blurred vision, swelling around the eyes, eye pain, sensitivity to light, excessive tearing, conjunctivitis, eyelid inflammation, corneal inflammation, scar formation on the eyelid, eyelid adhesion, and rarely narrowing of the tear ducts. A study reported that half of the patients using 5-FU developed defects in the outer layer of the cornea, which resolved after several weeks (8, 10). In a separate study, the estimated prevalence rates of ocular surface lesions associated with systemic 5-fluorouracil use were reported as follows: ocular irritation, 5.8%; conjunctivitis, 3.8%; keratitis, 3.8%; tearing, 26.9%; and blurred vision, 11.5% (11).

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Capecitabine

Capecitabine, utilized in the treatment of colorectal cancer, gastric cancer, and breast cancer, frequently in combination with docetaxel, has been associated with adverse effects on the ocular surface. These side effects encompass reduced vision clarity, corneal deposits, eye discomfort, narrowing of the tear ducts, inflammation of the conjunctiva, and inflammation of the eyelids (12).

Interferon

Interferon is a chemotherapeutic medication used to treat renal cell carcinoma, non-Hodgkin's lymphoma, malignant melanoma, multiple myeloma, and chronic myelogenous leukemia (13), and is also widely employed in the management of chronic hepatitis. Ocular complications such as cotton wool spots and splinter hemorrhages in the retina were noted in 42% of patients receiving interferon. Earlier research indicated that retinal hemorrhages were found in 24% of patients, and among these cases, 66% also exhibited cotton wool spots. These retinal findings typically resolve gradually with treatment cessation. Additionally, one case study documented the development of vitiligo in a patient during the eighth week of interferon alpha-2a therapy for active chronic hepatitis C (13). Interferon is known to cause retinopathy. This condition typically presents with retinal hemorrhages and cotton wool spots in the posterior fundus, although it generally preserves visual function. However, there is a risk of macular edema, which can lead to decreased visual acuity in some cases. Patients with cancer who are asymptomatic may also develop ischemic retinopathy produced by interferon. Many times, these alterations in the retina are reversible when interferon medication is stopped. Therefore, regular dilated fundoscopy is essential at baseline and during follow-up, ideally every three months, for all cancer patients undergoing interferon treatment to promptly detect any signs of retinal toxicity (11).

Cytarabine

Cytarabine is a medication used in the management and treatment of leukemias and lymphomas, belonging to the antimetabolic group of medications. This review explores its indications, action, and contraindications, focusing on its role as a crucial agent in treating acute myeloid leukemia and other leukemias. The mechanism of action, adverse event profile, and other key considerations (including off-label uses, dosing, pharmacodynamics, pharmacokinetics, monitoring, and relevant interactions) relevant to healthcare professionals involved in leukemia treatment are highlighted (14). The main adverse effect of cytarabine is hematologic toxicity, which can range in severity based on dosage and treatment regimen. High doses (3 g/m^2) of systemic cytarabine in leukemia patients have been associated with corneal toxicity. Specifically, patients have reported painful keratitis with fine opacities in the corneal epithelium shortly after starting treatment, which typically resolves within a week after stopping the medication. Moreover, two leukemia patients in remission experienced significant bilateral vision loss following combined chemotherapy, CNS irradiation prophylaxis, and intrathecal cytarabine administration (14).

Methotrexate

Methotrexate (MTX) is an anticancer medication used to treat various malignant diseases. It functions as a therapeutic agent for treating both cancers and autoimmune conditions, acting through chemotherapy and immunosuppression (13). In addition, it can be administered orally or through injection and acts by blocking the action of dihydrofolate reductase, leading to a reduction in purine

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and thymine nucleotides. This inhibition disrupts DNA, RNA, and protein synthesis, primarily affecting cells in the S phase of the cell cycle and particularly targeting rapidly dividing cells (13). Ocular complications associated with MTX use include reduced tear production, changes to the optic nerve and retina, conjunctivitis, sensitivity to light, development of cataracts, and excessive tearing (10).

Pemetrexed

When treating advanced or metastatic non-small cell lung cancer, pemetrexed is given intravenously (15, 16). It can also be used in conjunction with cisplatin to treat malignant pleural mesothelioma that is incurable. Research has shown that 1% to 5% of individuals may encounter heightened tear production and may develop eye surface issues like conjunctivitis as adverse effects of pemetrexed (16).

Suramin sodium

By inhibiting some autocrine growth factors, suramin sodium is used to treat adrenocortical carcinoma and metastatic prostate cancer (8). Ocular side effects associated with this medication include sensitivity to light, swelling of the conjunctiva, swelling of the eyelids, inflammation of the iris, optic nerve damage, and a specific type of corneal opacity (9, 10). According to research by Hemady et al., 16.6% of patients treated with suramin sodium developed eye-related symptoms, with 11.4% experiencing bilateral corneal deposits resembling whirls, along with sensations of having a foreign body in the eye and increased tear production. These symptoms improved with the use of lubricating eye drops. Furthermore, 6.2% of patients experienced a change towards farsightedness (13).

Mitomycin C

Systemically, mitomycin C is utilized for a variety of small tumors by inhibiting carbonic anhydrase and ATPase in cells (13). When combined with other agents, it may offer palliative benefits for patients with breast, gastric, or pancreatic carcinomas (8). However, topical application of mitomycin C can lead to serious ocular complications (13). Systemic administration of mitomycin C has been associated with blurred vision. Rubinfeld et al. documented several cases of severe vision-threatening complications following the use of mitomycin C eye drops after pterygium surgery. Ocular side effects included intense pain, photophobia, severe secondary glaucoma, corneal edema and perforation, scleral calcification, and sudden onset of cataract. These cases suggest that certain pre-existing conditions or high cumulative dosages may elevate the risk of corneal or scleral ulceration. Delayed epithelial healing and reduced vascularity of the sclera and cornea are potential explanations for the ocular toxicity associated with this medication (8).

Taxanes

Taxanes are widely used chemotherapy agents for various solid malignancies, functioning as microtubule inhibitors that induce cell cycle arrest and activate apoptosis. They are essential in treatment regimens for breast, ovarian, non-small cell lung, and head and neck cancers (17).

Ocular side effects linked to taxanes include conjunctival and eyelid pain, dry eye (18, 19), epiphora, CME, and optic neuropathy (20), nasolacrimal and lacrimal duct obstruction (18, 21), erosive conjunctivitis, punctate keratopathy (22), corneal lesions (23), chalazion, and chalazion, corneal disorders (24), and limbal stem cell deficiency (18). Taxanes rarely affect intraocular tissues like the lens and vitreous. Kuwata et al. (25) found that injecting paclitaxel into newborn rats

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led to apoptotic changes in lens epithelial cells and degeneration of lens fibers within seven days (18). Taxane-induced macular edema usually presents with impaired visual acuity. Kaya et al. (26) studied 202 patients on taxane-based therapy and identified cystoid macular edema (CME) in one patient treated with paclitaxel, resulting in a total incidence of 0.5% (1 out of 202) (18). Docetaxel and paclitaxel are key members of the taxane class used to treat various cancers. Studies (27-29) indicate that docetaxel is effective for gastric, prostate, non-small cell lung, head and neck cancers, and locally advanced breast cancer. Research has also shown nasolacrimal canaliculus occlusion in breast cancer patients receiving docetaxel (30-32), with weekly docetaxel treatment associated with higher rates of excessive tearing (33).

Temozolomide

Temozolomide, an alkylating agent approved for melanoma, anaplastic astrocytoma, and glioblastoma, has good penetration across the blood-retinal barrier and generally exhibits a favorable side-effect profile. No ocular toxicity has been noted (34).

Rituximab

Rituximab is used to treat refractory rheumatoid arthritis, chronic lymphocytic leukemia (the most common adult leukemia), and non-Hodgkin's lymphoma (either alone or in combination with other therapies).

It targets the surface-presented CD20 antigen on B-cells. It is also prescribed in the US for diseases such acute B-cell leukemia in children, pemphigus vulgaris, certain vasculitides, and Burkitt's lymphoma (35). Ocular adverse effects that may arise from taking Rituximab include burning in the eyes, lacrimation, conjunctivitis, and in rare cases, loss or impairment of eyesight (9).

Venetoclax

Venetoclax inhibits the BCL-2 protein, promoting apoptosis via mitochondrial pathways. It is mainly used for hematological malignancies, particularly acute myeloid leukemia. Its primary side effects are myelosuppression and tumor lysis syndrome, with no documented ocular side effects (34).

Cetuximab

The monoclonal antibody cetuximab is approved for the treatment of metastatic colorectal cancer, metastatic non-small cell lung cancer, and metastatic head and neck cancer. It targets the epidermal growth factor receptor (EGFR), which is typically overexpressed in cancer cells. It functions by preventing the spread and growth of tumors. Patients receiving cetuximab for colorectal cancer treatment have reported experiencing bilateral corneal erosions (36).

Bevacizumab

Bevacizumab, a monoclonal antibody that blocks vascular endothelial growth factor (VEGF), is employed alongside other anticancer medications for treating metastatic colorectal cancer, metastatic non-small cell lung cancer, advanced renal cell carcinoma, stage IV glioblastoma, relapsed or metastatic cervical cancer, and advanced hepatocellular carcinoma (37). Although ocular hyperemia has been noted on the surface of the eye, the more critical concerns involve adverse effects affecting the posterior segment of the eye (9, 37).

Doxorubicin

Doxorubicin, an anthracycline antibiotic (38-43), is often used in combination with other chemotherapy agents to treat various cancers such as ovarian cancer, non-Hodgkin's lymphoma, sarcoma, breast cancer, and acute leukemia. Ocular surface effects commonly linked to doxorubicin treatment include conjunctivitis and excessive tearing (epiphora) (44). Research indicates that ocular side effects

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related to intravenous doxorubicin are infrequent, with only a small percentage of patients experiencing symptoms like increased tearing and conjunctivitis (8).

Mitotane

Mitotane is the sole approved medication for managing advanced adrenocortical carcinoma and for postoperative adjuvant therapy. Its primary action involves destroying the adrenal cortex, which disrupts steroid hormone production, although the precise molecular mechanism remains uncertain. Nonetheless, certain confounding factors in in vitro experiments might diminish the applicability of specific studies (45). Ocular adverse effects are rare but can include impaired vision, diplopia, lens opacities, toxic retinopathy with papilledema, and retinal hemorrhage. Systemic side effects are common in patients receiving mitotane (14).

Tamoxifen

For the majority of instances of metastatic breast cancer, tamoxifen, an estrogen antagonist, is seen to be the best course of action. By decreasing the number of cytoplasmic receptors and causing competitive inhibition at the receptor location, it prevents estradiol from attaching to its intended tissues. Studies reported on two patients who took 30 mg of tamoxifen every day for nine to fourteen months, developing retinopathy and temporary vision impairment.

In addition, 4 out of 63 patients receiving 20 mg of tamoxifen daily (total dose of 14.4 gm) with a median treatment period of 35 months showed signs of impaired visual acuity, bilateral macular edema, retinal yellow-white spots, and corneal opacities. With the exception of retinal opacities, all ocular abnormalities were shown to be reversible upon stopping medication. According to finding of one study, two patients receiving low-dose tamoxifen experienced bilateral optic neuritis and retinal hemorrhage. These anomalies were observed three weeks after the start of therapy and went away entirely when the tamoxifen (8) was stopped. Furthermore, there are notable adverse effects of tamoxifen on the optic nerve, retina (retinopathy), and lens (cataracts) (9).

Plant alkaloids

Vinca alkaloids, such as vincristine, vinblastine, vindesine, and vinorelbine are widely used in oncology as antineoplastic drugs, either alone or in combination with polychemotherapy. These agents exert their cell cycle-dependent action by inhibiting tubulin polymerization into microtubules. Ocular toxicity associated with these plant alkaloids includes cranial nerve palsies, optic neuropathy and atrophy, cortical blindness, and night blindness. A recent study demonstrated optic neuropathy in three patients after a cumulative 48 mg dose of vincristine, presenting with poor visual acuity and optic disc pallor. One case of bilateral optic atrophy resulted in blindness. Additionally, night blindness was observed in a melanoma patient, and transient cortical blindness occurred in three children treated for leukemia (8). Vincristine and vinblastine work by blocking metaphase and disrupting the mitotic spindle. These medications are usually given through intravenous administration and are advised to be used alongside other anticancer drugs for conditions such as Hodgkin's disease, non-Hodgkin lymphomas, Ewing's sarcoma, malignant melanoma, neuroblastomas, and rhabdomyosarcomas. The likelihood of neurotoxic effects increases with the dosage administered (9).

Melphalan

Nitrogen mustard's phenylalanine derivative is melphalan, sometimes referred to as L-phenylalanine mustard. Melphalan is a bifunctional alkylating agent that exhibits activity against specific types of human cancers. It has FDA

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approval for nonresectable ovarian epithelial carcinoma and multiple myeloma palliative therapy (44). Melphalan hydrochloride intravitreous injections are becoming more widely used in the treatment of vitreous seeding of retinoblastoma. These injections can cause retinal abnormalities as well as toxic effects on the anterior segment of the eye. They also seem to occur more frequently in the injection meridian where the drug concentration is highest (45).

Cisplatin

Cisplatin is a chemotherapy drug (46-55). It is a chemical containing heavy metal that has been used for a long time to treat non-Hodgkin lymphoma, upper gastrointestinal malignancies, testicular, lung, and ovarian cancer. It can be administered intravenously or intratracheally, and it is frequently used in conjunction with other chemotherapeutics such paclitaxel, docetaxel, cyclophosphamide, 5-fluorouracil, and Carmustine (BCNU). Since cisplatin is known to cause neurotoxicity, reports of high dose and cumulative dosage regimens have included cases of nonspecific impaired vision, papilledema, unilateral and bilateral retrobulbar neuritis, and optic neuritis. High-dose intravenous regimens are more likely to cause transient cortical blindness, transient homonymous hemianopsia, and retinal pigmentary alterations. However, all of these toxicities are reversible, except the pigmentary alterations (56).

Oxaliplatin

Palliative care for testicular cancer, advanced colon and rectal cancer, recurrent non-Hodgkin's lymphoma, advanced ovarian and esophageal cancer, and metastatic or locally advanced pancreatic cancer are among the conditions for which oxaliplatin is used. Research has pinpointed hyperlacrima, conjunctivitis, reduced visual acuity, and visual field constriction as potential eye-related adverse effects linked with this medication (8).

Fludarabine

Fludarabine, used for lymphoproliferative disorders, rarely causes ocular toxicity. However, opportunistic eye infections and varicella-zoster virus reactivation involving acute retinal necrosis have been reported (34).

Obinutuzumab

Obinutuzumab may have more adverse effects than rituximab due to a stronger cytokine release, including higher rates of neutropenia and severe infections; though no significant ocular side effects have been observed (34).

Conclusion

Ocular toxicities induced by chemotherapeutic agents are typically unavoidable; hence, clinicians should remain vigilant regarding potential vision-threatening complications. Timely consultation with an ophthalmologist can facilitate early detection, accurate diagnosis, and appropriate therapeutic interventions. Adjusting the dosage or discontinuing implicated drugs may mitigate the severity and duration of side effects. Therefore, healthcare professionals treating cancer patients should be aware of the potential ocular and visual side effects of common chemotherapeutic drugs. More research is needed to understand the mechanisms behind these ocular side effects, as current studies often do not explore this fully.

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