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OCULAR TOXICITY IN A PATIENT WITH ADVANCED GIST, TREATED WITH SUNITINIB. A CASE REPORT

R. SORCE[1,3], V. PUMO[2,3], A. DI MARI[2,3], M. IACONO[2,3], E. TATA[2], P. TRALONGO[2,3]

[1]Ophthalmic Unit, Umberto I Hospital, Siracusa, Italy
[2]Medical Oncolgy Unit, Umberto I Hospital, RAO, Siracusa, Italy
[3]UILOC Umberto I Hospital, RAO, Siracusa, Italy

Abstract: *The oral multitargeted agents, imatinib first, has changed the survival in gastrointestinal stromal tumor (GIST). Sunitinib has been approved for treatment of GIST after disease progression to imatinib. The side effects of Sunitib are well known and are represented mainly by fatigue, HFS, skin rash and diarrhoea. We report a case of ocular toxicity observed in a patient with advanced GIST treated with sunitinib.*

INTRODUCTION

The advent of oral multitargeted agents has changed the prognosis for survival in gastrointestinal stromal tumor (GIST). Sunitinib malate, targets multiple tyrosine kinases including stem cell factor (KIT), platelet-derived growth factor (PDGFR) and the vascular endothelial growth factor (VEGF) receptors, has been approved for treatment of GIST after disease progression to imatinib mesylate, with good tolerability[1]. We report, for the first time, a case of ocular toxicity observed in a patient with advanced GIST treated with sunitinib.

CASE REPORT

In march 2008 a radical gastrectomy was performed in 68 years old man for a gastrointestinal stroomal tumour (diameter 5 cm, tumour free surgical margins, invasion limited to the mucosa that appeared ulcerated, signs of necrosis, CD 34+, KIT exon 11 mutation, mitosis >10x50HPF) with multiple liver metastases, which measured 1 cm in diameter in the second, fourth, sixth segments and other lesion which measured 26 mm in diameter in the eighth hepatic segment. Based on this a first-line therapy with imatinib at dose of 400 mg p. o. daily was started.

In December 2010, the dose of imatinib was increased to 800 mg p. o. daily and administered for 2 months for recurrence of tumour with significant metabolic activity at the gastrojejunal anastomosis.

In March 2011 due the progression a second-line therapy with sunitinib was started. The initially dose was 50 mg p. o., for 4 weeks followed by 2 weeks off. After two months of treatment, the patient reported fatigue G2, stomatitis G2, skin toxicity G2 and mild hypertension which led to discontinuation of the drug for 2 weeks, with reversibility of adverse events and re-treatment. The dose of sunitinib was reduced at 25 mg, after 7 months, due to skin toxicity and mucositis G3.

In September 2012 the patient, previuosly subjected to ophtalmologic examination for corneal dystrophy of the left eye, manifested in the same eye a marked reduction in visual acuity and considerable conjunctival hyperemia. The cornea was edematous with ulcer in the optical zone which later evolved into melting (Figure 1). Intraocular pressure was digitally high and behind the ocular structures were not explored for corneal opacity. Sunitinib treatmen was stopped and a treatment with betamethasone, chloramphenicol, topical atropine (for cycloplegic and mydriatic effect), brinzolamide and timolol was started. The combination of steroid and antibiotic used was in the form of

Corresponding Author: Paolo Tralongo, MD; e-mail: tralongo@raosr.it

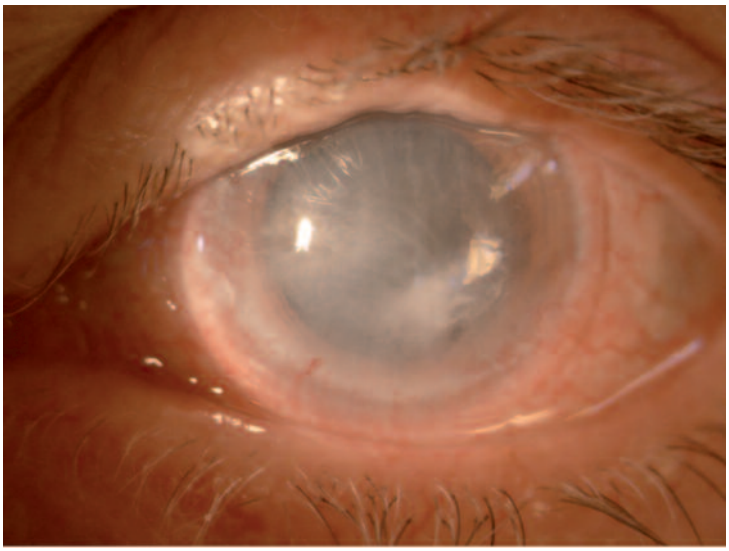

Figure 1. Ulcer corneal with melting evolution and reparative neovascularization.

gel three times a day for ten days with dose-ranging; atropine eye drops and hypotonic solution twice a day. Has been applied to a contact lens (Quotidia therapeutic) that has been replaced every ten days for the duration of about one month with complete resolution (Figure 2).

DISCUSSION

Generally, adverse events reported in the fase III studies with sunitinib were diarrhoea, nausea, anorexia, dysgeusia, haematological laboratory abnormalities and among the most common were fatigue, hypertension and hand-foot syndrome[2,3]. Only one case of ocular toxicity, specifically neurosensory retinal detachment, has been reported in patient with metastatic renal cell cancer (mRCC)[4]. Unlike this case, where the retinal detachment is probably caused by a variation of choroidal vascular permeability, in our case the pathogenetic hypothesis could be probably related to the presence of drug in the tears, being the corneal an avascular tissue. The tear film is the only source of nutritive support for the surface layers corneal, its alteration quantitatively or qualitatively, makes this surface suffering. It's may justify blepharitis and chalazion well as the dry eye and keratitis.

However, the incidence of adverse events appear to be different in patients with mRCC and those with advanced GIST; the reasons for these apparent differences in tolerability profile are still unclear[2,5-7].

Our experience, the first of ocular toxicity in GIST patient, indicates that the sunitinib treatment

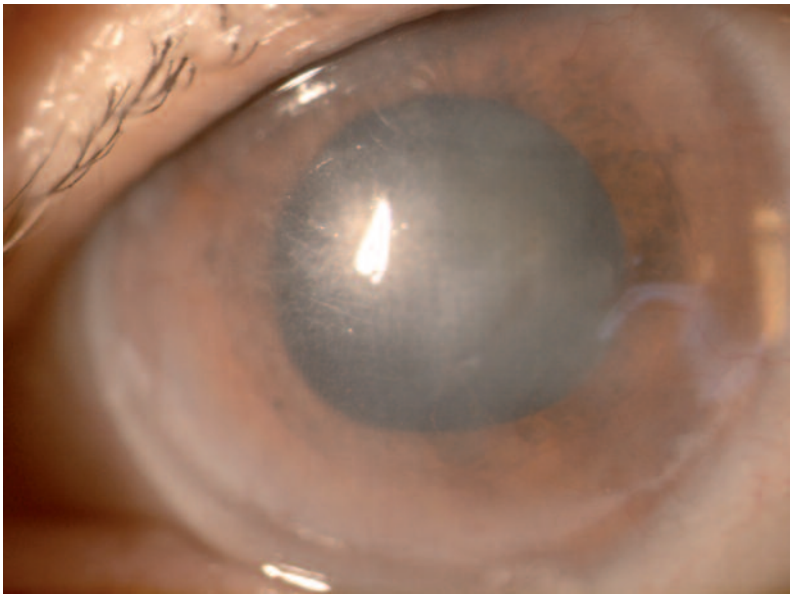

Figure 2. Corneal ulceration and melting in resolution.

required to monitor ocular toxicity also in this patients and that should be investigate the mechanism of action and drug clearance, considering that the use of new targeted agents directed against aberrations present in cancer cells but including also eyelid tissue may be associated with potential ocular toxicity.

Conflict of Interests:
The Authors declare that they have no conflict of interests.

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