

THERAPEUTIC REVIEW

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Ocular Complications of Systemic Cancer Chemotherapy

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Abstract. Cancer chemotherapy has changed rapidly in recent years. New agents are constantly being developed. Established agents are being used with increased frequency, in new combinations, at higher dosages, and via new routes of administration. Enhanced survival, as well as increased drug toxicity, has resulted. Ocular toxicity is not uncommon and can greatly impact on quality of life. Practitioners in all fields are increasingly caring for patients who are receiving cancer chemotherapy. The recognition of eye disease resulting from chemotherapy is essential to appropriate patient management. We provide a review of the rapidly growing body of literature on the ocular toxicity of systemic cancer chemotherapy with particular attention to context, clinical course, mechanism, prevention and treatment. (*Surv Ophthalmol* 34:209-230, 1989)

Key words. antineoplastics • cancer chemotherapy • drug side effects • ocular toxicity

The science of cancer chemotherapy has changed at an accelerating rate since the initial observation that chemotherapy could be used to successfully treat clinically apparent malignant disease that had spread beyond the range of surgical excision or localized radiation therapy fields.¹⁴⁴ The advent of sophisticated supportive care techniques, including blood banking and transfusion services, the use of protected environments, the administration of improved antibiotics, and the greater understanding of drug pharmacokinetics has set the stage for the development of new strategies. Examples include chemotherapeutic agents being used in new combinations that take advantage of synergistic or additive effects, in adjuvant therapy for patients who have a high risk of relapse with no detectable evidence of disease, and in neo-adjuvant therapy to reduce tumor size and permit more conservative surgery. Intrathecal and carotid artery infusions are being employed. Significantly higher dose regimens, previously fatal to the patient, are now possi-

ble with the advent of bone marrow transplantation.

Innovations have enhanced patient survival. Unfortunately, new regimens can also be associated with an increased severity of or newly recognized side effects. We will recount many reports of agents, previously nontoxic to the eye, which, due to a new mode of delivery, have manifested ocular toxicity. Intrathecal methotrexate and cytosine arabinoside are examples that are associated with neuroophthalmologic complications.^{76,141} We will cite several examples of the intracarotid administration of a chemotherapeutic agent proximal to the ophthalmic artery resulting in disastrous ocular toxicity.^{4,74,91,95,133,149,156,197,205,208} Indeed, almost any antineoplastic gaining access to the carotid artery in high concentrations would be expected to produce significant toxicity.

Although not fatal, ocular side effects can greatly impact on the quality of life. As the cancer patient survives longer, the treatment of these toxicities be-

TABLE 1
Ocular Toxicity of Cancer Chemotherapy

BCG	Uveitis, vitiligo
Busulfan	Cataract, keratoconjunctivitis sicca, blurred vision
Chlorambucil	Keratitis, oculomotor disturbance, disc edema, retinopathy
Cis-platinum	Disc edema, retrobulbar neuritis, cortical blindness, retinopathy, ERG abnormalities, cavernous sinus syndrome, blurred vision, color blindness
Corticosteroids	Cataract, glaucoma, infection, visual field defects, blurred vision, diplopia, exophthalmos, scleral discoloration
Cyclophosphamide	Keratoconjunctivitis sicca, blurred vision, pinpoint pupils, blepharoconjunctivitis
Cytosine arabinoside	Keratitis, conjunctivitis
Dibromomannitol	Cataracts
Doxorubicin	Conjunctivitis
Fludarabine	Optic neuritis, disc edema, cortical blindness
5-Fluorouracil	Keratoconjunctivitis, cicatricial ectropion, ankyloblepharon, blepharospasm, tear duct fibrosis, punctal occlusion, oculomotor disturbances, blurred vision, photophobia, nystagmus, increased lid necrosis after cryotherapy, ocular pain, circumorbital edema, blepharitis
Interferon	Disc edema
Isosfamide	Blurred vision
Laetrile	Ptosis, oculomotor dysfunction
Methotrexate	Blepharoconjunctivitis, periorbital edema, photophobia, ocular pain, optic neuropathy
Mitomycin C	Blurred vision
Mitotane	Retinopathy, disc edema, cataract, diplopia
Nafoxidine	Cataracts
Nitrogen mustard	Necrotizing uveitis
Nitrosoureas	Optic neuritis and atrophy, hyperemia, orbital pain, retinopathy, corneal opacities and edema, orbital arteriovenous shunts, secondary glaucoma, internal ophthalmoplegia, blurred vision, vitreal opacification, extraocular muscle fibrosis, diplopia
Plicamycin	Periorbital pallor
Procarbazine	Retinopathy, nystagmus, disc edema, diplopia
Tamoxifen	Corneal opacities, retinopathy
Tilorone	Keratopathy, retinopathy
Vincristine	Cranial nerve palsies, optic neuropathy and atrophy, cortical blindness

comes increasingly important. Information on the ocular complications of systemic cancer therapy has grown rapidly in both the ophthalmic and medical literature. We describe the responsible agents by structure, mechanism of action, main clinical uses, and systemic side effects. Ocular side effects are then detailed in terms of incidence, clinical setting, dose relationship, route of drug administration, natural history, pathology, mechanism of toxicity, prevention, and treatment. Animal data are included, if relevant. Ocular complications in the treatment of ocular neoplasia is a large and inherently separate topic which, for practicality, we have chosen not to address.

This review is designed to serve as a clinical and research resource for both the ophthalmologist and medical specialist. A listing of each drug's ocular side effects and a grouping of toxicity by anatomic site are given in Tables 1 and 2, respectively, to serve as a rapid reference while reading the text and when referring to it in the future. One must realize that, for several of the drug toxicities reported, as we will specify, a direct cause and effect relationship is not fully established. Often this is due to the effects of the underlying disease, concurrent

and frequently complex treatment regimens, and the rarity of some complications. With these factors in mind, we have made an attempt to render an opinion regarding the likelihood of cause and effect and/or have included relevant circumstances and statistics to allow the reader to render his or her own. Increased awareness of the ocular toxicity of cancer chemotherapy will hopefully lead to enhanced recognition of causality, prevention and treatment that will reduce the cancer patient's exposure to treatment-related morbidity.

I. Alkylating Agents

The alkylating agents are a class of chemotherapy drugs that have resulted largely from modifications of the initial agent, nitrogen mustard (mechlorethamine).³ Nitrogen mustard contains two β -chloroethyl groups which transfer into ethylenimonium derivatives. These positively charged groups combine with negatively charged guanine moieties of complementary DNA strands, causing cross-linking. This results in miscoding errors, depurination or with modifications of the drug structure, interference with mitosis by cross-linking of adjacent DNA. Cell death is not cycle-specific and can result

TABLE 2
Cancer Chemotherapy Toxicity by Anatomic Site

Site	Side Effect	Drugs
Orbit	AV shunts Cavernous sinus syndrome Edema Exophthalmos Pallor Pain Cicatricial ectropion Ankyloblepharon Increased lid necrosis following cryotherapy Hyperpigmentation Tear duct fibrosis, and Punctal occlusion Keratoconjunctivitis sicca Conjunctivitis	Nitrosoureas Cis-platinum 5-FU, Methotrexate Corticosteroids Plicamycin Nitrosoureas, 5-FU, and Methotrexate 5-FU 5-FU 5-FU 5-FU, Busulfan 5-FU Busulfan, and Cyclophosphamide Doxorubicin, Cyclophosphamide, Cytosine arabinoside, 5-FU, Methotrexate, and Nitrosoureas Corticosteroids Tamoxifen, Tilorone, and Nitrosoureas Chlorambucil, Cytosine arabinoside, and 5-FU Cyclophosphamide Nitrosoureas BCG, Busulfan, and Nitrogen Mustard
Lids		
Lacrimal drainage		
Lacrimal gland		
Conjunctiva		
Sclera	Discoloration	Corticosteroids
Cornea	Keratopathy Keratitis	Tamoxifen, Tilorone, and Nitrosoureas Chlorambucil, Cytosine arabinoside, and 5-FU
Pupil	Pinpoint pupils	Cyclophosphamide
Uvea	Internal ophthalmoplegia	Nitrosoureas
Trabecular meshwork and/or Ciliary Body	Uveitis	BCG, Busulfan, and Nitrogen Mustard
Lens	Increased IOP Cataract	Corticosteroids and Nitrosoureas Busulfan, Corticosteroids, Dibromomannitol, Methotrexate, Mitotane, and Nafoxidine
Retina	Toxic retinopathy	Chlorambucil, Cis-platinum, Mitotane, Nitrosoureas, Procarbazine, Tamoxifen, and Tilorone
Vitreous	Opacification	Nitrosoureas
Optic nerve	Disc edema, Optic neuritis, and/or Optic atrophy	Chlorambucil, Cis-platinum, Cytosine arabinoside, Fludarabine, 5-FU, Interferon, Laetile, Methotrexate, Mitotane, Nitrosoureas, Procarbazine, and Vincristine
Cranial nerves 3, 4, 5 and 6	Ptosis, Paresis with or without Diplopia	Chlorambucil, Corticosteroids, Fludarabine, 5-FU, Laetile, Procarbazine, and Vincristine
Extraocular muscles	Corneal hypesthesia	Vincristine
Central nervous system	Fibrosis Cortical blindness	Nitrosoureas Cis-platinum, Fludarabine, and Vincristine
	Internuclear ophthalmoplegia	Nitrosoureas
	Blepharospasm	5-FU

from damage to RNA and protein as well as DNA.

A. NITROGEN MUSTARD

Nitrogen mustard was the first widely used anti-neoplastic agent.³ It continues to be an important agent in the combination therapy of Hodgkin's and non-Hodgkin's lymphoma. Systemic toxicity is mainly severe nausea and vomiting and bone marrow suppression.

Intracarotid infusion is employed for several anti-neoplastics to enhance drug delivery to primary

brain tumors and reduce dose-limiting systemic side effects. An ipsilateral necrotizing uveitis developed in approximately 25% (3/12) of patients with inoperable brain tumors who received an intracarotid infusion of nitrogen mustard.^{4,208} A selective necrotizing vasculitis of the choroid was observed at autopsy.⁴ The drug's selectivity for the choroid may result from increased contact time secondary to the relatively high flow volume and low flow rate of the choroid as compared to the retinal circulation.⁴ Although few patients were studied, like many re-

ports of ocular toxicity from intracarotid chemotherapy administration we will discuss, the likelihood of cause and effect in all these cases is high given the ipsilateral findings and the logical probability of toxicity from delivering a cytotoxic agent in a high concentration to the ophthalmic artery.

B. CYCLOPHOSPHAMIDE

Cyclophosphamide is an alkylating antineoplastic, activated in the liver, with potent immunosuppressive properties. It is used orally and intravenously in a variety of cancers, commonly in lymphoma and breast cancer, and as an immunosuppressive in conditions such as Wegener's granulomatosis, rheumatoid arthritis, and pediatric nephrotic syndrome. Systemic toxicity includes acute nausea and vomiting, bone marrow suppression, alopecia, fluid retention, and hemorrhagic cystitis. Cardiomyopathy and sterility can result from high dose use as part of bone marrow transplantation.

Ocular toxicity has been reported in the form of blurred vision,¹²⁷ keratoconjunctivitis sicca,¹¹⁶ blepharoconjunctivitis and pinpoint pupils.⁸¹ In combination with steroids it has been reported to potentiate cataract formation^{98,131,172} and cause a Stevens-Johnson syndrome.¹⁴⁰ The potentiation of cataract formation is not well established and has occurred exclusively in patients having renal disease.

Reversible blurred vision without ophthalmoscopic findings occurred in 5 of 59 (17%) patients studied within minutes to 24 hours of high dose (750 mg/m² on alternate days for five doses) intravenous therapy and lasted less than one hour or up to two weeks.¹²⁷ The low incidence, nonspecificity and variable nature of this side effect should raise questions regarding a cause and effect relationship. Keratoconjunctivitis sicca is fairly well established, occurring in approximately 50% of patients when cyclophosphamide is used alone or in combination with other agents.⁸¹ Pinpoint pupils are thought to be secondary to the parasympathomimetic effect of alkylating agents in general.¹²⁷ The mechanism for ocular toxicity from cyclophosphamide is otherwise unknown.

C. IFOSFAMIDE

Ifosfamide, an analog of cyclophosphamide, has demonstrated antitumor activity in the treatment of adult sarcomas, testicular, ovarian, breast, cervical, pancreatic, bladder, and lung cancers, and lymphomas.²⁶ Like cyclophosphamide, it has been reported to cause a reversible blurred vision and conjunctivitis.³⁹

D. CIS-PLATINUM

Cis-platinum is a heavy metal alkylating agent. Its main uses are in testicular and ovarian cancer and, less commonly, in lymphoma, osteogenic sarcoma, gastrointestinal, head and neck, breast and lung cancers.^{69,146,239} Systemic toxicity consists of acute nausea and vomiting, nephrotoxicity, ototoxicity, bone marrow suppression, chronic peripheral neuropathies, and seizures.^{146,182,209}

Intracarotid cis-platinum (60–120 mg/m²) results in a dose related, clinically apparent, ipsilateral visual loss in approximately 15–60% of patients from severe retinal and/or optic nerve ischemia.^{74,133,205} This serious side effect can be prevented if the infusion catheter is advanced beyond the ophthalmic artery, at the cost, however, of increased cerebral toxicity.¹³³ Preinfusion high dose dexamethasone has not helped prevent toxicity.²⁰⁵ Cavernous sinus syndrome and a pigmentary retinopathy similar to other heavy metals (i.e., copper, iron, mercury and cobalt) have also been reported with intracarotid use.^{74,158}

Ocular toxicity with intravenous cis-platinum is mainly neuroretinal and consists of electroretinogram (ERG) abnormalities, nonspecific blurred vision and color blindness,²³¹ disc edema, retrobulbar neuritis and cortical blindness.^{10,14,24,35,48,54,62,165,169,222,231} Standard intravenous doses (60–100 mg/m²) can be considered uncommonly associated with neuroretinal toxicity, which is usually mild, after 2–3 courses.^{69,239} Toxicity with high dose intravenous therapy (200 mg/m² in five divided daily doses) is better established and documented. A causal relationship between therapy and ocular pathology was supported by 3 of 13 patients who were studied prospectively and noted to have normal ophthalmologic exams prior to initiation of therapy.²³¹ It resulted in complaints of nonspecific blurred vision in 8 of 13 (62%) and altered color perception along the blue-yellow axis in 3 of 13 (23%) patients with ovarian cancer.²³¹ Eleven of 13 (84%) patients displayed retinal toxicity in the form of cone dysfunction documented on electroretinography and color vision testing.²³¹ Visual acuity was rarely described below 20/25. Loss of contrast sensitivity by spatial contrast measurements best displayed altered vision.²³¹ Moderate central visual field contraction was observed in four of ten patients tested by Goldmann perimetry.²³¹ Clinically, funduscopic exam showed only a mild irregular macular pigmentation in 6 of 13 (46%) patients presumed secondary to retinal pigment epithelial changes.²³¹ Although blurred vision uniformly resolved after cessation of therapy, color vision abnormalities persisted as long as 16 months.²³¹ Caruso and coworkers reported similar findings.³⁵

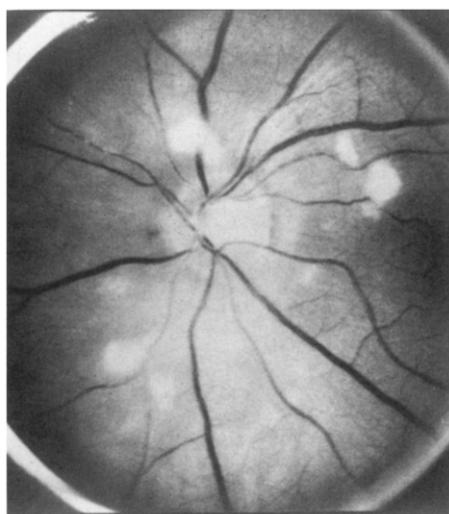
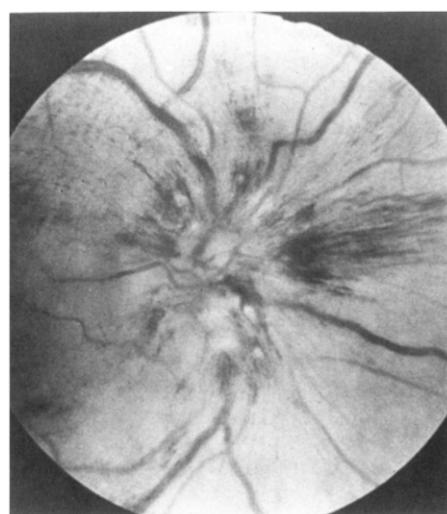


Fig. 1. Left: Fundus photograph of a patient who received an ipsilateral intracarotid artery injection of BCNU demonstrates multiple nerve fiber-layer infarcts. *Right:* Fundus photograph of another patient who received similar treatment demonstrates peripapillary hemorrhages and disc edema. (Reprinted from Shingleton BJ, Bienfang DC, Albert DM, et al¹⁹⁷ with permission of the authors and the American Medical Association.)



Risk factors for the development of ocular toxicity may be the same as for peripheral neuropathy, i.e., older age and female gender, since ocular toxicity is not observed in young males receiving identical doses of cis-platinum for testicular cancer.¹⁶⁶ A cumulative dose-toxicity relationship is apparent, since an increase in side effects from 50% to 80% occurs when the total dose exceeds 600 mg/m².²³¹

High dose cis-platinum therapy (85–200 mg/m²) alone or in combination with vinblastine and bleomycin has been reported in a number of case reports and small series to cause a sudden, reversible cortical blindness accompanied by encephalopathy, seizures and/or abnormal EEG.^{10,14,48,62,165,169,222,235} Disc edema and retrobulbar neuritis were also reported in isolated cases.^{10,165} The cerebrospinal fluid of one patient showed unusually high levels of cis-platinum which were equal to those measured in the serum.¹⁴ This observation suggested that, in patients with blindness and encephalopathy, there is an unusually high CNS accumulation of cis-platinum after repeated doses, which leads to a reversible segmental demyelination similar to other heavy metal poisoning as seen with gold, lead, mercury or thallium.^{120,165} The number of reports of CNS toxicity support a reasonably logical cause and effect relationship. However, multiagent therapy and underlying CNS pathology in many cases makes documentation difficult. It is important to stress that a search for intracranial metastases, infection, infarction and hemorrhage must usually be done before making the diagnosis of cis-platinum toxicity in this setting.

E. CHLORAMBUCIL

Chlorambucil is an alkylating agent with immunosuppressive properties. Uses include oral therapy of chronic lymphocytic leukemia, vasculitis

associated with rheumatoid arthritis and autoimmune hemolytic anemia. Systemic toxicity is mainly pulmonary and bone marrow suppression with longterm use.

Ocular toxicity can take the form of keratitis, oculomotor disturbances, hemorrhagic retinopathy and/or disc edema.²¹⁷ These toxicities are uncommon and not well established, consisting mainly of single case reports, and generally occur after several years of longterm oral therapy. The mechanism is unknown.

F. NITROSOUREAS

The nitrosoureas; BCNU, CCNU and methyl-CCNU are alkylating agents used in primary CNS tumors, Hodgkin's lymphoma, non-Hodgkin's lymphoma, multiple myeloma, colon and gastric cancer.^{163,225} Systemic toxicity consists of acute nausea and vomiting, pneumonitis, chronic renal failure, hepatic dysfunction, delayed bone marrow suppression, skin pigmentation and pulmonary fibrosis.^{163,225} Ocular toxicity includes nonspecific blurred vision,¹⁴⁷ orbital vasodilation, orbital arteriovenous shunting,^{84,158} glaucoma secondary to orbital congestion or rubeosis,^{95,121,158} severe orbital pain, acute conjunctival hyperemia,^{91,95,149,156,158,197} corneal edema and/or opacities,¹²¹ internal ophthalmoplegia from ciliary ganglion damage,¹⁵⁸ fibrosis of extraocular muscles,¹²¹ diplopia, vitreous opacification,¹²¹ retinopathy,^{91,95,149,156,158,197} and optic neuritis and atrophy.¹⁶⁸

The route of nitrosourea administration is an important determinant in ocular toxicity. Oral therapy is usually benign except for the occasional potentiation of radiation optic neuropathy observed with CCNU.²³⁴ High dose (800 mg/m²) intravenous therapy is weakly associated with mild, nonspecific forms of ocular toxicity, such as conjunctival hyper-

emia and nonspecific blurred vision, after days to weeks of therapy in only about 4% of patients.¹⁹⁷ During intravenous therapy optic neuritis has been observed, although this association has been called into question.¹⁴⁹

Intracarotid administration of nitrosoureas accounts for the majority of the well-established and common toxicity associated with this agent. Acutely, patients can experience transient ipsilateral periorbital edema, orbital pain, conjunctivitis and/or chemosis.¹⁹⁷ A delayed, severe, ipsilateral, neuroretinal toxicity occurs in approximately 70% of patients.^{91,95,149,156,197} Of these patients, 40–75% progress to no light perception vision.¹⁹⁷ Onset occurs 2–14 weeks (mean 6 weeks) after therapy.^{91,95,156,197} Incidence is dependent on the dose, number and rapidity of intracarotid infusions.^{91,95,156,197} The delay in development of toxicity implicates long-acting active metabolites.^{43,163}

Clinically, the fundoscopic findings of intracarotid toxicity consist of arterial narrowing, nerve fiber-layer infarcts, intraretinal hemorrhages and disc edema (Fig. 1).^{91,95,156,197} Fluorescein angiography shows segmental perivasculär staining, widespread late capillary leakage and optic nerve head hyperfluorescence.¹⁹⁷ Pathologically, cilioretinal artery occlusion and choroidal fibrin thrombi have been documented in humans¹⁹⁷ and severe necrotizing arteriolitis in dogs.⁶⁰

In contrast, one study showed a comparatively low incidence of visual loss from BCNU; only one of 14 patients, which was secondary to a central retinal artery occlusion.¹³³ The authors attributed the relatively mild toxicity to a shorter duration of infusion (10–15 minutes as opposed to 45) and/or pretreatment with intravenous corticosteroids. Despite a lack of visual loss, these patients did manifest retinal rod dysfunction (100%) and cone dysfunction (67%) on ERG. One patient displayed an abnormal ERG in the eye contralateral to the infusion, presumably secondary to diffusion of BCNU across the anterior communicating artery.

Orbital toxicity, consisting of increased orbital vascularity, vasodilation, arteriovenous shunting and glaucoma secondary to orbital congestion is another complication of intracarotid infusion.^{84,158} Additionally, there has been a case of ischemic optic neuropathy.¹⁶⁸ A vasculopathy, analogous to that described in the retina,¹⁹⁷ was thought to occur in the posterior ciliary artery circulation.

The ability of nitrosoureas to penetrate the blood-brain and blood-retinal barriers contributes to their neuro-retinal toxicity.¹⁶³ Ocular toxicity, however, is rarely seen with intravenous therapy and occurs mainly ipsilateral to intracarotid infusion.^{91,95,156,197} In a rabbit model, BCNU adminis-

tered subtenon-retrobulbarly, intracamerally and intravitreally was tolerated with no significant ocular changes.¹⁴⁵ It is evident that a very high local nitrosourea concentration, as occurs with intracarotid infusion, is necessary to produce significant ocular toxicity.

Ocular toxicity can be prevented if the infracarotid catheter is advanced beyond the origin of the ophthalmic artery. However, this results in delayed cerebral necrosis in approximately 80% of patients.^{43,77} Toxicity might also be prevented with pressure on the eye during infusion⁸⁴ or by decreasing orbital and ocular blood flow with a Honan balloon.¹⁵⁸ Ethanol, used as a solvent, has been implicated in causing or contributing to the toxic effects of nitrosoureas.⁹¹ As an alternative, 4% dextrose and water has been suggested.⁴³ However, in the absence of ethanol, toxicity has still occurred.¹⁵⁸ A shorter duration of infusion and/or reduced ocular perfusion are, therefore, the best demonstrated ways to reduce toxicity.

G. BUSULFAN

Busulfan is an alkylating agent mainly used orally in the therapy of chronic myelocytic leukemia (CML), polycythemia vera and myelofibrosis with myeloid metaplasia. Systemic toxicity includes testicular atrophy, malaise, diarrhea, weight loss, amenorrhea, bone marrow suppression, pulmonary fibrosis, Addison's-like syndrome, myasthenia gravis, endocardial fibrosis and atypical epithelial cell accumulations.^{55,63,202,227}

Ocular toxicity is most frequently cataract formation, typically a posterior subcapsular cataract (PSC) with a polychromatic sheen.^{55,170,173,199,202} Busulfan-induced cataracts are well established. Less commonly, patients can develop non-specific blurred vision and keratoconjunctivitis sicca.^{82,199}

PSC is usually seen after months to years of chronic busulfan therapy, 2–6 mg/day, for CML.^{55,171,173,202} Approximately 10% of patients develop definite PSC and 30% early PSC.¹⁷¹ Of the patients with definite PSC only 25% have visual impairment necessitating cataract extraction.¹⁷¹ The incidence and severity of PSC increase with duration and total dose of busulfan therapy. Patients with PSC had a mean duration of therapy of 113.5 months.¹⁷¹ Patients with early PSC or no PSC had mean durations of therapy of 27.2 and 12 months, respectively.¹⁷¹ There was no correlation with patient age or duration of disease.¹⁷¹

Busulfan-induced PSC is reproducible in a rat animal model.²¹⁸ The mechanism of busulfan toxicity has been postulated to be decreased DNA synthesis in the lens epithelium.^{93,94,171} This is supported by animal work in rats showing decreased

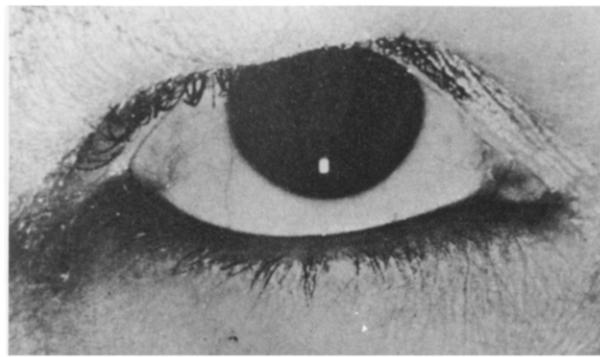
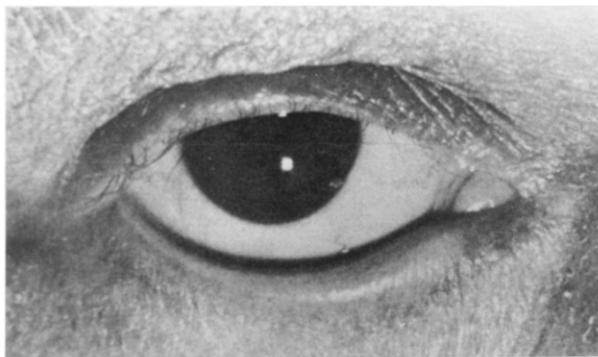


Fig. 2. Left: Patient demonstrating cicatricial ectropion while on 5-FU. *Right:* Same patient demonstrating resolution of cicatricial ectropion after discontinuation of 5-FU. (Reprinted from Straus DJ, Mausolf FA, Ellerby RA, McCracken JD²⁰⁷ with permission of the authors and publishers of *Medical and Pediatric Oncology*.)

mitotic activity in the lens epithelium and nuclear disintegration with chromatin aggregation.⁹⁴ Pathologically, a busulfan PSC is no different from the PSC seen typically with aging or corticosteroids.¹⁰⁰

II. Pyrimidine Analogs

A. 5-FLUOROURACIL

5-Fluorouracil (5-FU) is a pyrimidine analogue which blocks thymidylate synthetase, an enzyme necessary for DNA and thymidylate synthesis. It is a commonly used agent, especially in breast, gastrointestinal and genitourinary tract cancers. Topically and/or locally it is also used in glaucoma filtering surgery and in the treatment of actinic keratoses and basal-cell carcinoma.

Systematic toxicity consists of nausea, vomiting, diarrhea, mucositis, bone marrow suppression, alopecia, and a dose-related cerebellar ataxia.²⁴ Ocular toxicity is manifest as a variety of ocular surface and/or neuroophthalmologic problems. These include blurred vision, circumorbital edema, ocular pain, photophobia, excessive lacrimation, conjunctivitis, blepharitis, keratitis,^{24,42,99,113} cicatricial ectropion,²⁰⁷ ankyloblepharon,¹¹⁵ punctal-canicular stenosis,^{32,97,191} necrosis after lid cryotherapy,¹²⁸ blepharospasm,¹⁸⁴ oculomotor disturbances,¹⁷ nystagmus⁹²⁸ and optic neuropathy.^{1,5,227} It is notable that skin, mucous membrane, corneal and optic nerve toxicities are potentiated by concurrent radiation therapy.¹⁸⁷

Cicatricial ectropion, (Fig. 2, left), ankyloblepharon, and punctal-canicular stenosis with epiphora are longterm complications noted in several case reports after 6–14 months of 5-FU therapy.^{32,97,115,207} Although uncommon, a cause and effect seems likely since these fairly specific toxicities have been reported independently by several au-

thors. If recognized early and if 5-FU is able to be discontinued, these complications can resolve with lid massage and topical corticosteroids (Fig. 2, right).²⁰⁷ If 5-FU therapy cannot be stopped, prophylactic silastic intubation of the lacrimal system is advocated.³² Eyelid and/or lacrimal system complications may be irreversible and necessitate surgery, which has a variable prognosis.^{97,191,207}

Blurred vision, excessive lacrimation, blepharitis, conjunctivitis and keratitis are well established, acute, and fairly common side effects, which occur in 25–38% of patients.^{24,32,42,97,99,191} The etiology of these ocular surface toxicities is multifactorial. Inhibition of DNA synthesis in rapidly proliferating tear duct, conjunctival, and corneal epithelial cells certainly plays a major role.¹⁹⁴ Several local factors also contribute. Excessive lacrimation may be a reflex phenomenon from irritation to the cornea or conjunctiva and/or from an induced decrease in basal tear secretion.³² The incidence and severity of lacrimation are correlated with the concentration of 5-FU in the tears.⁴² However, lacrimation and tear concentrations are not directly related to plasma concentrations.⁴² 5-FU perhaps causes lacrimal gland irritation in susceptible individuals and then secondarily gains access to the tears via the lacrimal gland, causing further ocular surface toxicity.⁴² Concurrent 5-FU-induced ectropion and/or dacryostenosis will further worsen toxicity through corneal exposure problems and increased 5-FU tear concentration and contact time.^{32,97,115,207} Fortunately, acute surface toxicity appears gradually and almost uniformly resolves 2–3 weeks after cessation of 5-FU therapy with or without using topical antibiotic-corticosteroid combinations.^{24,32,42,99}

A cause and effect relationship between systemic 5-FU and ocular toxicity is supported by the observation of similar ocular surface problems when 5-FU is used subconjunctivally to inhibit fibroblast

proliferation in glaucoma filtering surgery. Approximately 50% of these patients develop corneal epithelial defects which resolve in several weeks.^{130,138} Other, less common, toxicities noted with subconjunctival 5-FU include conjunctival epithelial defects, conjunctival wound leaks, keratinizing corneal plaque with stromal infiltration, and bacterial and sterile corneal ulceration.^{130,138}

Neuroophthalmologic toxicity from 5-FU is much less common and less well established than surface toxicity. Several authors have reported an acute, recurrent toxic optic neuropathy.^{1,5,227} Cerebellar dysfunction is common and can uncommonly be associated with a coarse nystagmus.²²⁸ Diplopia, secondary to convergence or divergence weaknesses and medial and lateral rectus muscle palsies, were reported in two patients in whom these signs predated the onset of cerebellar dysfunction.¹⁷

Severe blepharospasm, in the absence of other eye findings, has been noted in two patients receiving tagafur, a prodromal drug of 5-FU, in combination with mitomycin or cyclophosphamide and adriamycin.¹⁸⁴ A direct irritation of the sensory nerve endings and/or of the central nervous system was proposed.

Increased lid necrosis was manifested in one patient on systemic 5-FU who underwent cryoablation of eyelash hairs for coincidental entropion and subsequently developed full thickness lid necrosis.¹²⁸ Inhibition of DNA synthesis by 5-FU was thought to be impairing cellular repair and thus resulting in tissue devitalization.

B. CYTOSINE ARABINOSIDE

Cytosine arabinoside interferes with DNA synthesis by inhibiting DNA polymerase. It is primarily used in a high dose regimen (3 gms/m² intravenously every 12 hours for 5–6 days) to treat acute myelogenous leukemia and refractory lymphomas.^{108,183} Systemic side effects are acute nausea and vomiting, bone marrow suppression, cerebral and cerebellar dysfunction, alopecia, neuropathy, anaphylaxis, hepatotoxicity, stomatitis and dermatopathy.^{9,107,137,183}

Ocular toxicity with high dose therapy typically consists of a keratoconjunctivitis.^{37,112,135,178} Less commonly, severe visual loss secondary to optic neuropathy results from intrathecal administration during therapy of leukemia.¹⁵³ The development of optic neuropathy in this setting may be potentiated by concurrent therapeutic cranial irradiation.¹⁵³

After 5–7 days of high dose cytosine arabinoside the patient frequently presents with pain, lacrimation, foreign body sensation, photophobia, and blurred vision.^{37,112,135,178} Corneal findings include central punctate opacities with subepithelial granu-

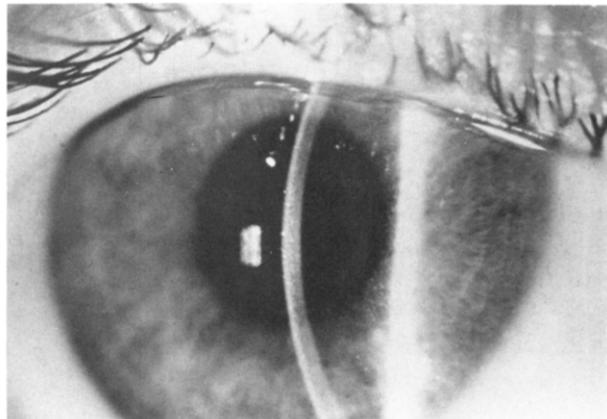


Fig. 3. Corneal epithelial microcysts and superficial punctate keratitis in a patient who received high dose intravenous cytosine arabinoside therapy.

lar deposits, refractile microcysts, superficial punctate keratitis, mild stromal edema, and striae in Descemet's membrane (Fig. 3).^{112,125,135,178} The severity of these signs and symptoms is related to dose and duration of therapy.^{135,178} The incidence of keratitis with high dose therapy is well established and common, ranging from 38–100%.^{135,178} Symptoms resolve after several days, visual acuity improves after two weeks and corneal opacities resolve after four weeks off cytosine arabinoside.^{135,178}

The mechanism of cytosine arabinoside-induced keratitis is thought to be nonselective inhibition of DNA synthesis.^{125,135} The corneal epithelium is particularly susceptible, due to its rapid cell replication.^{125,135} Resulting cellular degeneration has been demonstrated in vitro²⁵ and histopathologically.^{70,112,125} Similar corneal toxicity during topical cytosine arabinoside administration further supports a cause and effect relationship.^{70,125} Drug-induced keratitis remains a major obstacle to widespread use of topical cytosine arabinoside in the treatment of herpes simplex keratitis.

The high frequency of keratitis may be explained several ways. First, cytosine arabinoside penetrates the blood-brain barrier and would be expected to similarly penetrate the blood-aqueous barrier.^{112,135,137} Second, the high doses of cytosine arabinoside associated with ocular toxicity saturates the body's deaminase inactivation system.¹¹² This system normally inactivates the agent and limits its toxicity.¹¹² Finally, tear concentrations after high-dose cytosine arabinoside therapy are in the range which have caused corneal toxicity in vitro and in vivo.^{25,101}

Resolution of symptoms and gradual clearing of keratitis occur several weeks after completion of

therapy.¹³⁵ Since the incidence of keratitis is high, prophylaxis is warranted. Prednisolone phosphate (1%) given prophylactically four times a day topically, was prospectively compared with placebo in patients receiving high dose cytosine arabinoside. Of 11 patients, 10 had significant reduction in signs and symptoms, experiencing only mild irritation and showing only conjunctival erythema and a slight number of microcysts, as compared to controls.¹³⁵ Topical corticosteroids were thought to be protective against cytosine arabinoside toxicity by reducing inflammation and/or by slowing cell replication through inhibition of DNA and protein synthesis.¹³⁵

Use of topical corticosteroids for prolonged periods can also cause ocular toxicity. Opportunistic infections, in an already immunocompromised group of patients, are a particularly hazardous potential side effect. The search for an alternative method of prophylaxis against cytosine arabinoside-induced keratitis led to using topical 2-deoxy-cytidine, a competitive, nontoxic inhibitor of cytosine arabinoside at the level of DNA synthesis.¹³² 2-deoxycytidine was shown to prevent cytosine arabinoside toxicity in several in vitro and in vivo models.^{25,44,72,125,152} Prospectively it was evaluated and noted to be equivalent to 1% prednisolone phosphate; both agents were significantly better than placebo in preventing keratitis in 12 patients on high dose cytosine arabinoside.¹³⁶

III. Purine analogs-Fludarabine

Fludarabine is a relatively new agent which, similar to other purine analogs, is incorporated into RNA and DNA thus inhibiting DNA synthesis.⁴⁵ It is currently being evaluated in clinical trials as therapy for a variety of neoplasms.²²⁴ Systemic side effects include bone marrow suppression, gastrointestinal upset, hepatic toxicity and encephalopathy.²²⁴

Decreased visual acuity was the most common presenting sign prior to the development of progressive encephalopathy in a group of patients studied by Chun and associates.⁴⁵ Although detailed ophthalmologic data were not presented, it appeared that loss of vision was secondary either to optic neuritis, with or without disc edema, and/or cortical blindness. Several cases of diplopia and photophobia were also reported. CNS toxicity was dose-related; occurring in 13 of 36 (36%) receiving $\geq 96 \text{ mg/m}^2/\text{day}$ for 5–7 days versus 1 of 443 (0.2%) who received low dose therapy ($\leq 125 \text{ mg/m}^2$ total). Progressive demyelination appeared to be the likely mechanism. Further documentation and prospective detailed ophthalmologic evaluations are needed to establish this agent's ocular toxicity.

IV. Vinca alkaloids-Vincristine

Vincristine is a plant alkaloid derived from the periwinkle. It binds to intracellular tubulin protein producing DNA metaphase arrest by interfering with spindle protein synthesis.¹⁷⁶ This agent is used in a variety of leukemias, lymphomas and solid tumors. Dose limiting systemic toxicity is a reversible neurologic dysfunction, occurring in up to 80% of patients. The first manifestation of neurotoxicity usually is hyporeflexia, later followed by paresthesias, motor weakness, constipation, ileus, bladder atony, diffuse cerebral dysfunction, seizures and autonomic dysfunction. Other systemic side effects include nausea, bone marrow suppression, alopecia, hypertension and the syndrome of inappropriate antidiuretic hormone.^{33,126,181,185,192} Ocular toxicity also is primarily neurologic and is manifested by cranial nerve palsies, optic neuropathy and atrophy, cortical blindness, and night blindness.^{2,3,8,76,103,162,177,185,186,192,198} Intravitreal vincristine in animal models has resulted in profound pathology in all retinal cell types.^{90,103,220} Vincristine-induced neuromyopathy in human subjects has been detailed extensively by Bradley, et al clinically, electrophysiologically and pathologically.²⁷ Neurotoxicity has been associated with neurofibrillary degeneration, loss of neurotubules, accumulation of neurofilaments, paracrystalline optic nerve terminal inclusions and/or impairment of axonal flow.^{13,27,29,36,196,211}

Cranial nerve palsies have resulted in the ocular signs of ptosis, extraocular muscle palsies, internal ophthalmoplegia, corneal hypesthesia and lagophthalmos, with ptosis being the most common.^{2,185} Cranial nerve palsies are the most frequent and well established ocular side effect of vincristine, occurring in up to 50% of patients.² The incidence is dose-related. On the average, patients developing cranial nerve palsies received a mean total of 17.7 mg of vincristine (range 2.6–136 mg) over a mean of 10 weeks (range 2–44 weeks).² Patients with hepatic dysfunction have a higher incidence of cranial nerve palsies secondary to impaired vincristine deactivation.^{23,185,195} Hepatic toxicity is thought to be the mechanism by which L-asparagine and isoniazid result in synergistic neurotoxicity, including ocular neurotoxicity, when given with vincristine.^{110,134,228} Cranial nerve palsies fortunately resolve in approximately 90% of patients anywhere from 2–24 weeks (mean 11 weeks) after cessation of therapy.²

Optic neuropathy linked to vincristine was first reported in 1976 in a patient who had received 48 mg of intravenous vincristine over 14 months and developed poor visual acuity, decreased pupillary response to light, and faulty color discrimination

with pallor of the optic discs.¹⁸⁶ Autopsy revealed bilateral loss of retinal ganglion cells, thinning of the retinal nerve fiber layer, and loss of nerve fibers together with extensive demyelination posterior to the lamina cribrosa. Other reports of bilateral¹⁹⁸ and unilateral¹⁶² optic neuropathy linked to vincristine followed and strengthened the association. Optic neuropathy can resolve off of therapy.^{162,198} However, irreversible blindness with optic atrophy has been reported.^{8,153} Optic neuropathy, although less common than cranial nerve palsies, is therefore a potentially more serious complication.

The low incidence of central nervous system (CNS) side effects, excluding cranial nerve palsies, with vincristine is explained by its poor penetration of the blood brain barrier.^{103,198,220} Vincristine may gain access to the CNS and cause toxicity in individuals who have vascular changes from their underlying disease and/or radiation therapy.¹⁹⁸ Vincristine-induced optic neuropathy is difficult to differentiate from optic neuropathy caused by underlying disease, especially CNS leukemia with optic nerve infiltration, and/or by concurrent radiation therapy.¹⁹⁸ Therefore, although vincristine-induced optic neuropathy is a fairly well established entity, complaints of blurred vision in a patient receiving vincristine should receive prompt attention with regard to delineating a cause, e.g., tumor infiltration, radiation or drug toxicity, which can be managed appropriately. An orbital and head CT scan looking for leukemic infiltration and a lumbar puncture searching for evidence of leukemic cells is useful in this context.

Vincristine-induced night blindness, reported in one case, is identical to recessively inherited stationary night blindness.¹⁷⁷ This finding is thought to occur in patients with an altered blood-retinal barrier secondary to underlying disease and/or concurrent radiation therapy. The dark adaptation curve is monophasic, lacking a scotopic branch; rhodopsin kinetics are normal; spectral threshold data reveal residual rod-mediated vision; and the ERG b-wave is grossly depressed with a normal a-wave. The mechanism appears to be interference with synaptic transmission between photoreceptors and their second order neurons by disruption of neuronal microtubules. Photoreceptors are otherwise functionally normal. Although well documented, this isolated phenomenon needs further case reports for substantiation.

Transient cortical blindness was reported in three children receiving intravenous vincristine.³¹ None had received any radiation therapy. Two had received methotrexate and/or L-asparaginase in addition to vincristine. Vincristine was implicated because of the time course in all three patients and

the recurrence of severe CNS toxicity with blindness in one patient who was rechallenged. All recovered from 24 hours to 14 days without visual field defect. The low number of patients and concurrent therapy should make one cautious about attributing this toxicity to vincristine.

V. Folic Acid Analogs-Methotrexate

Methotrexate inhibits dihydrofolate reductase which transforms folic acid into coenzymes necessary for DNA synthesis. It is used in leukemias and a variety of solid tumors including uveal carcinoma.⁸⁰ As an immunosuppressive, it is increasingly being employed in conditions such as chronic uveitis and rheumatoid arthritis. Systemic toxicity includes nausea, vomiting, stomatitis, bone marrow suppression, gastrointestinal disturbance, renal failure, arachnoiditis and CNS dysfunction.^{80,206} High dose intravenous therapy (30–250 mg/kg) results in complete bone marrow aplasia and must be followed by leukovorin "rescue" to replace depleted folate pools in normal cells so that DNA synthesis may resume.²⁰⁶

Ocular toxicity with high dose therapy is well established, occurs in approximately 25% of patients and consists of periorbital edema, photophobia, ocular pain and burning, blepharitis, aggravation of seborrheic blepharitis, conjunctivitis and decreased reflex tear production.^{24,65,82,117} Toxicity occurs 2–7 days after initiation of therapy, before leukovorin rescue, usually resolves off therapy within one week, and recurs with reinstitution of the drug.⁶⁵ Symptoms are partially relieved by artificial tear drops.⁶⁵

The mechanism of toxicity probably relates to inhibition of DNA synthesis in the rapidly dividing cells of the corneal and conjunctival epithelium. The concentration of methotrexate in the tears is similar to that associated with inhibition of DNA synthesis in the bone marrow and gastrointestinal mucosa.^{38,65} There is a direct relationship between plasma and tear drug levels.⁶⁵ However, concentration of drug in tears did not correlate with ocular toxicity.⁶⁵ One explanation for this finding is that some patients may secrete tears that are acidic, decreasing methotrexate solubility and increasing its toxicity. Topical ophthalmic leukovorin would be expected to reduce ocular toxicity in this context.⁶⁵

Methotrexate administered intrathecally and by carotid artery infusion also produces ocular toxicity. Optic neuropathy and/or internuclear ophthalmoplegia are seen with intrathecal use and potentiated by the use of concurrent cranial radiation.⁴¹ Intracarotid infusion of methotrexate, following intracarotid mannitol, to open the blood brain barrier, and intravenous cyclophosphamide, can pro-

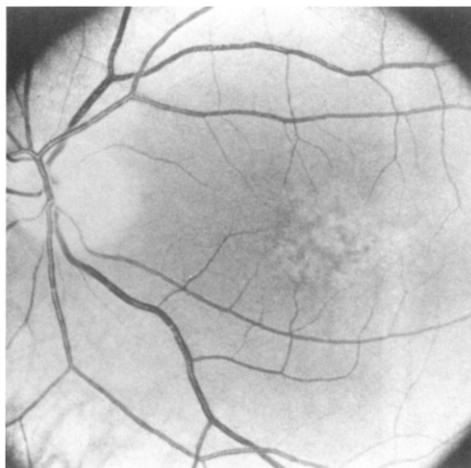
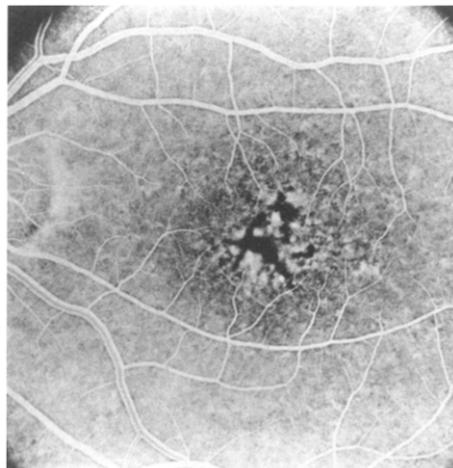


Fig. 4. Left: Fundus photograph of a patient who received an ipsilateral intracarotid artery injection of mannitol and methotrexate demonstrates macular retinal pigment epithelial changes. *Right:* Fluorescein angiogram of same eye. (Reprinted from Millay RH, Klein ML, Shults WT, et al.¹⁵⁷ with permission of the authors and The Ophthalmic Publishing Company.)



duce macular edema and retinal pigment epithelial changes (Fig. 4).¹⁵⁷

VI. Methyl Hydrazine Derivatives- Procarbazine

Procarbazine inhibits monoamine oxidase resulting in auto-oxidation leading to DNA denaturation. It is employed mainly in patients who have Hodgkin's disease and small cell lung cancer. Systemic toxicity consists of nausea, vomiting, bone marrow suppression, rash, side effects common to monoamine oxidase inhibitors, CNS dysfunction, immunosuppression and an Antabuse-like effect.

Ocular toxicity is uncommon, not well established, and takes the form of photophobia, retinal hemorrhages, nystagmus, diplopia and/or disc edema.²¹⁷

VII. Antihormonals

A. TAMOXIFEN

Tamoxifen, an estrogen antagonist, is the hormonal therapy of choice in disseminated breast cancer. Tamoxifen interferes with the binding of estradiol to its target tissues via depletion of cytoplasmic receptors and competitive inhibition at the receptor site.⁴⁶ A 60% remission rate is achieved if the patient's breast cancer tissue is estrogen-receptor-positive, compared to less than 10% for estrogen-receptor-negative patients.⁷¹ Other hormonal therapies — oophorectomy, adrenalectomy, estrogens, androgens and corticosteroids — give similar results. However, in several clinical trials, tamoxifen has proven to be the safest alternative.^{50,109,139,212,214} Systemic side effects with the standard dose of 10–20 mg twice a day have been limited to mild nausea, hot flashes, mild fluid retention and, rarely, cytopenias.^{50,109,139,212,214}

Kaiser-Kupfer and Lippman¹¹⁸ first described a

unique keratopathy and retinopathy in four patients on high dose therapy (60–100 mg/m² twice a day) for more than one year. The keratopathy consisted of bilateral white, whorl-like, central, subepithelial opacities (Fig. 5, left), resulted in decreased visual acuity, and was reversible on cessation of therapy in one of four patients. The retinopathy was characterized by white refractile opacities superficial to retinal blood vessels, forming clusters located in the paramacular and foveal areas with the greatest number temporally (Fig. 5, right). Retinopathy was associated with cystoid macular edema clinically and on fluorescein angiography, and was irreversible on cessation of therapy. Subsequently McKeown et al¹⁵⁵ supported the association by independently reporting identical findings in another patient on high dose therapy.¹⁵⁵ Ocular toxicity with standard dose tamoxifen has not been reported in several large clinical trials,^{50,109,139,212,214} nor was it found when specifically looked for.¹¹ However, there has been a report of similar retinopathy, with additional peripheral pigmentary changes, in two patients on only 30 mg daily for nine months.²¹⁵

In one of the four patients reported by Kaiser-Kupfer and Lippman¹¹⁹ a postmortem examination was performed. The macular lesions measured 3–10 microns and the paramacular lesions 30–35 microns in diameter.¹¹⁹ They were both seen confined to the nerve fiber and inner plexiform layers with positive staining for glycosaminoglycans. On electron microscopic examination the lesions were composed of filaments and vesicles. The smaller lesions were located intracellularly and the larger extracellularly. Their occurrence in and around axons explained their superficial and macular location clinically and indicated a unique type of axonal degeneration.

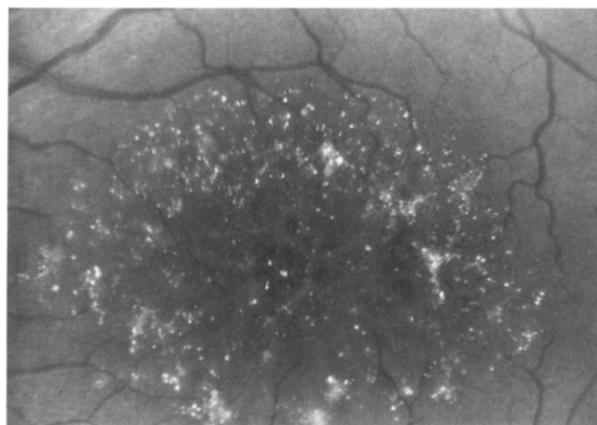
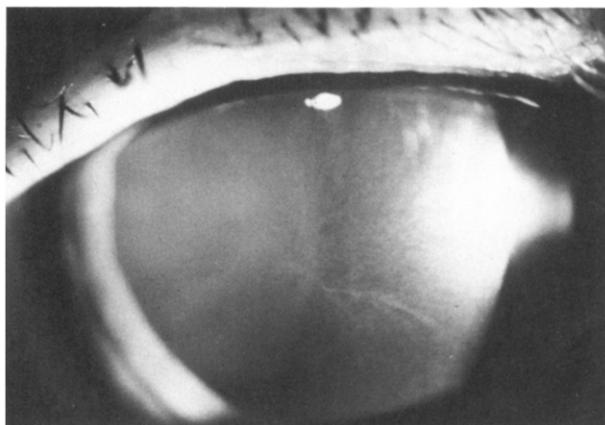


Fig. 5. Left: Cornea of a patient on high dose tamoxifen demonstrates superficial, white, subepithelial whorl-like opacities. *Right:* Fundus photograph of a patient on high dose tamoxifen demonstrates macular edema with multiple white refractile paramacular retinal opacities. (Reprinted from Kaiser-Kupfer MI, Lippman ME¹¹⁸ with permission of the authors and publishers of *Cancer Treatment Report*.)

The mechanism of tamoxifen keratopathy and retinopathy is unknown, as is the status of estrogen receptors in the eye. However, tamoxifen is structurally similar to a group of cationic amphiphilic compounds, which include triparanol, chloroquine, quinacrine, chlorpromazine, thioridazine, amiodarone, and tilorone. Several of these agents are known to produce a similar retinopathy and keratopathy. These agents are thought to produce toxicity by forming tight but reversible bonds with polar lipids, resulting in accumulation of drug-polar lipid complexes in lysosomes.^{22,66,150}

Although there have been few actual cases reported, the uniqueness of the findings and the thoroughness of the authors' investigations have led to tamoxifen keratopathy and retinopathy being considered a well established phenomenon.

B. NAFOXIDINE

Nafoxidine is another antiestrogen used infrequently in the treatment of breast cancer. This drug has been found to be cataractogenic in dogs and cause bilateral severe cataracts in one of 52 patients (2%) receiving 60–90 mg three times a day for three years.²⁰ More investigation is needed before ascribing a definite association with ocular toxicity.

VIII. Corticosteroids

Systemic corticosteroids are commonly used, alone and in combination with other antineoplastics, for a variety of cancers — in particular, lymphomas, leukemias, and multiple myeloma. Corticosteroids also are routinely employed to reduce edema associated with central nervous system metastases and metastatic spinal cord compression,

and to treat paraneoplastic disorders such as hypercalcemia and immune hemolysis. Their mechanism of antineoplastic action is not clear. They are immunosuppressive, cause lysis of lymphocytic elements by inhibiting cell protein synthesis, suppress mitoses, and bind to certain proteins produced by leukemic cells.

Systemic toxicity from corticosteroids is well established and includes fluid retention, hyperglycemia, hypokalemia, gastric ulcers with bleeding, immunosuppression, osteoporosis, hypertension, myopathy, adrenal suppression, pancreatitis, cutaneous fragility, psychiatric reactions, growth impairment, weight gain, anaphylaxis, raised intracranial pressure, avascular necrosis of the femoral head, and Cushingoid redistribution of body fat.^{160,190} Many of these toxicities can be avoided if dose and duration do not exceed 100 mg of prednisone or its equivalent per day for up to three weeks.¹⁹⁰

The ocular toxicity of corticosteroids is well established and common. Toxicity includes blurred vision, acute myopia, subconjunctival and retinal hemorrhages secondary to blood vessel friability, myopathic extraocular muscle palsy,⁵⁷ exophthalmos,^{47,123,201} scleral discoloration and thinning,^{53,106} increased intraocular pressure and glaucoma,^{88,189} posterior subcapsular cataract (PSC),^{16,18} opportunistic infections,^{34,68,216,237} disc edema secondary to pseudotumor cerebri,^{49,221} and visual field defects.⁵⁷ Corticosteroids in combination with the antineoplastics azathioprine or cyclophosphamide result in an additive risk for development of PSC.^{98,131,172,210} Several of these toxicities have been reported and/or studied in other than cancer patients. However, because these studies enhance an understanding of

these toxicities and because corticosteroids are so commonly used in cancer chemotherapy, we have included these studies unless the toxicity was disease-dependent.

Posterior subcapsular cataracts, usually bilateral, are the most common ocular complication of systemic steroids. Diabetes mellitus^{129,238} and concurrent periocular radiation therapy⁵⁹ are significant risk factors for acceleration of corticosteroid-induced cataracts. Development of Cushingoid features may be an independent predictor for development of cataracts.⁷⁸ Cortisol-binding protein is found in the lens⁶⁴ and corticosteroids in rabbits have been observed to alter lens cation transport.¹⁰⁴ However, the mechanism of corticosteroid-induced cataracts remains unclear.

Corticosteroid-induced PSC was first described in patients with rheumatoid arthritis by Black et al¹⁸ in 1960. PSC have also been observed as a result of topical corticosteroids.^{12,30,83,238} In the 8–10 years following Black's initial observation, a large body of literature, listed elsewhere,¹⁶ confirmed the association in a variety of patients. The development of a PSC usually occurs chronically with duration of treatment greater than one year and a daily dose of more than 10 mg of prednisone or its equivalent.^{16,18,53,57,86,105} Overall incidence and severity ranges from 10–40% with 0–20% developing symptomatic visual impairment.^{16,18,53,57} Onset ranges from 1.1 to 8.8 years after initiation of chronic therapy with a mean of 3.7 years in one representative study.¹⁶ A wide variety of duration and dose relationships has been reported. However, the incidence of PSC generally increases with increasing dose and duration of therapy.

Children develop corticosteroid cataracts more commonly than adults. PSC from corticosteroids is usually seen in association with growth suppression and bone maturation delay.^{15,180} An alternate-day or inhaled regimen of chronic corticosteroids in children does not result in corticosteroid cataract.¹⁶⁰ However, the combination of alternate-day prednisone and daily inhaled beclomethasone has been observed to potentiate the development of cataracts.²³⁶

Exceptions exist to the usual relationship between corticosteroids and the development of cataracts. Rarely, short-term corticosteroid treatment, as little as 5 mg prednisone daily for two months, can induce cataracts.^{57,148} Reversibility of corticosteroid-induced cataracts has been observed on reduction of dose to less than 10 mg of prednisone per day.²⁰⁴ Conversely, progression of cataract after discontinuation of corticosteroids has also been reported.^{12,53} More recent studies uphold the association between corticosteroids and cataracts but

found no correlation to total amount or duration of treatment.^{78,148,200} These authors suggest that individual variability may be the most important factor in developing corticosteroid cataracts.²⁰⁰ Suffice it to say that there is no entirely safe dose. Early and regular ophthalmologic examinations with reduction in corticosteroid as indicated and allowed is the most appropriate course.

Exophthalmos induced by exogenous corticosteroids was first reported by Slansky et al²⁰¹ in four patients on prednisone for 3–12 years. Only three patients have been reported since.^{47,123} Exophthalmometry ranged from 22–28 mm.¹²³ All patients were euthyroid and no other etiology was evident, including a CT scan of the orbits in the two later studies. CT scan showed an increase in orbital fat and the absence of an orbital mass or extraocular muscle enlargement.^{47,123} Symptoms in all cases were limited to mild signs of exposure keratoconjunctivitis. There was no compromise of the anterior segment, alteration of vision, compression of optic nerves or progression of exophthalmos despite continuation of steroids. In one case there was a reduction of exophthalmos upon decreasing the dose of prednisone.²⁰¹

A 6–8% incidence of exophthalmos and identical CT findings results from endogenous overproduction of corticosteroids in Cushing's syndrome.¹⁵⁹ In addition, reproducible animal studies in rats, guinea pigs and rabbits show induction of exophthalmos by exogenously administered corticosteroids.^{6,7,232,233} These findings support the association between therapeutic corticosteroids and exophthalmos. However, critics point out the possibility of euthyroid Graves' disease and the lack of any trial off corticosteroids to observe regression.¹²³ Obviously, further investigation and case reports are needed before a definite association is made. Although none of the patients reported had cancer we mention this toxicity to help differentiate it, if it occurred in a cancer patient, from exophthalmos secondary to metastatic disease.

Scleral thinning and bluish-gray discoloration has been reported in a patient with systemic lupus erythematosus after six years of up to 60 mg/day of prednisone.¹⁰⁶ This finding is also seen in children with growth impairment from corticosteroid therapy and in patients with scleritis treated with corticosteroids.⁵³ Luckily, it appears to be only of cosmetic significance. Since corticosteroids are often given concurrently with chemotherapy agents that can produce ocular inflammation and/or growth suppression in children this side effect is possible, although, based on lack of reports, unlikely in the cancer patient.

A reversible rise in intraocular pressure (IOP)

can occur with systemic corticosteroid therapy of months to years duration^{57,88,189,210} and, more commonly, with topical corticosteroids where the incidence is approximately 30%.^{30,161,240} No rise in IOP was seen with alternate day prednisone or daily inhaled beclomethasone dipropionate.¹⁶⁰ The mechanism of corticosteroid-induced IOP increase is suggested to be a decrease in aqueous outflow from edema of collagen in the trabecular meshwork and/or an increase in aqueous production.^{57,104,142} Risk factors are pre-existing glaucoma, a positive family history of glaucoma, diabetes mellitus, and myopia.^{57,189}

Immunosuppression leading to infectious complications is a potential side effect of systemic corticosteroids. An in-depth discussion of the mechanisms and spectrum of ocular infections is beyond the scope of this paper. However, three types of unusual opportunistic infections deserve mention. Candida endophthalmitis, cytomegalovirus retinitis and ocular toxoplasmosis are becoming an increasing problem and must be included in the differential diagnosis of posterior uveitis in the cancer patient.^{12,34,68,216,237}

Corticosteroids are commonly used to treat increased intracranial pressure secondary to CNS metastases. Ironically, they can also be a cause of increased intracranial pressure and papilledema. Pseudotumor cerebri secondary to corticosteroids has been reported in approximately 30 patients and recognized in many more.^{49,221} Typically, it is a younger patient on corticosteroids for months to years, mean 2.5 years, who presents with a headache and mild papilledema, without retinal hemorrhage, within days to weeks after a change in dose or type of corticosteroid.^{49,221} Approximately one-third also have sixth nerve palsies.^{49,221} Although the mechanism is considered unknown, one postulate has involved a transient hypophyseal adrenal suppression as occurs in pseudotumor cerebri associated with Addison's disease.²²¹

IX. Antimicrobials

A. DOXORUBICIN

Doxorubicin (adriamycin) is an anthracycline antibiotic that binds with DNA, resulting in helical untwisting, intercalation and impairment of template synthesis. It has a broad spectrum of antitumor activity. Systemic toxicity consists of acute nausea and vomiting, mucositis, bone marrow suppression, alopecia, and cardiomyopathy. The latter may occur in an acute form or chronically after doses greater than 600 mg/m².²¹

Ocular toxicity has not been extensively documented but is reported to consist of excessive lacrimation in approximately 25% and rarely conjuncti-

vitis.^{21,217}

B. PLICAMYCIN

Plicamycin (mithramycin) is an antibiotic which inhibits DNA-dependent RNA synthesis by binding with DNA. It is used for treating testicular cancer and hypercalcemia. One specific ocular side effect, rarely reported and needing further documentation, is a unique periorbital pallor.²¹⁷

C. MITOMYCIN C

Mitomycin-C is an antibiotic that causes cross-linking of DNA, similar to the alkylating agents, after an intracellular enzymatic reduction. It is used in a variety of solid tumors. Ocular toxicity takes the form of blurred vision without ophthalmoscopic findings.²¹⁷ It is unusual and needs further documentation.

D. TILORONE

Tilorone is a cationic amphiphilic compound with antiviral, antiinflammatory, immunoregulatory and antitumor properties, without bone marrow suppression, which is being investigated in clinical trials.^{223,229} It appears to have a potential role in immunoadjuvant control of cancer and in the management of graft versus host disease.²²⁹ Systemic side effects include nausea, vomiting, diarrhea, weakness, lethargy, dizziness and insomnia.²²³

Ocular toxicity takes the form of keratopathy²²⁹ and retinopathy.²³⁰ Weiss and coworkers²²⁹ reported five patients on tilorone (2.5–8.4 mg/kg/day orally) who developed bilateral, diffuse, white epithelial and subepithelial corneal opacities in a whorl-like pattern (Fig. 6) associated with mild cornea edema, blurred vision and blue haloes around lights without decrease in measured visual acuity. This keratopathy occurred in 21% 2–4 months after the initiation of therapy. It seemed related to total dose received, and resolved slowly several months after cessation of therapy. Tilorone keratopathy has been reproduced in animals, where it was thought to cytologically mimic mucopolysaccharidosis.¹⁵¹ Similar corneal changes and symptomatology were produced in human volunteers who received the drug topically in a 20% concentration for 10 days.¹²⁴

Conjunctival scraping and lamellar corneal biopsy in two patients showed degenerative changes, cloudy swelling of the epithelium and cytoplasmic inclusions found on electron microscopy to be myelinoid bodies, which were also present in peripheral blood leukocytes.²²⁹ Analysis of conjunctival and corneal specimens showed the presence of tilorone in concentrations of 120 and 400 parts per million, respectively.²²⁹ Biomicroscopic corneal exam and/or conjunctival cytology may be a simple way to

monitor the tissue storage and potential toxicity of the drug elsewhere in the body.²²⁹

Two of the patients reported required continuation of tilorone for 8 to 14 months for total doses of 152 and 189 gms.²³⁰ With continuation of therapy, keratopathy progressed and a retinopathy, consisting of arteriolar narrowing and bilateral fine pigment mottling of the peripheral fundus and macula, developed (Fig. 7). Fluorescein angiography only showed the arteriolar narrowing. Color discrimination was reduced and Goldmann perimetry showed restriction of visual field to the central 20–25 degrees. The photopic electroretinogram (ERG) response was absent and the electro-oculogram (EOG) ratios of the light peak to dark trough were attenuated. Follow-up showed resolution of visual field defects, partial resolution of ERG and EOG attenuation, and no change in ophthalmoscopic exam.

Chloroquine produces a keratopathy and toxic retinopathy with strikingly similar ophthalmoscopic, visual field, color vision, ERG and EOG findings. Chloroquine, and perhaps tilorone, may form free radicals, either from reduction of the quinone group to a semi-quinone radical or, more likely, from hydroxylation by cytochrome P-450. The free radicals may damage the retina directly or by reducing oxygen to superoxide which, if superoxide dismutase is insufficient, may produce toxicity.²³⁰ Ophthalmoscopic, EOG and red light perimetric threshold testing for detection of early chloroquine retinopathy may also be applicable to patients on tilorone. Tilorone is related to a group of cationic amphiphilic compounds; chloroquine, quinacrine, tamoxifen, triparanol, perhexilene, thorazine, mellaril and amiodarone, which produce a similar keratopathy and/or retinopathy thought secondary to accumulation of drug-lipid complexes in lysosomes similar to the mucopolysaccharides.^{22,56,66,85,89,150,155}

Although uncommon, tilorone keratopathy and retinopathy have been well documented and a cause and effect relationship seems very likely.

E. MITOTANE

Mitotane (*o,p'*-DDD) is a derivative of the insecticide DDT.¹¹¹ Secondary to its effects on the adrenal gland, it has been used with some success in the treatment of metastatic adrenocortical carcinoma. It is thought to interfere with steroidogenesis and produce hemorrhagic necrosis in the adrenal cortex by reducing the production, availability and/or utilization of reduced triphosphopyridine nucleotides within adrenal cortical cells. Systemic side effects are nausea, vomiting, diarrhea, malaise, depression, CNS dysfunction, cranial and peripheral



Fig. 6. Cornea of a patient on tilorone demonstrates clouding from edema and white, subepithelial opacities in a whorl pattern. (Reprinted from Weiss JN, Weinberg RS, Regelson W²²⁹ with permission of the authors and The Ophthalmic Publishing Company.)

neuropathies, vertigo and extrapyramidal signs.¹¹¹

Three of 19 patients (16%) in one study receiving 1–10 gms daily for 5–19 months developed a toxic neuroretinopathy with disc edema, retinal hemorrhages and retinal edema while one other patient developed a posterior subcapsular cataract.¹¹¹ In contrast, in a group of 138 similar patients only four (3%) developed ocular toxicity consisting of reversible lens opacities, blurred vision, diplopia, disc edema, and retinal hemorrhages.¹¹⁴ The discrepancy in these studies reveals a need for further investigation before mitotane ocular toxicity can be considered well established. Given the seriousness of the toxicities reported, this type of investigation seems warranted.

X. IMMUNOSTIMULATORS

A. BCG

BCG (bacillus Calmette-Guerin) is a live tuberculin-like bacillus which is an active nonspecific stimulator of humoral and cellular immunity. It is given by a variety of routes. BCG is administered intradermally for patients with recurrent breast carcinomas and malignant melanoma, intralesionally in cutaneous metastases due to malignant melanoma,

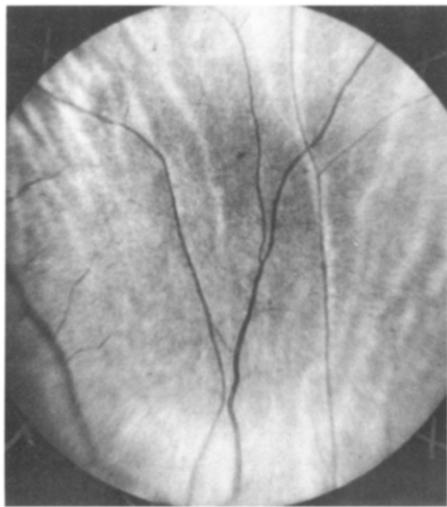


Fig. 7. Left: Fundus photograph of a patient on tilorone demonstrates mild arteriolar attenuation. *Right:* Same eye demonstrates fine pigment mottling of the macula. (Reprinted from Weiss JN, Ochs AL, Abedi S, Selhorst JB²³⁰ with permission of the authors and The Ophthalmic Publishing Company.)



intrapleurally in resectable squamous cell lung carcinoma patients, and intravenously to acute leukemia patients during consolidation or maintenance therapy. Systemic toxicity is usually manifest as fever and rarely BCG septicemia in the immunocompromised host. Donaldson et al⁶⁴ reported the development of uveitis and vitiligo in two patients receiving intradermal treatment with BCG for malignant melanoma. The ocular findings developed 6–9 months after receiving 2–9 site standard intradermal immunizations of BCG and resolved 1–2 months off therapy without sequelae.

In the first patient eye findings recurred six months after an additional 2-site immunization. Additional findings at this time were multiple, small, yellow elevated choroidal lesions with a fluorescein angiographic picture compatible with Vogt-Koyanagi-Harada syndrome. The second patient received several additional 1–2 site immunizations without recurrence of eye disease. In both patients local immunization produced a severe local skin reaction. The development of uveitis and vitiligo was associated with an intense local skin reaction at the immunization site and remission of malignant melanoma. Patients who did not develop these immunologic findings did not have as favorable a prognosis. No eye findings were reported in 155 patients who received BCG injections for a variety of cancers other than malignant melanoma.⁶⁴

Based on their findings, Donaldson et al⁶⁴ suggest that BCG, and perhaps concurrent isoniazid, may augment a cytotoxic autoimmune reaction to melanin-producing cells that results in uveitis, vitiligo, and enhanced regression of malignant melanoma. Their postulate is supported by the naturally occurring autoimmune syndromes — sympathetic ophthalmia and the Vogt-Koyanagi-Harada syndrome

— which produce a similar uveitis and vitiligo. Despite a small number of patients, the uniqueness of these interesting findings and the logic of the underlying pathophysiology makes a causal relationship between drug and toxicity seem likely.

B. INTERFERON

Interferon is a naturally occurring product of human leukocytes which possesses immunoregulatory, antineoplastic, and antiviral properties. Three types of interferon (alpha, beta and gamma) exist. Recombinant DNA techniques have enabled large quantities to be made available for clinical trials. Interferon has been shown to possess antitumor activity in a variety of diseases, including chronic myelogenous leukemia, multiple myeloma, malignant melanoma, non-Hodgkin's lymphoma, and renal cell carcinoma.

Significant systemic side effects may include fever, chills, malaise, nausea, leukopenia, anemia, thrombocytopenia, cardiac and hepatic dysfunction, cognitive dysfunction, syndrome of inappropriate antidiuretic hormone secretion, and a clinical picture of acute encephalitis.^{73,154,179}

In six patients receiving high dose interferon for amyotrophic lateral sclerosis three developed mild disc edema⁷³ which was reversible with cessation of therapy. Further utilization of this agent in the future may reveal a stronger relationship to ocular toxicity.

C. LAETRILE

Laetrile is not an approved cancer chemotherapy agent, but it has been used and ocular toxicity has been encountered. Smith and associates²⁰³ reported a patient who developed reversible bilateral lid ptosis and medial rectus muscle paresis together with

TABLE 3
Ocular Toxicity of Combination Cancer Therapy, Including Radiotherapy

Agent/Treatment	Route	Toxicity	Reference
Methotrexate + Cranial irradiation	Intrathecal (IT)	Bilateral internuclear ophthalmoplegia	141
5-Fluorouracil + Local radiation	Intravenous (IV)	Increased ocular surface toxicity	187
Methotrexate + Cytosine arabinoside + CCNU + 5-Fluorouracil	IT IT Oral (PO) Intra-arterial (IA)	Potentiation of radiation optic neuropathy	87,76,153,234
Corticosteroids + Local radiation	Any	Increased cataracts	59
Cyclophosphamide + Prednisone	IV PO	Steven's-Johnson syndrome	140
BCNU + Procarbazine	IV IV	Optic neuritis, retinitis	156
Azathioprine or Cyclophosphamide + Corticosteroids	IV Any	Increased cataracts	98,131,172,75,210
L-asparaginase + Vincristine	IV IV	Increased neurotoxicity	110,228,134
Cisplatinum + Vinblastine + Bleomycin	IV IV	Optic neuritis, cortical blindness	54
Cytosine arabinoside + Mitoxantrone	IV IV	Bilateral lateral rectus palsy	213

proximal arm and leg weakness after seven months of laetile therapy; symptoms resolved after cessation of therapy. Other reports of extraocular muscle dysfunction have been noted¹⁴³ and these toxicities have been reproduced in a dog model.¹⁸⁸ Further documentation will probably not be possible.

XI. Miscellaneous-Dibromomannitol

Dibromomannitol is an agent used in treating chronic myelogenous leukemia. When it is fed to rats, anterior and posterior subcapsular cataracts develop.²¹⁹ In a series of 18 humans, three (17%) developed early lens changes and two others (11%) developed cataracts, similar to patients receiving busulfan.¹⁷⁰ Further investigation may help to strengthen this association.

XII. Combination Therapy

A combination of two or more antineoplastic agents will often result in an enhanced antitumor effect. Combinations can also result in increased and/or unique toxicities. Table 3 consists of a summary of the ocular side effects unique to combination chemotherapy. Important interactions between chemotherapy and concurrent radiation therapy are also mentioned.

XII. Conclusion

We have presented a review of the ocular complications of cancer chemotherapy. The fund and

complexity of knowledge in this area has continued to grow. A detailed description of each antineoplastic agent's ocular toxicity in the context of incidence, dose, route of administration, risk factors, natural history, mechanism, interaction with other agents, severity, likelihood of causation, prevention and treatment has been presented. For the oncologist, this review should lead to an awareness of the potential for serious ocular morbidity when administering antineoplastics. Prompt consultation with an ophthalmologist can lead to proper diagnosis and, as we have noted, prevention or amelioration of side effects. Ophthalmologists, upon study of this review, should realize the special circumstances of the cancer patient with eye complaints. Knowledge that the patient's problem may be due to their cancer therapy is crucial for proper diagnosis and treatment. We hope to have contributed to a greater understanding of these agents in relation to the eye, which will increase recognition and collaboration among oncologists and ophthalmologists thus enhancing patient care.

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