

Ulcerative Keratitis in Gastrointestinal Stromal Tumor Patients Treated with Perifosine

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Purpose: Perifosine is a novel alkylphospholipid with antiproliferative properties attributed to protein kinase B inhibition. The authors describe a form of ulcerative keratitis in 5 patients with advanced gastrointestinal stromal tumor (GIST) enrolled in a phase I/II trial of perifosine in combination with imatinib.

Design: Interventional case series.

Participants: Five patients (1 man, 4 women) with imatinib-resistant metastatic GIST who received a combination of imatinib and perifosine orally.

Methods: The medical records were reviewed retrospectively.

Main Outcome Measures: Ocular toxicity and ulcerative keratitis associated with perifosine.

Results: The ocular symptoms included redness, irritation, tearing, photophobia, and a gradual decrease in vision. Slit-lamp biomicroscopy in each case revealed a peripheral, paralimbal, ring-shaped, superficial corneal stromal infiltration and ulcerative keratitis, reminiscent of the autoimmune keratitis in conditions such as rheumatoid arthritis. The ulcerative keratitis was unilateral in 3 and bilateral in 2 patients; it was National Cancer Institute grade II (symptoms interfering with function but not interfering with activities of daily living) in all patients. All 5 patients had imatinib-resistant metastatic GIST and had continued on the highest dose of imatinib tolerated and initiated therapy with perifosine 100 mg daily or 900 mg weekly. A combination of topical steroids, topical antibiotics, and lubricating drops were used to manage ulcerative keratitis. In the first 3 patients, ulcerative keratitis initially was treated with topical antibiotics without improvement, but subsequently they improved significantly after topical steroids were added.

Conclusions: A vision-threatening form of ulcerative keratitis may occur in patients taking perifosine. It is possible that imatinib in combination with perifosine contributes to this corneal toxicity; however, the authors are unaware of this ocular toxicity having been reported for imatinib when used without perifosine. The visual loss associated with perifosine may be reversible if detected and treated early and with judicious early use of topical steroids, topical antibiotic coverage, and lubrication. *Ophthalmology* 2008;115:483-487 © 2008 by the American Academy of Ophthalmology.

Perifosine (octadecyl-(1,1-dimethyl-4-piperidyl)phosphate), a synthetic alkylphospholipid, is a novel antineoplastic drug that inhibits protein kinase B activation, causes cell cycle arrest, and has displayed significant antiproliferative activ-

ity in vitro and in vivo in several human tumor model systems.^{1,2}

Imatinib mesylate (imatinib [Glivec/Gleevec, Novartis, Basel, Switzerland]), an orally administered 2-phenylamino-pyrimidine derivative, is a competitive inhibitor of the tyrosine kinases associated with platelet-derived growth factor receptors and the *KIT* protein. *KIT* is the gene that encodes the human homolog of the protooncogene *c-Kit*. The *KIT* tyrosine kinase is expressed abnormally in gastrointestinal stromal tumor (GIST), a neoplasm arising from mesenchymal cells, for which there has been no effective systemic therapy.³ Imatinib semiselectively inhibits the tyrosine kinase activity associated with *KIT*, which forms the rationale for its use in GIST. However, most cases of GIST eventually develop resistance to imatinib mesylate.⁴ Protein kinase B, a protein associated with tumor survival and growth, is activated in approximately 10% to 50% of these tumor types by phosphorylation and is thought to be involved in development of resistance to therapy with imatinib by inhibiting apoptosis.^{1,2}

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Given that perifosine inhibits protein kinase B activation, it has been used in several phase I and II trials in combination with Gleevec for treatment of GIST patients refractory to prior therapy with Gleevec.¹ The authors herein report ulcerative keratitis as a previously undescribed vision-threatening ocular complication of combination therapy with perifosine and imatinib.

Case Reports

Five eligible patients who enrolled in a phase I/II trial of perifosine and imatinib at The University of Texas M. D. Anderson Cancer Center between August 2005 and October 2006 are the subject of this report. All 5 patients had imatinib-resistant metastatic GIST and had continued on the highest dose of imatinib tolerated. Each patient also received perifosine orally over a 28-day cycle. The patients in this protocol were randomized to one of the two arms of the study. In arm A, the patients receive perifosine 100 mg daily in 2 divided doses of 50 mg each. In arm B, the patients receive 900 mg of perifosine per week, in 3 divided doses of 300 mg each, given on the days 1, 8, 15, and 22 of a 28-day-cycle. A total of 27 patients have been treated on this combination chemotherapy during the study period. Of these, various degrees of peripheral ulcerative keratitis developed in 5 patients. The interval from the start of combination therapy with perifosine and imatinib to diagnosis of ulcerative keratitis in the patients described in this report ranged from 1 to 3 months (median, 2 months). Each of the 5 patients are described in detail.

Patient 1

A 57-year-old man sought treatment at the Ophthalmology Clinic at the authors' tertiary cancer center for redness, pain, and photophobia in both eyes. He was on arm A of the protocol. His ocular problem started 3 months after initiating treatment on protocol. On examination, his best-corrected visual acuity (BCVA) was 20/40 in the right eye and 20/20 in the left eye. Slit-lamp biomicroscopy revealed a perilimbal corneal infiltration in both eyes, more severe in the right eye (Fig 1), with thinning of the temporal aspect of the right cornea. The remaining ocular examination results were un-

remarkable. It was thought that the patient had a possible immune-mediated peripheral ulcerative keratitis. He had received several weeks of topical antibiotic therapy that had been initiated before referral to the authors' department, and his keratopathy had been progressive despite topical antibiotic therapy. The corneal cultures had been negative. Thus, he was started on oral and topical prednisolone acetate and topical lubricants. On review three weeks later, the infiltration mostly had resolved. The BCVA was 20/20 in both eyes. The oral and topical steroids were tapered slowly. The perifosine was stopped after 6 months of therapy, because the GIST had progressed and the patient was administered another alternative imatinib-based chemotherapy protocol. The patient was stable at his last visit, one year later.

Patient 2

A 57-year-old woman sought treatment for ocular symptoms of irritation, injection, photophobia, and swelling of her left eye 3 months after initiating treatment on arm B of the protocol. She had a history of amblyopia in the left eye because of congenital left VIth nerve palsy. On examination, her BCVA was 20/20 in the right eye and 20/300 in the left eye. Slit-lamp biomicroscopy demonstrated a ring-shaped paralimbal infiltrate in the left eye, without any associated epithelial defect or thinning (Fig 2A). There were trace cells and flare in the anterior chamber. The ocular examination results were otherwise unremarkable except for the presence of an abduction deficit and esotropia of the left eye, as expected with her history of congenital VIth nerve palsy. She already had been receiving topical antibiotics for several weeks before referral to the authors' clinic. Corneal culture results were negative. Topical prednisolone acetate was added for the left eye, eight times daily, with slow weekly taper. Initially, the patient responded to topical steroid therapy with improvement of the corneal stromal ring-shaped infiltration. But, on further tapering of the steroid drops, the paralimbal corneal infiltration recurred with associated corneal thinning in the left eye, 6 weeks later (Fig 2B). This time, in consultation with her medical oncologist, and given the severity of her symptoms in the left eye, perifosine was discontinued and topical prednisolone acetate drops were restarted, 4 times daily. In addition, oral prednisone was also started, 40 mg daily, with a 10-mg reduction every week. On follow-up, 4 weeks later, the infiltration had resolved completely. However, the pe-

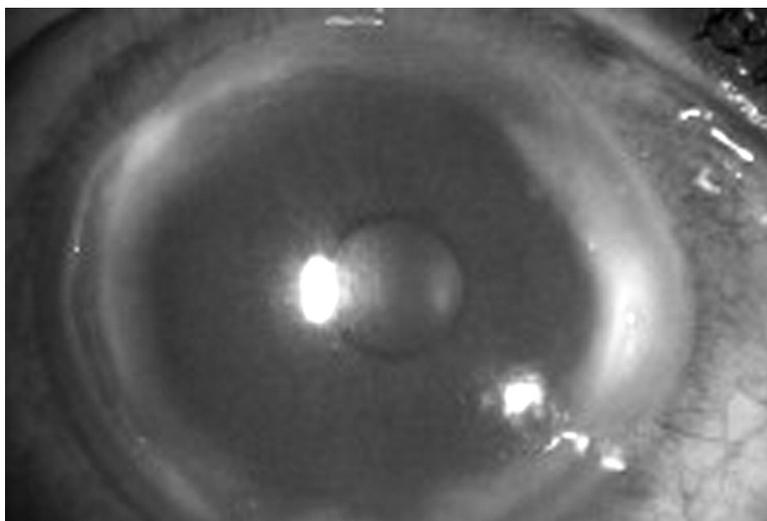


Figure 1. Slit-lamp photograph from patient 1 showing a ring-shaped paralimbal infiltrate in the left cornea.

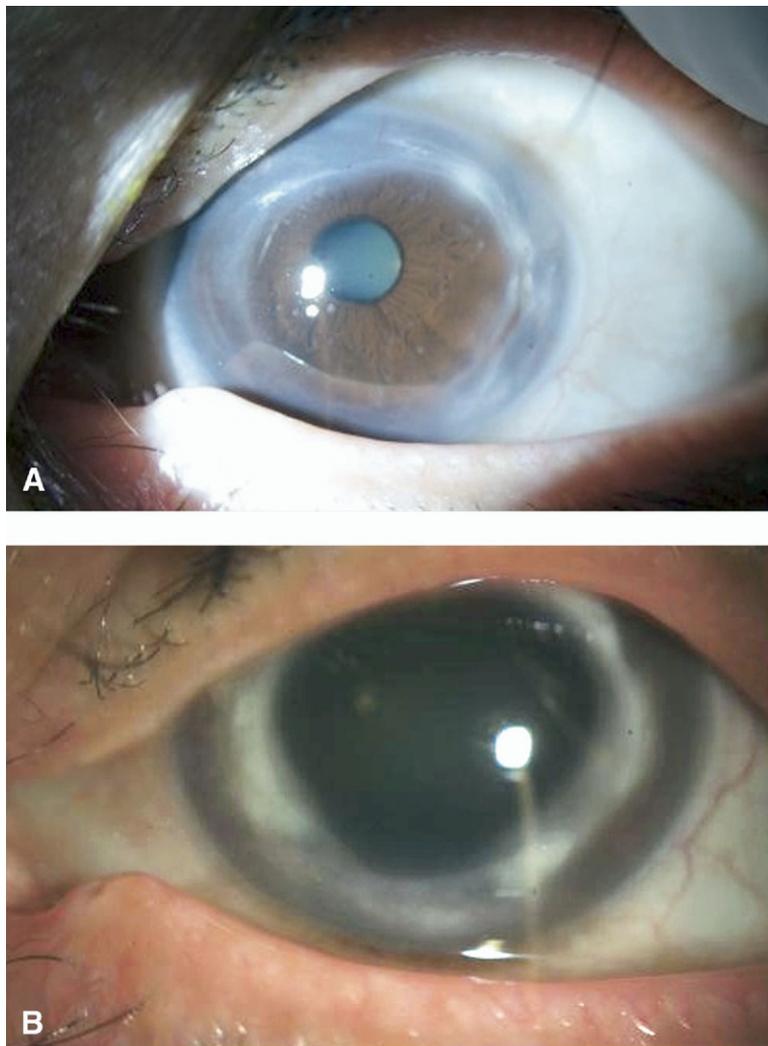


Figure 2. A, Slit-lamp photograph from patient 2 showing a ring-shaped paralimbal infiltrate in the left eye, very similar in appearance to the finding in patient 1 (Fig 1). B, Slit-lamp photograph from patient 2 obtained 6 weeks later showing a ring-shaped paralimbal infiltrate and stromal haziness, with mild corneal thinning (after dilation of pupil).

ripheral stromal haziness remained with associated superficial vascularization and mild thinning. The patient remained off perifosine and was started on alternative imatinib-based chemotherapy, and there were no relapses in the ocular condition over an 18-month follow-up.

Patient 3

A 72-year-old woman sought treatment for photophobia and irritation in both eyes 1 month after initiation of treatment on arm A of the protocol. On examination, the BCVA was 20/200 in the right eye and 20/70 in the left eye. Slit-lamp biomicroscopy showed early, patchy, paralimbal infiltrations. The remaining ocular examination results were unremarkable. Topical prednisolone acetate 1% was started in combination with topical antibiotics. The patient was taken off perifosine after 2 months of treatment because of progression of the GIST and was administered alternative imatinib-based chemotherapy. The ocular condition started improving after stopping perifosine, and the patient discontinued the topical therapy. At a follow-up visit, 1 month later, her ocular symptoms had resolved. The BCVA was 20/50 in the right eye

and 20/30 in the left eye. There was no evidence of corneal infiltration.

Patient 4

A 54-year-old woman sought treatment for irritation in the left eye 2 months after enrollment in the arm B of the protocol. On examination, the BCVA was 20/20 bilaterally. Slit-lamp biomicroscopy demonstrated mild paralimbal infiltration from the 9- to 1-o'clock positions and from the 4- to 8-o'clock positions on the left cornea, without any thinning or epithelial defect. Topical prednisolone acetate eye drops were prescribed, 6 times daily, in combination with topical antibiotics. At a follow-up visit, 3 weeks later, it was noted that her symptoms and the findings on slit-lamp biomicroscopy had resolved completely.

Patient 5

A 43-year-old woman sought treatment for irritation in the left eye 2 months after initiation of therapy on arm B of the protocol. On examination, the BCVA was 20/20 bilaterally. Slit-lamp biomi-

scopy demonstrated mild paralimbal infiltration present from the 4- to 8-o'clock positions on the left cornea, without any thinning or epithelial defect. Topical tobramycin plus dexamethasone combination eye drops were prescribed, 6 times daily. At the follow-up visit, 3 weeks later, her ocular symptoms and the findings on slit-lamp biomicroscopy had resolved completely.

Discussion

We describe 5 patients in whom paralimbal corneal infiltration and peripheral corneal thinning developed after combination therapy with imatinib and perifosine for treatment of advanced GIST. The corneal findings in these patients were most consistent with a form of peripheral ulcerative keratitis, reminiscent in appearance to a Mooren's ulcer or other types of autoimmune keratitis seen, for example in patients with rheumatoid arthritis. The ulcerative keratitis in these patients responded well to topical and systemic steroids. To the authors' knowledge, ulcerative keratitis as a side effect has not been reported previously with imatinib when used as a single agent. Furthermore, in 3 of 5 patients, ulcerative keratitis abated on withdrawal of perifosine only, without recurring when patients were restarted on imatinib-based alternative chemotherapy without perifosine, suggesting that perifosine by itself or the combination of perifosine with imatinib may be the cause of this ocular toxicity. Moreover, the authors have not seen this ocular side effect in their experience in more than 200 GIST patients who have enrolled in various clinical trials using imatinib alone.⁵⁻⁷ The most common ocular side effect associated with imatinib is periorbital edema,⁵⁻⁸ followed by epiphora.⁷ Other rare ocular side effects have been reported to be associated with imatinib therapy, such as cystoid macular edema⁹ and optic neuritis.¹⁰

The interval from the start of combination therapy with perifosine and imatinib to diagnosis of ulcerative keratitis in the current patients ranged from 1 to 3 months (median, 2 months). A combination of topical steroids, topical antibiotics and lubricating drops, and oral steroids (in 2 patients) were used to manage ulcerative keratitis. In all 5 patients, topical antibiotic therapy had been started either for several weeks before initiation of topical steroids or, in the milder cases, simultaneously with topical steroids. In patients 1, 2, and 3, who were the earliest patients in whom this side effect was noted, the lack of response to several weeks of antibiotic therapy and negative bacterial and fungal culture results further supported the diagnosis of possible autoimmune-based peripheral keratitis and justified initiation of topical steroid therapy.

Other adverse effects reported with perifosine include nausea, vomiting, diarrhea, and fatigue. Renal insufficiency manifesting as increased creatinine levels and hypercalcemia also have been reported.¹ The use of perifosine in high doses (an initial loading dose of 900 mg, followed by 100 mg every day) in a phase II trial of perifosine in locally advanced, unresectable, or metastatic pancreatic adenocarcinoma was associated with an unacceptable level of systemic side effects including fatigue, dehydration, acidosis, and hypoxia and had to be discontinued.¹¹ However, to the

authors' knowledge, ocular complications have not been reported previously in association with perifosine other than in their preliminary report of the same patients described in the current manuscript, which was presented as an abstract at a recent meeting of the American Society of Clinical Oncology Meeting (unpublished data).

The visual loss caused by ulcerative keratitis described in this report may be more readily reversible if detected and treated early, as demonstrated in patients 4 and 5. Early judicious use of topical steroids along with topical antibiotic coverage and lubrication seem to be the effective treatment. The average length of time on the study protocol was 4 months. It is possible that the keratitis described in these patients would have been much more severe and would have been accompanied by much worse permanent sequelae if the patients had continued using perifosine for longer periods. The mechanism for development of ulcerative keratitis associated with perifosine use is unknown. Given the similarity in appearance of the cornea to other forms of autoimmune keratopathy and the response to topical steroid therapy, the authors hypothesize that either perifosine by itself or in combination with imatinib may induce an autoimmune reaction that is the underlying mechanism for development of ulcerative keratitis.

In conclusion, peripheral ulcerative keratitis may occur as a side effect of combination therapy with perifosine and imatinib and shares features of other autoimmune forms of keratitis. To the authors' knowledge, this serious ocular side effect is not seen when imatinib is used by itself and is likely caused by perifosine or its use in combination with imatinib. Early detection of this potentially vision-threatening ocular toxicity is very important because response to therapy seems to be much better in early stages of ulcerative keratitis. In view of this ocular adverse event, the authors suggest that patients receiving perifosine be monitored for this side effect on a regular basis while receiving therapy.

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Answers for CME credit:

1. B; 2. C; 3. B; 4. A