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JA Gonzalez-Martin[1], P Hiscott[2] and P Palimar[1]

[1]Warrington Hospital
Kendrick Wing Lovely Lane
Warrington
Cheshire WA5 1QG, UK
[2]Royal Liverpool University Hospital
Prescot Road
Liverpool, UK

Correspondence: P Palimar
Tel/Fax: +44 1925 662 395
E-mail: palimar@tinyonline.co.uk

Sir,

Cytarabine-induced corneal toxicity

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Cytarabine (cytosine arabinoside) is a powerful antimetabolite used in the treatment of acute myeloid leukaemia (AML). Corneal toxicity from high-dose intravenous cytarabine therapy has been described in the literature[1] and routine prophylaxis with topical steroids is now an established part of the treatment protocol.[2] Only two cases have been reported of corneal toxicity occurring at low doses. One case occurred with an intermittent subcutaneous regimen.[3] A second case was reported with a continuous intravenous regimen.[4] The cytotoxic activity of cytarabine is related to the concentration and duration of exposure, both of which vary with different modes of administration. There are no reports of corneal toxicity in patients receiving an intermittent, intravenous low-dose regimen, and currently no recommendations have been made for prophylaxis in these cases.

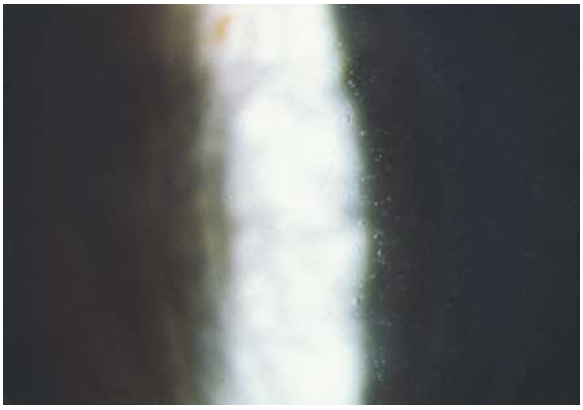

Figure 1 Corneal epithelial microcysts visible with direct slit-beam illumination.

Case report

A 39-year-old male presented with a 1-day history of blurred vision, severe discomfort and photophobia following a 10-day course of intermittent low-dose intravenous cytarabine therapy for AML. He had received 200 mg/m^2 every 12 h for 9 days prior to the onset of symptoms and had not been using topical steroid prophylaxis. On examination he had an uncorrected visual acuity of 6/9 in each eye. Severe blepharospasm and moderate conjunctival inflammation were present. Bilateral corneal epithelial microcysts, more densely distributed in the centre of the cornea than in the midperiphery were noted, with a clear zone of about 1.5 mm in the corneal periphery (Figure 1). The anterior chamber in both eyes was free of inflammation and the intraocular pressure was normal. Treatment was commenced with G. dexamethasone 0.1% 2 hourly and the symptoms resolved completely within 3 days. The microcysts disappeared after 7 days and the steroid drops were subsequently tapered and then stopped over the following week.

Comment

Cytarabine corneal toxicity has mainly been associated with high-dose intravenous therapy (>1 g/m^2). This drug is known to penetrate the blood–brain barrier after intravenous infusion and is also found in the aqueous and tears. Typically, corneal toxicity occurs after 5–7 days of treatment and can be prevented by using topical corticosteroids.[1,2] In this patient, because of the relatively low-dose regimen, prophylactic steroid therapy was not used and typical corneal toxicity occurred as a consequence.

The mechanism of cytarabine-induced microcyst formation is not currently known. Rapid cycling cells are most sensitive to the actions of cytarabine. Corneal

epithelial stem cells have a long cell cycle time and consequently are unlikely to be vulnerable to its effects. They give rise to more differentiated transient amplifying cells (TACs) located within the basal cell layer, which divide more frequently and therefore might be expected to be more vulnerable. In the patient studied here there was a peripheral clear zone in the corneal epithelium, suggesting that the central epithelial cells were relatively more sensitive than the peripheral TACs. These 'transitional' peripheral epithelial cells appear to be a population of very early TACs, which display some of the characteristics of stem cells.[5] A functional difference in behaviour between this peripheral zone of epithelium and the central zone is suggested clinically by findings in the βig-h3 corneal dystrophies (eg Granular, Lattice, Avelino and Honeycomb dystrophies). Characteristically, the peripheral epithelium is clear in these disorders.

The mechanism by which a topical corticosteroid reduces this toxic effect is unclear. As cytarabine inhibits DNA synthesis at the level of the DNA polymerase, a reduction in DNA replication by the steroid would make the corneal epithelial cells less susceptible to the effects of this drug.[2]

Although uncommon, this case confirms that cytarabine corneal toxicity can occur with low-dose regimens and it is recommended that all patients receiving cytarabine therapy should receive prophylactic topical steroids.

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J Lochhead, JF Salmon and AJ Bron

The Oxford Eye Hospital
Radcliffe Infirmary Woodstock Road
Oxford OX2 6HE, UK

Correspondence: Dr J Lochhead
Tel: +44 01865 224360
Fax: +44 01865 224515
E-mail: jonlochh@AOL.com