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Adverse Effects of the Oral Anticancer Drug S-1: Lacrimal Passage Impairment and Specific Features of Corneal Epitheliopathy

Ken-ichi Sato* and Shin-ichi Nishimura

Department of Ophthalmology, Nikko Memorial Hospital, Muroran, Hokkaido, Japan

Abstract: We report the incidence of lacrimal passage impairment and specific features of corneal epitheliopathy as adverse effects of the oral anticancer drug S-1, and examine the relationship between the two pathologies. We conducted a retrospective chart review of 84 patients prescribed the anticancer drug S-1. The incidence of lacrimal passage impairment and corneal epitheliopathy was 8% and 6%, respectively. Three patients experienced both pathologies, demonstrating a moderate probability of both occurring in the same patient (kappa coefficient = 0.46). The findings show that lacrimal passage impairment and specific features of corneal epitheliopathy are likely to occur in the same individual as adverse effects of S-1.

Keywords: Antineoplastic agents, adverse effects, lacrimal duct obstruction, corneal diseases.

TO THE EDITOR,

The oral anticancer drug S-1 was originally approved in 1999, and it is now widely used for gastric, colorectal, pancreatic, biliary tract, breast, head and neck, and non-small-cell lung cancer treatment in Japan. It has also been approved in Korea, China, Singapore, Hong Kong, Taiwan, Thailand, and Europe [1]. However, Sasaki *et al*. reported that 9.6% of patients prescribed S-1 experienced ophthalmic adverse effects in the form of lacrimal passage impairment (LPI) [2]. The incidence of specific features of corneal epitheliopathy associated with S-1 administration (SCE), another ophthalmic side effect which extends from the inferior and posterior areas to the center, remains unknown [3]. In addition, the relationship between these two pathologies has yet to be sufficiently investigated. Here, we report the incidence of LPI and SCE, and examine the relationship between the two.

We retrospectively examined the medical charts of 84 consecutive patients (41 men and 43 women; mean age ± SD: 71 ± 10 years) in Nikko Memorial Hospital who received S-1 according to its indication and dosage at some time between January and May 2012. Patients who had started S-1 treatment before the January were also included.

Patients who presented with new complaints during S-1 administration such as epiphora, blurred vision or a foreign body sensation in the eyes underwent slit lamp examination and lacrimal irrigation to confirm LPI and SCE. Patients with a history of facial trauma, lid anomaly, herpes, paranasal sinus disease or lacrimal surgery were excluded. None of the included patients had undergone subconjunctival 5-fluorouracil (5-FU) injection following glaucoma surgery.

*Address correspondence to this author at the Department of Ophthalmology, Nikko Memorial Hospital, Muroran, Hokkaido, Japan;
Tel: +81-143-24-1331; Fax: +81-143-22-5296;
E-mail: vze04311@nifty.ne.jp

Informed consent was obtained from all subjects prior to the examinations, and the study adhered to the tenets of the Declaration of Helsinki.

Of the 84 patients, 20 consulted our ophthalmology department during the study period: among them, 11 were referred due to symptoms suggestive of LPI or SCE.

Seven patients (8%; 4 men and 3 women) experienced LPI, which presented unilaterally in 3 patients and bilaterally in 4. Mean time from initiation of S-1 administration to onset of LPI was 5.7 months (range: 0-12 months). In 3 cases, the disorder occurred within 1 month of initiation.

SCE occurred in 5 patients (6%; 2 men and 3 women), and was bilateral in all cases. Mean time from initiation of S-1 administration to onset of SCE was 6.5 months (range: 2-11 months).

Three patients (2 men and 1 woman) experienced both pathologies, all with unilateral LPI. Both pathologies occurred almost simultaneously in one of the 3 patients, while in the remaining 2, SCE occurred 3 and 5 months before LPI, respectively. There was a moderate probability of LPI and SCE occurring in the same patient (kappa coefficient = 0.46).

Two other patients presented with epiphora. Neither patient had LPI or SCE: one had exposure keratopathy and the other had dry eye due to Sjogren's syndrome.

S-1 contains tegafur, the prodrug of 5-FU, which has anticancer effects, and gimeracil which increases the blood concentration of 5-FU. Although corneal damage due to subconjunctival 5-FU therapy after unsuccessful glaucoma surgery is frequently reported [4], only a few papers have reported the occurrence of corneal epitheliopathy by systemic administration of 5-FU [5]. In contrast, LPI is a widely known adverse effect of systemic 5-FU therapy [6]. It is speculated that 5-FU concentrated in the blood as a result of gimeracil facilitates the manifestation of corneal epitheliopathy [3].

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In our study, the incidence of LPI was 8%, which is highly consistent with the findings of Sasaki *et al.* [2]. No report has yet described the incidence of SCE. The incidence found in the present study of 6% is also a relatively high rate. The moderate concordance of onset between the two pathologies further suggests that any patient showing one of these pathologies will likely present with the other in the near future, a finding that will help clinicians in their follow up of patients prescribed S-1.

Ito *et al*. surmised that tears containing 5-FU excessively accumulate in the conjunctival sac due to LPI, accelerating LPI itself and SCE [3]. Our results do not necessarily conflict with this speculation; however, in 2 of the 3 patients who experienced both pathologies, SCE preceded LPI by not less than 3 months. In addition, in all 3 patients, SCE was bilateral, despite LPI being unilateral. Thus, SCE can occur alone without preceding LPI, suggesting that another factor influences corneal pathology; for example, individual differences in sensitivity to 5-FU and in the inhibition of 5-FU degradation by gimeracil.

In this study we were unable to include patients who did not consult an ophthalmologist with mild subjective symptoms despite showing objective signs. A prospective study of all patients prescribed S-1 would therefore indicate the true incidence of LPI and SCE in these individuals.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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