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Ocular toxicity of fludarabine:

a purine analog

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Abstract

The purine analogs, fludarabine and cladribine represent an important class of chemotherapy agents used to treat a broad spectrum of lymphoid malignancies. Their toxicity profiles include dose-limiting myelosuppression, immunosuppression, opportunistic infection and severe neurotoxicity. This review summarizes the neurotoxicity of high- and standard-dose fludarabine, focusing on the clinical and pathological manifestations in the eye. The mechanisms of ocular toxicity are probably multifactorial. With increasing clinical use, an awareness of the neurological and ocular vulnerability, particularly to fludarabine, is important owing to the potential for life- and sight-threatening consequences.

Keywords

fludarabine; neurotoxicity; ocular toxicity; ophthalmic pathology; pharmacogenetics; purine analog

The two purine analogs fludarabine and cladribine constitute a major group of anti-metabolite cytotoxic drugs widely used in clinical practice. They are mainly used as agents in a broad spectrum of indolent lymphoid malignancies, including chronic lymphocytic leukemia (CLL), non-Hodgkin's lymphoma (NHL), Waldenström's macroglobulinemia (WM), hairy cell leukemia and cutaneous T-cell lymphoma. Other applications use fludarabine to suppress immunological function, for example in facilitating non-myeloablative stem cell transplantation [1]. Recently, fludarabine has also been used with the novel ribonucleotide reductase inhibitor, 3-aminopyridine-2-carboxaldehyde thiosemicarbazone, in adults with refractory acute leukemias and aggressive myeloproliferative disorders [2].

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The purine analogs share structural similarities and their toxicity profiles include doselimiting myelosuppression, immunosuppression, neutropenic fevers and opportunistic infections, pulmonary toxicity and severe neurotoxicity; however, this last complication has primarily occurred at significantly higher doses than those currently recommended for clinical use. This review summarizes the neurotoxicity of fludarabine, focusing on the ocular manifestations and the toxicities associated with the combination of fludarabine with other medications, specifically other chemotherapeutic agents.

Fludarabine

Preclinical studies on fludarabine

Fludarabine is an antineoplastic agent, which has been studied in patients with a variety of lymphoproliferative malignancies. Alternative names for this compound include 9-ᴅ-arabinofuranosyl-2-fluoroadenine 5′-monophosphate 2-fluoro-ara-AMP, and NSC 312887. It was originally synthesized by Montgomery and Hewson in 1969 [3]. Fludarabine has multiple mechanisms of action, most of which are directed toward disruption of DNA synthesis [4-6].

After preclinical experiments in a number of tumor cell lines, including HeLa cells [7], lymphoma cells and animal tumor systems, including L1210 leukemia [8] and P388 leukemia in mice [9] and dogs [10], this agent was approved for clinical trials in 1982 for the treatment of acute monocytic leukemia (AML) [11]. In an animal experiment, dogs were treated at doses of up to fourtimes the mouse equivalent lethal dose (LD)10 on either a single dose or a 5-day schedule, with no neurotoxicity detected [10]. No ocular toxicity was reported in any of these experiments.

Clinical dosage & pharmacokinetics of fludarabine

The pharmacokinetic properties of intravenously administered fludarabine are well established. During Phase I clinical investigation, the pharmacokinetics of high doses of fludarabine phosphate in low-grade lymphoproliferative malignancies, including CLL and NHL patients, were studied [12]. Following bolus intravenous rapid infusion (over 2-5 min) of doses ranging from 80-260 mg/m^2, fludarabine is in minutes almost quantitatively converted to cytotoxic F-ara-ATP within the plasma. It is then eliminated in three exponential phases [12]. Plasma concentrations were computer fitted to a three-compartment open model with sequential halflifes of $t_{1/2}\ \alpha = 4.97$ min, $t_{1/2}\ \beta = 1.38$ h, and $t_{1/2}\ \gamma = 10.41$ h, with the mean residence time calculated at 10.51 h [12]. Pharmacokinetic analysis of F-ara-A demonstrated a volume of distribution of 96.2 ± 26.0 l/m^2 with no plasma accumulation over several days and a mean clearance from the plasma of 9.07 ± 3.77 l/h·m^2 [13]. The main route of elimination is renal, with 40-60% of the intravenously administered dose excreted in the urine [12,14]. There appears to be a correlation between creatinine clearance and total body clearance of F-ara-A, necessitating special consideration in patients with impaired renal function.

The recommended intravenous dosage regimen for fludarabine in the treatment of CLL is 25 mg/m^2 once daily for 5 consecutive days, with the cycle repeated every 28 days until a maximal response is seen. The response usually requires six cycles of fludarabine therapy. The pharmacokinetics of the standard dose of fludarabine have also been studied. Plasma concentrations of approximately 3 μmol/l F-ara-A are achieved at the end of each infusion [6]. Intracellular levels of the cytotoxic moiety F-ara-ATP peak within 3-4 h of termination of fludarabine infusion and decline monophasically with a median half-life of 23 h [15].

Although used primarily in its intravenous form, fludarabine is now available in a 10 mg immediate-release tablet. After administration of a single oral dose of 50-90 mg of fludarabine to patients with various types of NHL, area under curve (AUC; 0-24 h) and C_{max} of F-ara-A were linear and dose proportional. C_{max} values were approximately 20-30% of those achieved

by intravenous infusion and were reached in 1-2 h. T_{max} (the time to C_{max}) was independent of the dosage [16]. The bioavailability of oral fludarabine after single or multiple doses is 50-65% [16]; it appears to be independent of dosage [16] and is unaffected or only slightly affected by food [17].

Systemic toxicity of fludarabine

The most frequent adverse events associated with fludarabine regimens are myelosuppression (neutropenia, thrombocytopenia and anemia), lymphocytopenia and infection (typically respiratory tract infections and fever) [18]. Other toxicities include gastrointestinal adverse effects, such as nausea, vomiting and elevation of liver enzymes.

Myelosuppression is the major dose-limiting adverse effect associated with fludarabine therapy in cancer patients. In large-scale randomized studies, the administration of 479 fludarabine treatment cycles to 96 patients with CLL resulted in the development of granulocytopenia, thrombocytopenia and anemia (WHO grade III/IV) during 19, 14 and 7% of treatment cycles, respectively, and affected 38, 15 and 18% of patients, respectively, during the first six treatment cycles [19].

Fludarabine's dramatic depletion of lymphocytic cells is associated with an increase in opportunistic infections that requires close monitoring and management [20]. The most frequent infectious complications are respiratory tract infections and unexplained fever. Fatal outcomes have also been reported [21]. Many of these opportunistic infections occur in cases where there was concomitant corticosteroid use [22].

Neurotoxicity of fludarabine

Although myelosuppressive toxicity develops in almost half of the patients receiving fludarabine, regardless of dosage, a critical obstacle in the further use of fludarabine is its neurotoxicity. Higher doses of fludarabine for acute leukemia can be associated with severe neurotoxicity leading to encephalopathy, coma and even death in 18% of patients [23-26]. The development of neurologic toxicity is characterized by delayed onset (21-60 days after last treatment) and a progressive degenerative clinical course. The clinical symptoms consist of altered mental status, seizures, paraparesis, progressive encephalopathy and coma. The results of diagnostic studies, including CSF examination, electroencephalogram and CT scans of the CNS, are also varied and nonspecific. MRI studies have shown extensive diffuse loss of white matter [25].

Spriggs *et al.* reported that 11 patients with relapsed acute leukemia received 14 courses of fludarabine phosphate as a 5-day continuous infusion administered at doses of 40-100 mg/m^2/day [24]. Three of these patients (27.3%) suffered neurotoxicity. Two of these three patients had a severe neurotoxicity syndrome characterized by blindness, encephalopathy and coma. Chun *et al.* reported that 13 out of 36 patients (36.1%) who received fludarabine at high doses ($\geq$ 96 mg/m^2/day for 5-7 days) developed neurotoxicity after receiving the drug [23]. Among these 13 patients, progressive deterioration of mental status or encephalopathy leading to a vegetative state developed in 11 patients. CT scan of the brain revealed no specific abnormalities except cortical atrophy in two patients. Follow-up MRI scans of these patients demonstrated an extensive diffuse loss of white matter. Analyses of CSF revealed an elevated protein level in five out of ten patients and ten out of ten negative cytologic examinations. The myelin-basic protein level was elevated in CSF from four out of ten patients examined. Visual-evoked potentials (VEP) were absent in three out of ten patients. The incidence and main manifestations of neurotoxicity with high-dose fludarabine treatment are listed in TABLE 1.

As a result of the severe toxic and occasionally lethal side effects of fludarabine, interest in fludarabine as a treatment for AML waned. However, careful examination of the Phase I/II clinical trial data revealed that neurotoxicity appears to be dose related. In Chun's report, 13 out of 36 patients (36.1%) who received fludarabine at high doses (≥ 96 mg/m^2/day for 5-7 days per course) developed neurotoxicity, while only 1 out of 443 patients (0.2%) who received the drug at lower doses (less than or equal to 125 mg/m^2 per course, equal to 25 mg/m^2/day for 5 days), developed similar toxicity [23]. This one patient represents the first reported case of cortical blindness, encephalopathy and death resulting from treatment with low-dose fludarabine. However, this patient also had a CNS mycosis fungoides, which may have allowed greater fludarabine penetration into the brain, with resultant neurotoxic sequelae at a lower dose.

In the early 1990s, lower doses of fludarabine (30 mg/m^2 per day for 5 days) were used successfully without neurotoxicity in the treatment of CLL, renewing interest in this agent [27-29]. Most large studies have reported no or few severe neurological side effects with standard-dose fludarabine therapy [30.31]. Investigators from a large European study reported the development of severe peripheral neuropathy (Grade III/IV) in two out of 479 fludarabine treatment cycles [19]. In 1994, Cheson *et al.* reviewed the literature for reports of adverse drug reactions from treatment with fludarabine [26]. In his review, 335 out of 2136 (16%) patients treated for a range of hematological malignancies with standard-dose fludarabine demonstrated neurotoxicity. The majority of cases were mild and reversible and the incidence was similar to that reported for cladribine [26]. Cases of adverse neurological events from treatment with low-dose fludarabine included both reversible neurotoxicity (seizures, loss of consciousness, blurred vision and leg weakness) and fatal neurotoxicity (multifocal leukoencephalopathy), and are listed in TABLE 2.

Postmortem examination of the CNS in cases of fludarabine toxicity revealed various degrees of demyelination, either multifocal or diffuse, in the brain and spinal cord [32]. The most striking findings were within the cerebral white matter. These areas showed a diffuse, necrotizing leukoencephalopathy, characterized by vacuolization, myelin loss with numerous PAS-positive macrophages and axonal swelling with spheroid formation.

Visual deficits were the most common presenting symptom and eventually developed in most cases with neurotoxicity [23]. Examination of the brain at autopsy revealed significant necrosis within the occipital and parietal lobes, while the frontal and temporal lobes were less extensively involved. These observations suggest that the mechanism of toxicity may be related to impairment of oligodendroglial or axonal function, which is most apparent in those areas of the brain with the greatest metabolic activity.

Ocular toxicity of fludarabine

Specific ocular toxicities caused by fludarabine have been documented, although they are infrequent. Opportunistic infections have been reported in the eye. Reactivation of varicella zoster virus in the eye including the anterior segment (cornea and conjunctiva) and posterior segment (acute retinal necrosis syndrome, [ARNS]) has been reported. Chee *et al.* described two patients treated with fludarabine who developed progressive bilateral visual loss with anterior uveitis, vitritis, retinal vasculitis and peripheral retinal necrotic lesions [33]. One patient had received five courses of 25 mg/m^3 for 3 days. At 2 weeks after treatment this patient developed progressive bilateral vision loss, was diagnosed with acute retinal necrosis, and then treated with high-dose intravenous acyclovir. Treatment prevented formation of new retinal lesions but did not improve visual acuity. The second patient received six courses of 25 mg/m^3 for 5 days. Approximately 1 year after treatment he developed floaters and left-sided visual loss. The patient was treated with intravenous acyclovir, followed by oral famciclovir, with resolution of bilateral vitritis and return of visual acuity to baseline.

Among the 13 patients receiving high-dose fludarabine (≥96 mg/m^2/day for 5-7 days per course) in Chun's study, 11 developed ocular toxicity, eight experienced complete loss of vision, two demonstrated cortical blindness and one described blurred vision [23]. Ocular findings were varied and included visual changes, hallucinations, visual field deficits, optic neuritis, papillitis and cortical blindness. Visual abnormalities were sometimes the initial presenting symptom in some patients. Spriggs *et al.* described a 32-year-old male who had received fludarabine (100 mg/m^2/day for 5 days), who initially complained of a slight decrease in visual acuity and photophobia 44 days after starting the medication [24]. The patient declined to no light perception vision within 3 days, followed by a generalized deterioration of mental status.

Ocular susceptibility to fludarabine toxicity is not limited to high-dose therapy. The patients surveyed by the Group C Protocol Mechanism of the National Cancer Institute represent the largest clinical investigation to date [34]. This trial enrolled more patients and had longer follow-up than any prior published trials and thereby provided valuable information on the toxicity profile of fludarabine [34]. In this study, 1 and 0.3% of patients developed Grade 3 and Grade 4 visual toxicity, respectively. The grading system was based on the common toxicity criteria of the National Cancer Institute. Grade 3 was defined as generalized symptomatic subtotal loss of vision, whereas Grade 4 was defined as blindness.

Recently, we have seen two patients who suffered total vision loss after receiving standard doses of fludarabine (25 mg/m^2/day for 5 days). The first patient had stage 4 malignant melanoma and received two cycles of fludarabine as part of a conditioning regimen in preparation for adoptive cell therapy, with the first cycle including total body irradiation. The second patient had a diagnosis of systemic lupus erythematosus (SLE) and received fludarabine prestem cell transplantation. The first patient, with 20/25 vision in both eyes, noted visual aberrations including floaters and hallucinations, approximately 1 month after beginning her second course of fludarabine. She then experienced rapid decline of vision within 3 days, deteriorating to 20/640 in the right eye and 20/800 in the left eye. Electroretinography at the time of vision loss revealed a dramatic decrease in retinal bipolar cell function. Over the ensuing weeks prior to her death, her vision deteriorated to light perception in the right eye, and possibly no light perception in the left. Ocular autopsy disclosed extensive loss of retinal ganglion cells (FIGURE 1), strong immunoreactivity against glial fibrillary acidic protein (GFAP) and CD68$^+$ cells in the areas of the optic nerve head and retinal inner layers of the posterior pole, including the macula, suggestive of gliosis and infiltration of microglia and macrophage. Protein kinase C (PKC-α), a marker of bipolar cells, was markedly decreased in the macular area. Our second similar case involved a 23-year-old African-American male who had received fludarabine prior to stem cell transplantation for SLE. Over the course of the patient's illness, he experienced fluctuations in visual acuity, with deterioration to possible light perception in both eyes. Pathological examination revealed neuronal cellular atrophy, hydrocephalus and cerebral edema with inferior cerebellar herniation. As with our first patient, dramatic loss of ganglion cells (FIGURE 2), loss of bipolar cells and GFAP-positive gliosis in the ganglion cell layer of the macula were seen. In addition, many microglia cells were found in the optic nerve. Antiretinal antibodies from both patients' sera collected prior to and after fludarabine treatment were negative. No other factors were identified that might have predisposed these two patients to experience such severe toxic reactions to fludarabine.

In the previous report, postmortem examination of the optic nerves post-fludarabine toxicity revealed severe necrosis with myelin loss, numerous periodic acid schiff (PAS)-positive macrophages, and early reactive astrocytosis [24]. The necrosis was most severe within the occipital and parietal lobes. Stillman's case of high-dose fludarabine neurotoxicity demonstrated multiple areas of leukoencephalopathy involving in particular the optic nerves,

chiasm and tract [35]. Postmortem examination of our two patients also revealed extensive optic nerve atrophy.

Neurotoxicity from fludarabine appears to be largely irreversible. Visual recovery, however, has been seen in some cases with immediate cessation of fludarabine administration at the first signs of neurotoxicity. For example, in Warrell's report one of the five patients who had developed total blindness and quadriparesis gradually regained both vision and strength [25]. The patient's only permanent neurologic deficit was an asymptomatic delay in visually evoked response. On the other hand, in Chun's study only one of the 13 patients who had experienced visual loss recovered vision [23].

The increasing clinical use of fludarabine necessitates a heightened awareness of the neurological vulnerability of some patients to low doses of fludarabine. The potential life-and sight-threatening consequences can be significant. The mechanisms of neurotoxicity may be multifactorial and at present cannot be predicted. Continued caution in the use of this antineoplastic agent is appropriate.

Combination therapy with fludarabine

There is a substantial body of evidence supporting the hypothesis that fludarabine potentiates the activity of other antitumor agents, such as cisplatin, cytarabine, mitoxantrone, and cyclophosphamide [4,36].

Combination chemotherapy with other antimetabolites

The efficacy of a combination regimen of cytarabine, currently the most widely used single agent in the treatment of AML, plus low-dose fludarabine has been investigated [37.38]. There is a direct correlation between the ability of leukemic blasts to form and retain Ara-CTP, and the clinical response of patients with AML to high-dose cytarabine. The rationale for this combination was based on the discovery that fludarabine is able to modulate the metabolism of cytarabine *in vitro*, thereby increasing the accumulation of Ara-CTP [37,38]. Studies were therefore designed with fludarabine infusions (30 mg/m^2) preceding cytarabine infusions, in order to enhance Ara-CTP accumulation. The regimen appears to be clinically effective. Assessment of its potential neurotoxicity is important because fludarabine, as noted previously, and cytarabine may independently produce neurological damage [39].

Kornblau *et al*. reported an overall incidence of neurotoxicity of 3.6% in eight out of 219 patients who received a combination of fludarabine and cytarabine [40]. In total, five patients developed peripheral neuropathy but there was no association with age, creatinine, dose of cytarabine or number of courses. Two patients developed severe progressive cerebral dysfunction that was ultimately fatal. The toxicity was similar to that seen with high-dose fludarabine therapy. Both of these patients were older than 60 years and had a serum creatine greater than or equal to 2.0 mg/dl. Since fludarabine is partially excreted by the kidneys, toxicity in these two patients was probably due to effectively receiving a high dose of fludarabine. Neither toxicity was observed in the 481 CLL patients treated with fludarabine alone at the same dose and on the same schedule, suggesting that combination with cytarabine is associated with the development of the peripheral neuropathy. In the eight patients with onset of neurological symptoms, only one experienced visual loss. Funduscopy and ophthalmic pathology of this patient were not described [40]. The incidence of neurotoxicity with the combination of fludarabine and cytarabine is still low in comparison with high-dose cytarabine therapy (3 g/m^2 over 2 h).

In Chun's report, five out of 13 patients with CNS toxicity had received prior high-dose cytarabine, and four had received prior intrathecal chemotherapy with either methotrexate,

cytarabine or both [23]. In fact, two of the 13 patients had a residual neurologic deficit from prior therapy at the time of entry to the fludarabine trial. Among the 23 patients without neurotoxicity receiving similar high-dose fludarabine, three patients had received prior high-dose cytarabine and eight had received prior intrathecal chemotherapy [23]. Based on these findings, the authors suggest that prior high-dose cytarabine appears not to be a predisposing factor for the development of CNS toxicity after fludarabine [23].

Fludarabine combined with alkylating agents

Fludarabine combined with cyclophosphamide—Coadministration of fludarabine and cyclophosphamide is the most fully investigated fludarabine combination. It has been examined in several trials, including trials with additional drugs such as filgrastim and mitoxantrone. In a Phase III trial of 362 patients with treatment-naive CLL, the overall response (OR), complete response (CR), progression-free survival time and treatment-free survival time were significantly higher in the combination group than in the fludarabine or cyclophosphamide monotherapy groups. The most common adverse event associated with the combination of fludarabine with cyclophosphamide was myelosuppression. Myelotoxicity, in particular leukocytopenia and thrombocytopenia, was significantly more frequent in the combination regimen. In spite of the higher rate of severe leukocytopenia, the incidence of severe infections was similar in both treatment groups [41]. A possible explanation is that the fludarabine and cyclophosphamide combination dosing was more frequently reduced or delayed as compared with fludarabine monotherapy. Gastrointestinal side effects such as nausea, vomiting, mucositis and gastritis were more common in the combined therapy group. No neurotoxicity or ocular toxicity has been associated with this combination, with fludarabine dosed at 96 mg/m^2/day for 5-7 days per course.

Recently, a large-scale randomized controlled trial studying 777 CLL patients reported a lower incidence of hemolytic anemia when using fludarabine plus cyclophosphamide (5%) than with fludarabine (11%) alone [42]. A meta-analysis of these data combined with two published Phase III trials revealed a consistent benefit from the fludarabine/cyclophosphamide regimen combination with respect to progression-free survival. In addition, responders in the combination group reported a higher quality of life. Ocular toxicity was not reported in this combination, with fludarabine dosed at 96 mg/m^2/day for 5-7 days per course.

Fludarabine combined with chlorambucil—A subsequent retrospective analysis revealed a significantly higher incidence of major infections among patients who received combination therapy with fludarabine and chlorambucil, requiring hospitalization or treatment with parenteral antibiotics [43]. Incidences of major infections were 29, 17, and 45% in the fludarabine, chlorambucil and fludarabine plus chlorambucil groups, respectively [44]. No ocular toxicity was mentioned.

Fludarabine combined with immunomodulating agents

Fludarabine is now used in combination with thalidomide, a first-generation immunomodulating agent that downregulates TNF-α and VEGF, to treat patients with CLL. A recent Phase I clinical trial of thalidomide in combination with fludarabine showed a high (100%) OR rate in treatment-naive patients with CLL, with 55% of patients achieving complete remission [45]. In this study, the most common toxicities noted were fatigue, constipation and peripheral sensory neuropathy. No severe neurotoxicity was noted. In a separate investigation involving daily treatments with thalidomide, oral fludarabine, and oral cyclophosphamide, one out of five patients with a prior history of Guillain-Barré syndrome, had to stop treatment after developing a sensory motor neuropathy [46]. Ocular toxicity was not reported in this study.

In conclusion, the combination of fludarabine with other chemotherapeutics does not appear to significantly change the adverse event profiles previously described. Most of the investigations of myelotoxicity and neurotoxicity following fludarabine combination therapy suggest that the incidence of these complications may be higher than previously reported for fludarabine monotherapy [46,47]. However, owing to differences among the populations of patients, combinations of chemotherapy agents and absence of specific toxicity data, it is unclear how much greater the complication rate of combination therapy might actually be.

Expert commentary & five-year view

Progressive demyelination of the CNS is the suggested pathologic process occurring after fludarabine phosphate treatment. Although ocular pathology confirms loss of ganglion cells and damage of bipolar cells, which could be due to direct neuronal toxicity from fludarabine and/or retrograde neuronal atrophy, the precise mechanism responsible for the injury to particular neuronal cells is unknown. Understanding the pharmacokinetic behavior and precise action of fludarabine in the CNS may further help the understanding of the pathophysiology. Further investigations, including *in vitro* and *in vivo* studies in animals will be necessary for a better understanding of fludarabine neurotoxicity.

A major clinical challenge in cancer treatment currently is identifying and managing individual variability to the drug regimen selected. Although fludarabine is highly active in lymphoproliferative disorders, a significant portion of patients are resistant, whereas others are susceptible to the toxicity of this agent. Some studies suggested that heterogenous responses to identical fludarabine treatment regimens may be explained, at least in part, by individual variability in the expression of certain gene products, such as the Concentrative Nucleoside Transporters (CNTs) [48,49]. CNTs are located on the apical membrane of the intestine and liver epithelia. This suggests that they may play an important role in the absorption and deposition of nucleosides. *CNT2*, and *CNT3* mRNAs were also expressed in rat retinal capillary endothelial cells, which were used as an *in vitro* model of the inner blood-retinal barrier [50]. As naturally occurring nucleosides and most synthetic nucleoside analogs are hydrophilic and require nucleoside transporters to traverse biological membranes, nucleoside transporters are critical determinants of cellular and whole-body homeostasis of nucleosides and are important players in the tissue-specific disposition and pharmacokinetics of nucleoside analog drugs. It is reported that *CNT3* is primarily responsible for the transport of several antileukemic drugs, including fludarabine and cladribine [48.49]. Badagnani and associates analyzed the genetic variants in the human *CNT3*; S*LC29A3* [51]. Analysis of expression levels of nucleoside transporters in leukemic cells suggests that *CNT3* has the highest interindividual variability. In addition, Gray *et al*. recently reported that several genetic variants of *CNT1* exhibited altered interaction with gemcitabine, suggesting that common *CNT1* variants may contribute to variation in systemic and intracellular levels of pyrimidine nucleoside analog drugs [52]. These genes may play an important role in mediating the cellular entry of a broad array of synthetic anticancer nucleoside analog drugs such as fludarabine. Further research on the pharmacogenetics of the drug may lead to a clearer explanation of the individual variability in toxicity seen during treatment.

With increased clinical use of fludarabine, its known toxicities of myelosuppression and immunosuppression have become more apparent. Myelosuppression can be managed with the use of growth factors, and infectious complications can be mitigated with adequate prophylactic antibiotics. However, there is no known prophylaxis or treatment for neurotoxicity to date, in particular to ocular toxicity. Increased awareness of potentially serious side effects and close observation of patients using this drug are recommended in the use of both high and low doses of fludarabine.

Key issues

- Ocular toxicities induced by fludarabine are infrequent but may be rapidly sight-threatening and largely irreversible.
- Susceptibility to fludarabine ocular toxicity is not limited to high-dose therapy.
- Pathology of eyes with fludarabine toxicity demonstrates atrophy of the optic nerve and inner retina, infiltration of microglia/macrophages and marked gliosis.
- The precise mechanism responsible for fludarabine toxicity remains an enigma.
- The incidence of neurotoxicity from the combination of fludarabine with other drugs may be higher than that from fludarabine alone.
- Increased awareness of potentially serious side effects and close observation of patients using this drug is recommended in the use of both high and low doses of fludarabine.
- A better understanding of interindividual variability in the effects of fludarabine might be attained through the elucidation of fludarabine metabolism in the CNS, including the pharmacokinetic profile of fludarabine and the pharmacogenetic factors influencing fludarabine activity and/or elimination.

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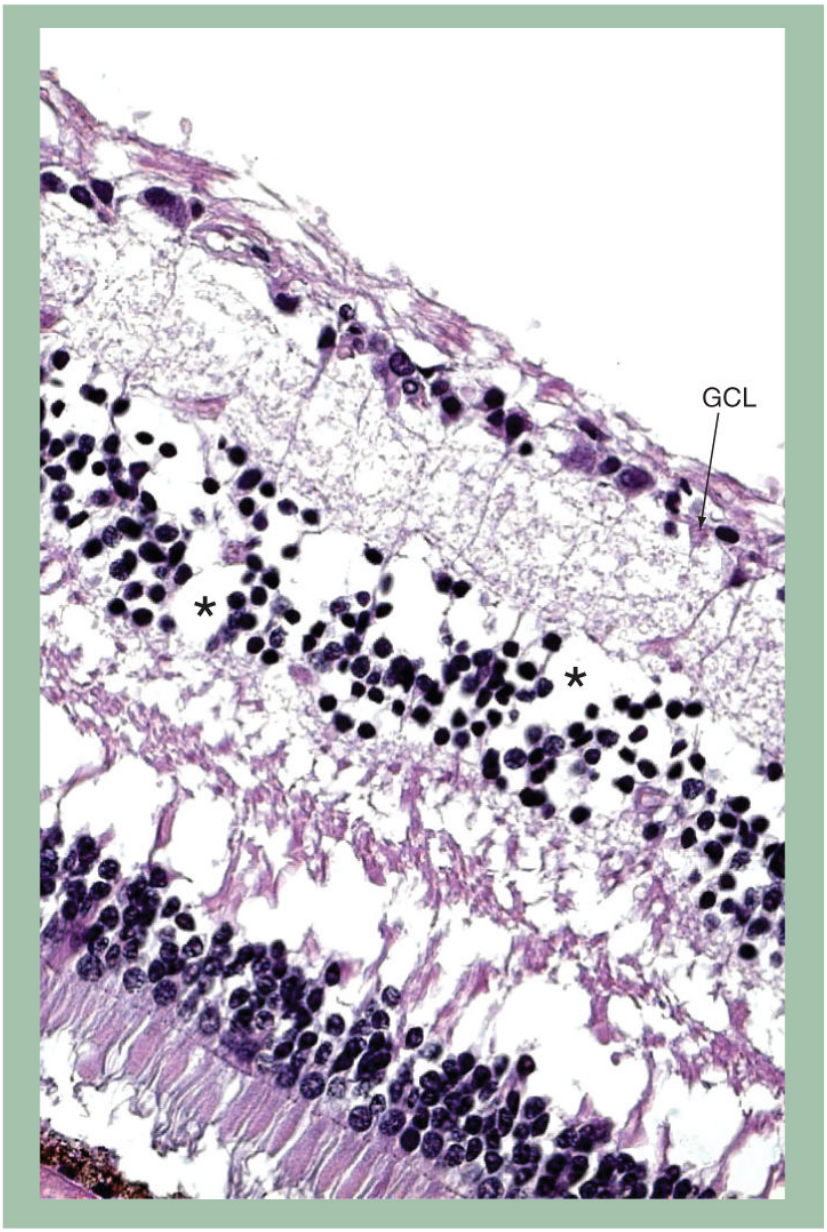

Figure 1. Photomicrograph of the retina discloses drastic reduction of ganglion cell layer from five to six cells to one cell layer in the macular area

Loss of cells (in the inner nuclear layer) is also noted.

Hematoxylin and eosin stain, original magnification, ×100

*Bipolar cells.

GCL: Ganglion cell layer.

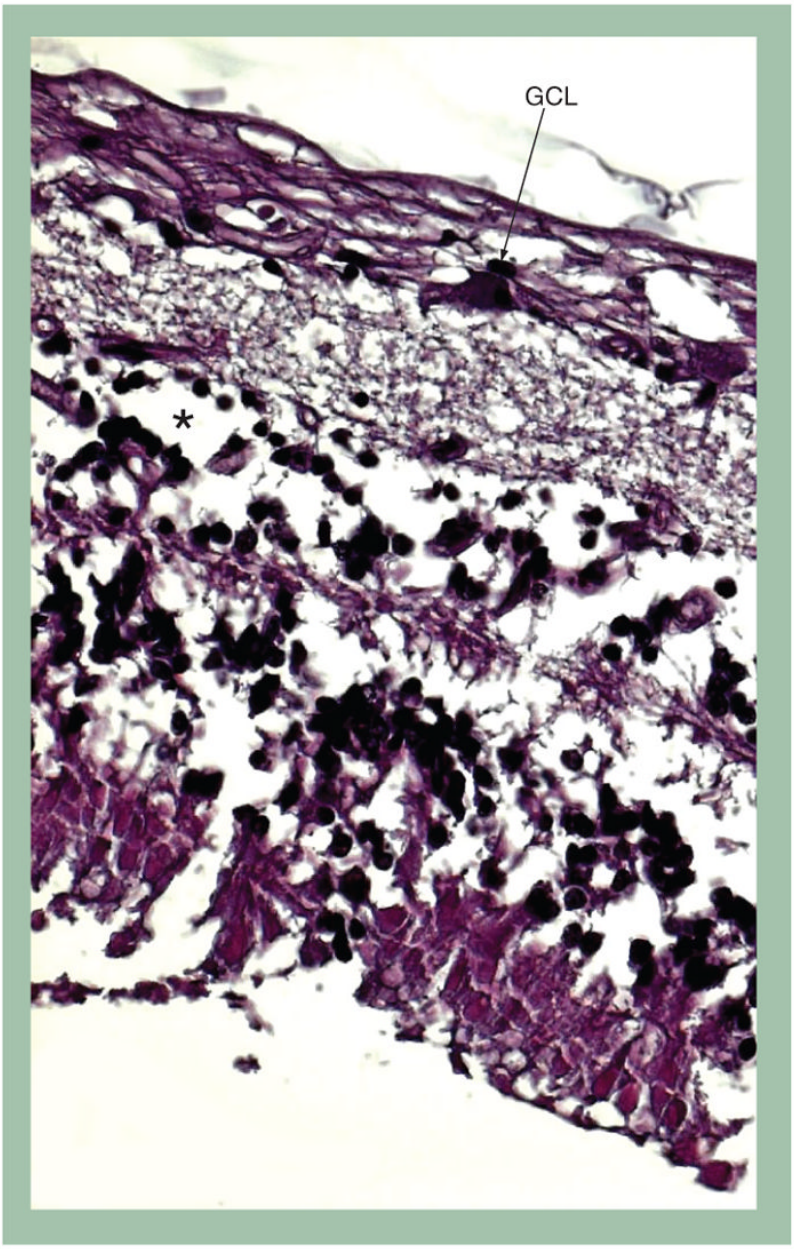

Figure 2. Photomicrograph of the retina illustrates similar changes to FIGURE 1 with severe decrease of ganglion cells and partial loss of bipolar cells in the macular area

Hematoxylin and eosin stain, original magnification, ×100.

*Bipolar cells.

GCL: Ganglion cell layer.

Table 1

Neurotoxicity and ocular toxicity of high-dose fludarabine

Study	Year	n	Dose/schedule	Patients with neurotoxicity (n)	Neurotoxicity	Patients withocular toxicity (n)	Ocular toxicity	Patients with vision recovery (n)	Ref.
Hutton *et al*.	1984	13	18-40 mg/m^2/day over 30 min × 5 days	8	Somnolence during infusion, quick cleared (n = 8)	NS	NS	NS	[53]

Warrell *et al*.	1986	25	50 mg/m^2/d CIV × 5 day;
			125 mg/m^2/d CIV × 7 days
				5	Mental status change (n = 2);
					quadriparesis (n = 1);
					seizures (n =1);
					coma (n = 4);
					paralysis (n = 4)
						5	Amaurosis (n = 1);
							Blurred vision (n = 1);
							Cortical blindness (n = 5)
								1	[25]

Chun *et al*.	1986	36	>96 mg/m^2/day CIV × 5 days	13	Encephalopathy (n = 7); coma (n = 6); spastic paraparesis (n = 3)	11	Hallucination (n = 1); Bilateral papillitis (n = 1); blurred vision (n = 1); loss of vision (n = 8); cortical blindness (n = 2)	1	[23]
Spriggs *et al*.	1986	11	40-100 mg/m^2/day CIV × 5 days	3	Encephalopathy (n = 2); coma (n = 2); resting tremor (n = 1)	2	Blindness (n = 2)	0	[24]

CIV: Continuous intravenous infusion; NS: Not stated.

Table 2

Neurotoxicity and ocular toxicity of low-dose fludarabine

Study	No. of patients	Dose/ schedule	Patients with neurotoxicity (n)	Neurotoxicity	Patients with ocular toxicity (n)	Ocular symptoms	Patients with vision recovery (n)	Ref.
Chun *et al.* (1986)	443	18-22.5 mg/ m^2/day × 5 days, 3 course	1	Weakness, somnolence, disorientation, encephalopathy, coma (n = 1)	1	Hallucinations; complete blindness	0	[23]
Harvey *et al*. (1987)	19	18.75-31.25 mg/m^2/day × 5 days	7	Mild somnolence during infusion (n = 7); mild paresthesias (n = 1)	NS	NS	NS	[54]
Balducci *et al*. (1987)	36	25 mg/m^2/ day × 5 days	2	Somnolence (n = 2)	NS	NS	NS	[55]
Weiss *et al*. (1986)	23	18-22mg/m^2/ day × 5 days	11	Mild-to-moderate somnolence or fatigue; transient paresthesias (n = 10), dementia, coma, death (n = 1)	NS	NS	NS	[56]
Rainey *et al*. (1988)	11	18 mg/m^2/ day × 5 days, with 25% dose escalation	2	Severe ataxia (n = 1); somnolence (n = 2); dizziness (n = 1)	0	0	0	[57]
Von Hoff *et al*. (1990)	20	18 mg/m^2/ day × 5 days	1	Transient somnolence (n = 1)	NS	NS	NS	[44]
Kantarjian *et al*. (1991)	17	30 mg/m^2/ day × 5 days	1	Mild sensory neuropathy (n = 1)	0	0	0	[58]
Hochster *et al*. (1992)	62	18 mg/m^2/ day × 5 days	32	Mild (n = 17); moderate (n = 9); severe (n = 6)	2	Visual changes	NS	[59]
Cohen *et al*. (1993)	NS	18-25 mg/ m^2/day × 5 days, 6-8 cycles	2	Focal motor seizure (n = 1); loss of consciousness, improved rapidly in 6 weeks (n = 1); gait disturbance (n = 1)	1	Blurred vision (n=1) *	Reversible after 6 months	[60]
Bishop *et al*. (2007)	1	25 mg/m^2/ day × 5 days, 2 cycles	0	Spinal cord syndrome Encephalomyelopathy	1	Visual changes	0	[UNPUBLISHED DATA]
Bishop *et al*. (2007)	1	30 mg/m^2/ day × 4 days	2	Leukoenchaphalopathy (pre-existing but progressed postfludarabine)	1	Visual changes	Slight recovery	[UNPUBLISHED DATA]

NS: Not stated.

* General anesthesia 1 day before the vision symptoms.