Journal of
Cancer Therapeutics & Research

HOAJ
Herbert Open Access Journals

Database Open Access

Ocular adverse effects of anti-cancer chemotherapy and targeted therapy

Parul Singh[1*] and Abhishek Singh[2#]

Abstract

Systemic anti-cancer therapies can produce acute and chronic organ damage. Ocular toxicity induced by anti-cancer chemotherapy is not uncommon, but underestimated and under-reported. The development of more aggressive regimens, use of newer agents and combination chemotherapies have resulted in a significant increase of reported cases of chemotherapies induced ocular side effects. Visual changes have been attributed to a number of chemotherapeutic agents such as antimetabolites, alkylating agents, taxanes and platinum agents. In addition to the eye itself, structures of the skin including the eye lids may be affected. Ocular toxicities induced by chemotherapeutic agents are generally not preventable; therefore clinicians must be aware of potential vision threatening complications. Prompt consultation with an ophthalmologist can lead to early detection, proper diagnosis and appropriate therapeutic measures. Dose reduction or discontinuation of incriminated drugs may help in reducing severity and duration of side effects. An ophthalmologist should be part of team caring for patients undergoing systemic chemotherapy for baseline examination and ongoing assessment. Baseline examination will help to diagnose adverse effects caused later due to chemotherapeutic agents and; diagnose any pre-existing conditions, especially in elderly patients. It is easy to miss association between chemotherapy and visual changes. This article document ocular changes that are believed to be related to the administration of certain chemotherapeutic agents.

Correspondence: parulophtha@gmail.com, hivneg@gmail.com

[1] Department of Ophthalmology, V.C.S.G.G.M.S & R.I., Srinagar Garhwal, Uttarakhand, India.

[2] Department of Radiotherapy and Clinical oncology, V.C.S.G.G.M.S & R.I., Srinagar Garhwal, Uttarakhand, India.

Introduction

Systemic anti-cancer therapies can produce acute and chronic organ damage. Bone marrow suppression, hepatic, pulmonary, cardiac, renal and gastrointestinal toxicities of chemotherapeutic agents used in treating cancer patients are well known. The development of more aggressive regimens as well as newer agents and combination chemotherapies have resulted in significant increase of reported cases of chemotherapy induced ocular side effects.

Besides this, patients undergoing chemotherapy may develop ocular problems due to other conditions, as in metastases to the eye or central nervous system. Metastases to eye can come from primaries of breast, lung, gastro-intestinal, melanoma, prostate, and kidney. Radiotherapy, when used with chemotherapy, may also contribute to ocular problems in patients treated with concurrent chemo-radiotherapy.

The increased use of chemotherapeutic agents has resulted in longer cancer patient survival. Consequently, the ophthalmologist is seeing more patients with adverse ocular side effects secondary to these antineoplastic agents. Ocular toxicity induced by cancer chemotherapy includes a broad spectrum of disorders reflecting the unique anatomical, physiological and biochemical features of the eye.

Combination chemotherapy regimens may make it difficult to attribute ocular toxicity to a particular drug. Infrequent and under-reporting of ocular adverse effects exists and literature consists mainly of case reports. This article reviews and lists commonly used cancer chemotherapeutic agents along with their ocular side effects.

1. Alkylating agents - Alkylating agents have the cytotoxic ability to substitute hydrogen atoms in certain organic compounds by alkyl groups. They include platinum complexes, nitrogen mustard derivatives, alkyl sulphonates and nitrosoureas.

A. Platinum complexes

(I) Cisplatin: Cisplatin, a heavy metal compound, is an established drug for treatment of head and neck, lung, cervical, ovarian and testicular cancer, upper gastrointestinal malignancies, osteogenic sarcoma, neuroblastoma, recurrent brain tumors in children, and urinary bladder cancer. Cisplatin is known to produce non-specific blurred vision, papilledema [1]. Unilateral as well as bilateral retrobulbar neuritis and optic neuritis have been reported for high doses as well as cumulative dose regimens [2]. Transient cortical blindness [3-5], temporary homonymous hemianopia [6,7] and macular pigmentary changes more likely to occur at high-dose intravenous regimens. Wilding *et al* reported 13 women who were treated with high cumulative doses of cisplatin for ovarian tumors. Blurred vision in eight patients, decreased color vision in three patients, irregular pigmentation in the macula in six patients and cone dysfunction on electro-retinogram (ERG) in nine patients were documented [8]. Another case reported a 55 year old man, who received cisplatin as salvage regimen for non-hodgkin's lymphoma, developed bilateral irreversible visual loss with visual field showing central scotoma bilaterally [9]. Intra-carotid administration of cisplatin has led to severe ocular and orbital toxicity like ipsilateral retrobulbar

neuritis [10,11]. Few cases of central retinal artery occlusion, leading to ipsilateral visual loss from severe retinal or optic nerve ischemia were also reported [12]. After supra-ophthalmic infusion of cisplatin, a single case of uveal effusion with exudative retinal detachment, enlarged recti muscles and inflammation of surrounding soft tissue has been reported [13].

(II) Carboplatin: Carboplatin is used as treatment primarily for lung cancer, head and neck cancer, ovarian cancer, breast cancer, gastro-intestinal cancers and osteogenic sarcoma. Carboplatin may cause maculopathy and optic neuropathy, weeks after intravenous administration [14,15]. Intra-carotid therapy can cause severe ocular and orbital toxicity [16]. Sub-tenon injection of carboplatin has been associated with limitation of ocular motility [17].

(III) Oxaliplatin: Oxaliplatin is third generation 1,2 diaminocyclohexane platinum derivative, used mainly for colon, recurrent or metastatic esophageal cancer, locally advanced or metastatic pancreatic cancer, recurrent epithelial ovarian, relapsed or refractory non-hodgkin's lymphoma and palliative treatment of testicular cancer. Leonard and co-workers conducted a survey to evaluate neurotoxicity secondary to oxaliplatin therapy [18]. Eighty-six patients with metastatic colorectal cancer reported blurred vision, eye pain, and visual field cuts. Besides this, low rate of visual disturbances, including tearing, conjunctivitis and abnormal lacrimation was also reported in trials [19].

B. Nitrogen mustard derivatives:

(I) Chlorambucil: Chlorambucil is indicated in adult hodgkin's disease, adult follicular non-hodgkin's disease and adult chronic lymphocytic leukemia. Keratitis was the most common side effect observed. A single case treated for nephrotic syndrome has been reported to develop diplopia, bilateral papilledema and retinal hemorrhages [20].

(II) Cyclophosphamide: Cyclophosphamide is used in treatment of many malignancies including breast cancer, lymphomas and leukemias, retinoblastoma, small cell lung cancer, ovarian cancer, sarcomas and multiple myeloma. Blurred vision, kerato-conjunctivitis sicca, blepharo-conjunctivitis and pin point hemorrhages have been reported as its ocular adverse effects [21,22]. A case of irreversible lacrimal duct stenosis in a women receiving adjuvant chemotherapy for early stage breast cancer was reported, while four other patients developed reversible epiphora [23].

(III) Ifosphamide: This drug is used in the treatment of soft tissue sarcoma, osteosarcoma, non-hodgkin's lymphoma, small cell lung cancer, ovarian, testicular and cervical cancer. Blurred vision and florid conjunctivitis has been reported [24].

C. Alkyl sulphonates:

(I) Busulphan: Busulphan is used for chronic myeloid leukemia and other myeloproliferative disorders. The most common ocular side effect is posterior sub-capsular cataract [25]. Non-specific blurred vision and kerato-conjunctivitis sicca may also occur after busulphan infusion[20].

D. Nitrosoureas:

(I) Carmustine: It is mainly used as treatment for brain neoplasms, palliative treatment of multiple myeloma, refractory or relapsed hodgkin's and non-hodgkin's lymphoma, cutaneous T-cell lymphoma and metastatic malignant melanoma. There have been several reports of ocular toxicities associated with their use. One patient with myeloma on carmustine therapy developed bilateral acute optic neuro-retinitis [26]. Loss of depth perception and blurring of vision was reported in two patients (out of 31 patients) with breast cancer treated with carmustine with adriamycin [27]. Several other cases of retinopathy, progressive blindness with diplopia, blurred vision, retrobulbar pain, optic neuritis and optic atrophy has also been reported [20,28,29]. A case of decreased visual acuity due to marked retinopathy with hemorrhages, exudates and retinal infarcts has been reported [30]. Shingleton *et al* evaluated 50 patients for ocular toxicity who received systemic high-dose intravenous BCNU alone. One patient developed counting fingers vision with a fundus picture, consistent with central retinal artery occlusion [31].

2. Antimetabolites

A. Pyrimidine analogs:

(I) Cytosine arabinoside: Cytosine arabinoside interferes with DNA synthesis by inhibiting DNA Polymerase enzyme. It is used for treatment of acute myeloid leukemia, acute lymphocytic leukemia, lymphomatous meningitis and during blast crisis of chronic myeloid leukemia. Numerous ocular side-effects such as ocular pain, tearing, foreign body sensation, photophobia, blurred vision with evidence of bilateral conjunctival hyperemia and fine corneal punctate opacities have been reported [32,33]. After intrathecal injection of cytosine arabinoside, severe visual loss due to optic neuropathy has been reported [34].

(II) 5-Fluorouracil (5-FU): 5-FU is an established anti-cancer agent used in skin, head and neck, breast, gastro-intestinal and cervical cancer. The ocular adverse effects reported include blurred vision, ocular pain, photophobia, excessive lacrimation, eye irritation, conjunctivitis, circumferential edema, ectropion and keratitis [35]. The topical use also impairs corneal and conjunctival re-epitheliazation [36]. A case of irreversible lacrimal duct stenosis was reported by Stevens *et al* in a women receiving adjuvant chemotherapy for early stage breast cancer [37]. Brink and Beex reported 18 patients, who received prolonged high doses of 5-FU and developed canalicular fibrosis leading to permanent intractable epiphora [38].

(III) Capecitabine: Capecitabine is a prodrug of 5-fluorouracil and shares its toxicities with it. It is used for treatment of metastatic breast cancer, colon cancer, and advanced gastric carcinoma. Waikhom *et al* reported two cases with ocular irritation, decreased vision and corneal deposits [39].

B. Folic acid analogues:

(I) Methotrexate: Methotrexate is a folic acid antagonist used in breast cancer, choriocarcinoma, osteogenic sarcoma, acute

leukemia, advanced mycosis fungoides (cutaneous lymphoma) and head and neck cancer. The ocular toxicities caused by methotrexate consists of peri-orbital edema, ocular pain, blurred vision, photophobia, conjunctivitis, blepharitis and decreased reflex tear secretions [20]. When methotrexate is administered by intrathecal route as in acute leukemias, optic neuropathy and internuclear ophthalmoplegia can develop and, this can be potentiated by concurrent cranial irradiation usually used in such cases [40, 41]. Intra-carotid administration of methotrexate in combination with intravenous cyclophosphamide, resulted in macular edema and retinal pigment epithelial changes in all patients, despite intra-carotid injection of mannitol [42]. A case was also reported by Penjavic *et al*, in which they described a reduced full field ERG in B-wave amplitude [43].

(II) Pemetrexed: It is indicated for use in malignant pleural mesothelioma and locally advanced or metastatic non–small cell lung cancer. Increased lacrimation, ocular surface disease including conjunctivitis has been reported in 1% to 5% patients.

C. Purines analogues:

(I) Fludarabine: It is used for treatment of refractory B-cell chronic lymphocytic leukemia, advanced low grade non-hodgkin's lymphoma, refractory or relapsed acute leukemias and mycosis fungoides. The ocular toxicities caused include diplopia, photophobia and, decreased visual acuity secondary to optic neuritis with or without disc edema or cortical blindness [44].

(II) Pentostatin: Pentostatin is used for treatment of hairy cell leukemia, cutaneous T-cell lymphoma and chronic lymphocytic leukemia. It has been found to be associated with abnormal vision, amblyopia, conjunctivitis, dry eye, problems with lacrimation, photophobia, retinopathy and watery eyes [45,46].

3. Mitotic inhibitors

A. Taxanes:

(I) Paclitaxel: Paclitaxel is known to produce neurotoxocity when used for its indications in metastatic or relapsed breast cancer and advanced ovarian cancer [47]. Both transient scintillating scotoma and visual impairment have been reported after its use [48]. Other ocular side-effects induced by paclitaxel include photopsia and possible ischemic optic neuropathy.

(II) Docetaxel: It is indicated in locally advanced, metastatic and refractory breast cancer, advanced gastric and gastro-esophageal adenocarcinoma, locally advanced head and neck cancer, metastatic prostate cancer and locally advanced or metastatic non-small cell lung carcinoma. S Kolnik and Doughman reported a case of erosive conjunctivitis and punctual stenosis secondary to docetaxel administration [49]. Esmaeli *et al* reported canalicular narrowing and naso-lacrimal duct obstruction in three patients [50, 51].

B. Plant alkaloids:

(I) Vincristine, vinblastine, vindesine, vinorelbine: They are used for acute lymphoblastic leukemia, ewing's sarcoma, hodgkin's disease, non-hodgkin's disease, lung cancer, breast cancer and soft tissue sarcomas. Cranial nerve palsies [52,53], optic neuropathy [54, 55], optic atropy [56], cortical blindness [57] and night blindness [58] are the ocular side-effects of these plant alkaloids. The cranial nerve palsies include ptosis, internal ophthalmoplegia, corneal hyperesthesia and lagophthalmos [10].

C. Topoisomerase Inhibitors:

(I) Topoisomerase inhibitor II: Etoposide is a topoisomerase-II inhibitor. Intra-arterially administered etoposide results in arterial thrombosis [59] which can affect the eye by occluding central retinal artery. Etoposide is used of treatment of retinoblastoma in combination with cisplatin or carboplatin. Due to synergistic effects with cisplatin two cases of retinal toxicities have been reported [60].

(II) Topoisomerase inhibitor I: Irinotecan and topotecan are topoisomerase-I inhibitors used for cytotoxic treatment of carcinoma. They do not have any significant ocular adverse effects reported yet.

4. Antibiotics

A. Anthracyclines:

(I) Doxorubicin: It is used in combination regimens in the treatment of breast cancer, ovarian cancer, non-hodgkin's lymphoma, sarcoma and acute leukemia. Excessive lacrimation and conjunctivitis have been reported as its ocular adverse effects [61].

(II) Mitomycin-C: Mitomycin-C is used in combination chemotherapy regimens in gastric, pancreatic, colon, lung, urinary bladder, breast and cervical cancer. It is also used as hypoxic cell selective cytotoxic agent in combination with radiation therapy in anal and head and neck cancers. The only known ocular toxicity after systemic use of mitomycin-c is blurred vision [61]. All other severe ocular toxicities were reported after topical use in ophthalmologic surgeries.

(III) Mithramycin (Plicamycin): Mithramycin is used in treatment of hypercalcemia of malignancies and for testicular cancer. There was a single case reported of peri-orbital pallor in absence of anemia as ocular adverse effect [20].

5. Hormonal agents

A. Tamoxifen: It is used as adjuvant therapy of estrogen dependent breast carcinoma. In 1978, Kaiser-Kupfer and Lippman described four patients who developed keratopathy and retinopathy after tamoxifen use [62,63]. Decreased visual acuity, bilateral macular edema, retinal yellow-white dots and corneal opacities, bilateral optic neuritis and retinal hemorrhages has also been reported [64, 65]. Gorin *et al* described intra-retinal crystals and posterior sub-capsular opacities with tamoxifen usage [66]. On the whole, the most common tamoxifen induced ocular toxicities remain to be the retinopathy and cataract, lesions of cornea and optic nerve.

B. Anastrazole: The incidence of cataract with anastrazole usage was found to be lesser than with tamoxifen. The ATAC (Armidex, Tamoxifen, alone or in combination) trial randomized patients with hormone receptor positive localized breast cancer to five years of anastrazole or tamoxifen use. Cataracts were described in 6% patients receiving anastrazole versus 7% receiving tamoxifen [67].

6. Monoclonal antibodies

A. Rituximab: Rituximab was approved by US-FDA (Food and Drug Administration, U.S.A.) in 1997 and is used to treat B-cell non-Hodgkin lymphoma. It is a monoclonal antibody against the CD20 antigen, found on B cells. It works, in part, by labeling cells so that the immune system can attack them. Ocular side-effects described with rituximab usage are conjunctivitis, transient ocular edema, burning sensation, transient visual changes or permanent and severe loss of visual acuity [68].

B. Alemtuzumab: Alemtuzumab is an antibody against the CD52 antigen, which is found on both B cells and T cells. It was FDA approved in 2001 to treat some patients with B-cell chronic lymphocytic leukemia. Adverse reactions identified during post-approval use of alemtuzumab are optic neuropathy and endophthalmitis [69].

C. Cetuximab: Cetuximab is an antibody against the EGFR (epidermal growth factor receptor) protein, which is present in large amounts on some tumor cells and helps them grow and divide. Cetuximab blocks the activation of EGFR. It was FDA approved in 2004 to treat some advanced colorectal cancers as well as some head and neck cancers. One case report described a patient with squamous blepharitis. A case treated with combined chemotherapy including cetuximab for colorectal carcinoma showed accelerated growth of eyelashes with persistent bilateral corneal erosions [70].

D. Panitumumab: It targets epidermal growth factor receptor (EGFR) antigen. It is used to treat EGFR-expressing, metastatic colo-rectal carcinoma with disease progression on or following fluoropyrimidine, oxaliplatin and irinotecan containing chemotherapy regimens. Ocular toxicities included but are not limited to growth of eyelashes; conjunctivitis; ocular hyperemia; increased lacrimation; eye/eyelid irritation [71].

E. Bevacizumab: Bevacizumab targets the VEGF (vascular endothelial growth factor) protein, which is normally made by tumor cells to attract new blood vessels to feed their growth. Bevacizumab attaches to VEGF and blocks it from signaling for new blood vessels formation. It was approved by FDA in 2004 and is used to treat metastatic colorectal cancer, with intravenous 5-florouracil–based chemotherapy for first- or second-line treatment, non-squamous non-small cell lung cancer, with carboplatin and paclitaxel for first line treatment of unresectable, locally advanced, recurrent or metastatic disease, metastatic breast cancer, with paclitaxel for treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer, glioblastoma, as a single agent for adult patients with progressive disease following prior therapy and, metastatic renal cell carcinoma with interferon alfa.

Ocular adverse reactions that have been reported from unapproved use for treatment of various ocular disorders during post-approval use of bevacizumab are endophthalmitis; intraocular inflammation such as iritis and vitritis; retinal detachment; other retinal disorders; increased intraocular pressure; hemorrhage following intraocular injection including conjunctival, vitreous hemorrhage or retinal hemorrhage; vitreous floaters; visual disturbances; ocular hyperemia; ocular pain and/or discomfort [72].

FDA recently revoked on 18-11-2011, the agency's accelerated approval of the breast cancer indication for bevacizumab [73].

7. Drugs targeting signal transduction

A. Imatinib: It is indicated in treatment of adults with newly diagnosed Philadelphia chromosome positive (Ph+) CML in chronic phase; treatment of adults with Ph+ ALL with resistance or intolerance to prior therapy. Peri-orbital edema due to fluid retention is reported in 47.2% of patients. Dry eyes, visual disorders including blurred vision, reduced visual acuity, and visual disturbance (1% to less than 10%) were reported [74].

B. Nilotinib: Clinical trials data show that ocular adverse effects caused by nilotinib are uncommon (less than 1%). Eye disorders reported are hemorrhage, reduced visual acuity, peri-orbital edema, conjunctivitis, eye irritation and dry eye [75].

C. Vemurafenib: It is a kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF mutation. Serious ophthalmologic reactions including uveitis, iritis and retinal vein occlusion, have been reported. Routine monitoring of patients on vemurafenib for ophthalmologic reactions is recommended [76].

D. Erlotinib: Corneal ulcerations and perforations, excessive eyelash growth including in-growing eyelashes, and thickening of the eyelashes have been reported. Grade 3 conjunctivitis and keratitis have been reported infrequently in patients receiving erlotinib therapy in non-small cell cancer and pancreatic cancer clinical trials [77].

E. Everolimus: Inhibitor of mammalian target of rapamycin (mTOR), which is a serine-threonine kinase. It is indicated in advanced pancreatic neuroendocrine tumors and advanced renal cell carcinoma. The ocular toxicities reported are eyelid edema, ocular hyperemia, conjunctivitis [78].

F. Temsirolimus: Temsirolimus is also inhibitor of mTOR and is indicated in treatment of advanced renal cell carcinoma. No ocular adverse effect associated with temsirolimus use has been reported so far.

Conclusion

Ophthalmic complications induced by cytotoxic chemotherapy are often under-estimated and under-reported due to priority given to other life-threatening conditions. The possible reversal of some of these side effects, if diagnosed timely, emphasizes the need for oncologists to be aware these ocular reactions and suggest immediate consultation with an ophthalmologist so that they can be recognized early and some ophthalmic intervention can be done before irreversible changes occur to hamper patient's quality of life. An ophthalmic baseline examination prior to anti-cancer treatment may help detect any pre-existing ocular condition and lead to reduction of ocular side effects when

predisposed patients are screened and examined regularly during and after chemotherapeutic therapy. Reporting of ocular adverse effects of chemotherapy should be encouraged for definite analysis of the burden. Anticipation of various treatment related toxicities may also provide the opportunity for pharmacists to develop intervention strategies that could minimize expected adverse effects. On the whole, oncologist and ophthalmologist should work together in order to prevent irreversible ocular toxicities of chemotherapeutic agents and to determine true cause of visual disturbance.

Table 1: Common ocular adverse effects and anti-cancer drugs associated.

Ocular Adverse effects	Common drugs associated
Blurred vision	Cisplatin
	Oxaliplatin
	Cyclophosphamide
	Ifosphamide
	Methotrexate
	Paclitaxel
	Capecitabine
	Imatinib
	Tamoxifen
	Rituximab
	Mitomycin-C
	Busulphan
	Carmustine
	Fludarabine
	Pentostatin
	Cytosine arabinoside
Photophobia	5-Florouracil (5-FU)
	Methotrexate
	Fludarabine
	Cytosine arabinoside
	Pentostatin
Conjunctivitis	Oxaliplatin
	Cyclophosphamide
	Ifosphamide
	Methotrexate
	5-FU
	Docetaxel
	Doxorubicin
	Capecitabine
	Rituximab
	Panitumumab
	Nilotinib
	Erlotinib
	Carmustine
	Busulphan
	Pentostatin
	Everolimus
Cataract	Tamoxifen
	Anastrazole
	Busulphan
Abnormal lacrimation	Oxaliplatin
	Cyclophosphamide
	5-FU
	Docetaxel
	Doxorubicin
	Cytosine arabinoside
	Pentostatin
	Panitumumab
Dry eye	Cyclophosphamide
	Imatinib
	Nilotinib
	Pentostatin
	Busulphan
Keratitis	5-FU
	Capecitabine
	Tamoxifen
	Cetuximab
	Erlotinib
	Chlorambucil
	Cytosine arabinoside
Optic neuropathy	Cisplatin
	Carboplatin
	Methotrexate
	Paclitaxel
	Vincristine
	Tamoxifen

Ocular Adverse effects	Common drugs associated
	Alemtuzumab
	Carmustin
	Cytosine arabinoside
	Fludarabine
Retinopathy	Cisplatin
	Carboplatin
	Methotrexate
	Etoposide
	Tamoxifen
	Carmustin
	Pentostatin
	Leuprolide
Cortical blindness	Cisplatin
	Vincristine
	Fludarabine
Eye pain	Oxaliplatin
	5-FU
	Carmustine
	Cytosine arabinoside
Accelerated growth of eyelashes	Cetuximab
	Panitumumab
Limitation of ocular motility	Carboplatin
	Methotrexate

Article History

Editor: Evan Yu, Fred Hutchinson Cancer Research Center, USA.
EIC: G.J. Peters, VU University Medical Center, Netherlands.
Received: 25 December 2011 Revised: 21 January 2012
Re-Revised: 31 January 2012 Accepted: 08 February 2012
Published: 14 February 2012

References

1. Ostrow, S. *et al.* **Ophthalmologic toxicity after cis-dichlorodiammineplatinum(II) therapy**. *Cancer Treat Rep* **62**, 1591-1594
2. Caraceni, A. *et al.* **Recovering optic neuritis during systemic cisplatin and carboplatin chemotherapy**. *Acta Neurol Scand* **96**, 260-261
3. Berman, I. J. *et al.* **Seizures and transient cortical blindness associated with cis-platinum (II) diamminedichloride (PDD) therapy in a thirty-year-old man**. *Cancer* **45**, 764-766
4. Diamond, S. B. *et al.* **Cerebral blindness in association with cis-platinum chemotherapy for advanced carcinoma of the fallopian tube**. *Obstet Gynecol* **59**, 84S-86S
5. Pippitt, C. H., Jr. *et al.* **Cisplatin-associated cortical blindness**. *Gynecol Oncol* **12**, 253-255
6. Cohen, R. J. *et al.* **Transient left homonymous hemianopsia and encephalopathy following treatment of testicular carcinoma with cisplatinum, vinblastine, and bleomycin**. *J Clin Oncol* **1**, 392-393
7. Crispino, S. *et al.* **Transient left homonymous hemianopsia during treatment of testicular carcinoma with cisplatinum, vinblastine, and bleomycin**. *Chemioterapia* **3**, 337-339
8. Wilding, G. *et al.* **Retinal toxicity after high-dose cisplatin therapy**. *J Clin Oncol* **3**, 1683-1689
9. Katz, B. J. *et al.* **Persistent severe visual and electroretinographic abnormalities after intravenous Cisplatin therapy**. *J Neuroophthalmol* **23**, 132-135
10. Imperia, P. S. *et al.* **Ocular complications of systemic cancer chemotherapy**. *Surv Ophthalmol* **34**, 209-230
11. Urba, S. *et al.* **Retrobulbar neuritis in a patient treated with intraarterial cisplatin for head and neck cancer**. *Cancer* **62**, 2094-2097
12. Stewart, D. J. *et al.* **A phase I study of intracarotid artery infusion of cis-Diamminedichloroplatinum(II) in patients with recurrent malignant intracerebral tumors**. *Cancer Res* **42**, 2059-2062
13. Margo, C. E. *et al.* **Ocular and orbital toxicity after intracarotid cisplatin therapy**. *Am J Ophthalmol* **116**, 508-509
14. Rankin, E. M. *et al.* **Ophthalmic toxicity during carboplatin therapy**. *Ann Oncol* **4**, 337-338
15. O'Brien, M. E. *et al.* **Blindness associated with high-dose carboplatin**. *Lancet* **339**, 558
16. Lauer, A. K. *et al.* **Severe ocular and orbital toxicity after intracarotid etoposide phosphate and carboplatin therapy**. *Am J Ophthalmol* **127**, 230-233
17. Mulvihill, A. *et al.* **Ocular motility changes after subtenon carboplatin chemotherapy for retinoblastoma**. *Arch Ophthalmol* **121**, 1120-1124
18. Leonard, G. D. *et al.* **Survey of oxaliplatin-associated neurotoxicity using an interview-based questionnaire in patients with metastatic colorectal cancer**. *BMC Cancer* **5**, 116
19. **Eloxatin (oxaliplatin for injection) prescribing information**
20. al-Tweigeri, T. *et al.* **Ocular toxicity and cancer chemotherapy. A review**. *Cancer* **78**, 1359-1373
21. Jack, M. K. *et al.* **Ocular complications in high-dose chemoradiotherapy and marrow transplantation**. *Ann Ophthalmol* **13**, 709-711
22. Kende, G. *et al.* **Blurring of vision: a previously undescribed complication of cyclophosphamide therapy**. *Cancer* **44**, 69-71
23. Stevens, A. *et al.* **Lacrimal duct stenosis and other ocular toxicity associated with adjuvant cyclophosphamide, methotrexate and 5-fluorouracil combination chemotherapy for early stage breast cancer**. *Clin Oncol (R Coll Radiol)* **13**, 438-440
24. Choonara, I. A. *et al*, **Blurring of vision due to ifosfamide**. *Cancer Chemother Pharmacol* **20**, 349
25. Kaida, T. *et al.* **Cataract induced by short-term administration of large doses of busulfan: a case report**. *Ophthalmologica* **213**, 397-399
26. Lokich, J. J. *et al.* **1,-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (methyl CCNU) and adriamycin combination therapy**. *Cancer* **34**, 1593-1597

27. Louie, A. C. *et al.* **Visual abnormalities following nitrosourea treatment**. *Med Pediatr Oncol* **5**, 245-247
28. Greenberg, H. S. *et al.* **Intra-arterial BCNU chemotherapy for treatment of malignant gliomas of the central nervous system**. *J Neurosurg* **61**, 423-429
29. Grimson, B. S. *et al.* **Ophthalmic and central nervous system complications following intracarotid BCNU (Carmustine)**. *J Clin Neuroophthalmol* **1**, 261-264
30. Johnson, D. W. *et al.* **Optic disc and retinal microvasculopathy after high-dose chemotherapy and autologous hematopoietic progenitor cell support**. *Bone Marrow Transplant* **24**, 785-792
31. Shingleton, B. J. *et al.* **Ocular toxicity associated with high-dose carmustine**. *Arch Ophthalmol* **100**, 1766-1772
32. Hopen, G. *et al.* **Corneal toxicity with systemic cytarabine**. *Am J Ophthalmol* **91**, 500-504
33. Percy DH, Danylchuk KD. **Experimental retinal dysplasia due to cytosine arabinoside**. Invest Ophthalmol *Vis Sci* **16**, 353-364
34. Margileth, D. A. *et al.* **Blindness during remission in two patients with acute lymphoblastic leukemia: a possible complication of multimodality therapy**. *Cancer* **39**, 58-61
35. Khaw, P. T. *et al.* **Five-minute treatments with fluorouracil, floxuridine, and mitomycin have long-term effects on human Tenon's capsule fibroblasts**. *Arch Ophthalmol* **110**, 1150-1154
36. Shapiro, M. S. *et al.* **5-Fluorouracil toxicity to the ocular surface epithelium**. *Invest Ophthalmol Vis Sci* **26**, 580-583
37. Stevens, A. *et al.* **Lacrimal duct stenosis and other ocular toxicity associated with adjuvant cyclophosphamide, methotrexate and 5-fluorouracil combination chemotherapy for early stage breast cancer**. *Clin Oncol (R Coll Radiol)* **13**, 438-440
38. Brink, H. M. *et al.* **Punctal and canalicular stenosis associated with systemic fluorouracil therapy. Report of five cases and review of the literature**. *Doc Ophthalmol* **90**, 1-6
39. Waikhom, B. *et al*, **Severe ocular irritation and corneal deposits associated with capecitabine use**. *N Engl J Med* **343,** 740-741
40. Fishman, M. L. *et al.* **Optic atrophy following prophylactic chemotherapy and cranial radiation for acute lymphocytic leukemia**. *Am J Ophthalmol* **82**, 571-576
41. Margileth, D. A. *et al.* **Blindness during remission in two patients with acute lymphoblastic leukemia: a possible complication of multimodality therapy**. *Cancer* **39**, 58-61
42. Millay, R. H. *et al.* **Maculopathy associated with combination chemotherapy and osmotic opening of the blood-brain barrier**. *Am J Ophthalmol* **102**, 626-632
43. Ponjavic, V. *et al.* **Reduced full-field electroretinogram (ERG) in a patient treated with methotrexate**. *Acta Ophthalmol Scand* **82**, 96-99
44. Chun, H. G. *et al.* **Central nervous system toxicity of fludarabine phosphate**. *Cancer Treat Rep* **70**, 1225-1228
45. Kraut, E. H. *et al.* **Pentostatin in the treatment of advanced hairy cell leukemia**. *J Clin Oncol* **7**, 168-172
46. Major, P. P. *et al.* **Clinical pharmacology of arabinofuranosyladenine in combination with deoxycoformycin**. *Cancer Chemother Pharmacol* **10**, 125-128
47. Damascelli, B. *et al.* **Intraarterial chemotherapy with polyoxyethylated castor oil free paclitaxel, incorporated in albumin nanoparticles (ABI-007): Phase II study of patients with squamous cell carcinoma of the head and neck and anal canal: preliminary evidence of clinical activity**. *Cancer* **92**, 2592-2602
48. Capri, G. *et al.* **Optic nerve disturbances: a new form of paclitaxel neurotoxicity**. *J Natl Cancer Inst* **86**, 1099-1101
49. Skolnick, C. A. *et al.* **Erosive conjunctivitis and punctal stenosis secondary to docetaxel (taxotere)**. *Eye Contact Lens* **29**, 134-135
50. Esmaeli, B. *et al.* **Docetaxel-induced histologic changes in the lacrimal sac and the nasal mucosa**. *Ophthal Plast Reconstr Surg* **19**, 305-308
51. Esmaeli, B. *et al.* **Blockage of the lacrimal drainage apparatus as a side effect of docetaxel therapy**. *Cancer* **98**, 504-507
52. Albert, D. M. *et al.* **Ocular complications of vincristine therapy**. *Arch Ophthalmol* **78**, 709-713
53. Alexander, P. **Radiation imitative chemicals**. *Sci Am* **202**, 99-108
54. Sanderson, P. A. *et al.* **Optic neuropathy presumably caused by vincristine therapy**. *Am J Ophthalmol* **81**, 146-150
55. Sandler, S. G. *et al.* **Vincristine-induced neuropathy. A clinical study of fifty leukemic patients**. *Neurology* **19**, 367-374
56. Shurin, S. B. *et al.* **Optic atrophy induced by vincristine**. *Pediatrics* **70**, 288-291
57. Byrd, R. L. *et al.* **Transient cortical blindness secondary to vincristine therapy in childhood malignancies**. *Cancer* **47**, 37-40
58. Ripps, H. *et al.* **Functional abnormalities in vincristine-induced night blindness**. *Invest Ophthalmol Vis Sci* **25**, 787-794
59. Schacter, L. **Etoposide phosphate: what, why, where, and how?** *Semin Oncol* **23**, 1-7
60. Hilliard, L. M. *et al.* **Retinal toxicity associated with cisplatin and etoposide in pediatric patients**. *Med Pediatr Oncol* **28**, 310-313
61. Vizel, M. *et al.* **Ocular side effects of cancer chemotherapy**. *Cancer* **49**, 1999-2002
62. Kaiser-Kupfer, M. I. *et al.* **Tamoxifen retinopathy. A clinicopathologic report**. *Ophthalmology* **88**, 89-93
63. Kaiser-Kupfer, M. I. *et al.* **Tamoxifen retinopathy**. *Cancer Treat Rep* **62**, 315-320
64. Pavlidis, N. A. *et al.* **Clear evidence that long-term, low-dose tamoxifen treatment can induce ocular toxicity. A prospective study of 63 patients**. *Cancer* **69**, 2961-2964
65. Ashford, A. R. *et al.* **Reversible ocular toxicity related to tamoxifen therapy**. *Cancer* **61**, 33-35
66. Gorin, M. B. *et al.* **Long-term tamoxifen citrate use and potential ocular toxicity**. *Am J Ophthalmol* **125**, 493-501
67. Howell, A. *et al.* **Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer**. *Lancet* **365**, 60-62
68. Rituximab prescribing information. Retreived on 18-12-2011
69. Alemtuzumab prescribing information. Retreived on 18-12-2011
70. Foerster, C. G. *et al.* **Persisting corneal erosion under cetuximab (Erbitux) treatment (epidermal growth factor receptor antibody)**. *Cornea* **27**, 612-614
71. Panitumumab prescribing information. Retreived on 18-12-2011
72. Bevacizumab prescribing information. Retreived on 18-12-2011
73. US-FDA newsroom report. Retrieved on 18-12-2011
74. Imatinib prescribing information. Retreived on 18-12-2011
75. Nilotinib prescribing information. Retreived on 18-12-2011
76. ZELBORAF full prescribing information. Retrieved on 18-12-2011
77. Tarceva full prescribing information. Retrieved on 18-12-2011
78. Afinitor full prescribing information. Retrieved on 18-12-2011