Usefulness of Topical Interferon Alpha-2b Eye Drop as an Adjunctive Therapy Following Surgical Resection in Ocular Surface Squamous Neoplasia

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Abstract. Aim: To report the clinical course of patients with ocular surface squamous neoplasia treated with topical interferon α-2b (IFNα-2b) after local excision of the tumor.

Patients and Methods: This study enrolled four consecutive Japanese patients comprising one eye with conjunctival carcinoma in situ, and three eyes with squamous cell carcinoma (SCC) diagnosed histopathologically. All of them initially visited Hokkaido University Hospital in 2016. After resecting the tumor tissues, topical IFNα-2b eye drops were given to the eye four times a day. This study retrospectively analyzed the ophthalmological and imaging findings before and after the surgery, based on the patients’ medical records.

Results: The mean follow-up duration was 37.8 months. All cases were males, and the mean age was 62.3 years. The tumor was located in the bulbar conjunctiva in three cases. Local pedunculated rotation flap, and free conjunctival flap were performed in one and two patients, respectively. In one case with SCC, the tumor involved the lower palpebral conjunctiva, already invading into the orbit at the first visit. The patient underwent extended resection of the lower lid, and reconstruction of the posterior lobe of the eyelid with Hughes flap. Cataract surgery was successfully conducted 18 months after tumor resection. All patients remain well without local recurrence or distant metastasis. Conclusion: Topical IFNα-2b treatment contributed to suppression of tumor recurrence and improvement of quality of vision in patients after local resection of ocular surface squamous neoplasia.

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diagnosed histopathologically. All of them initially were diagnosed at Hokkaido University Hospital in 2016. All the patients enrolled in this study were examined by ophthalmological tests including visual acuity, intraocular pressure, slit-lamp examination and fundus examination. The patients also underwent magnetic resonance imaging and systemic computed tomography (CT) as well as positron-emission tomography-CT once a year. After resecting the tumor tissues, topical IFN α-2 b eye drops were given to the eye, at one drop four times a day. Treatment generally lasted for 4 months; if the tumor was suggested to invade the orbit, longer duration was required. The endpoint of use was the result of repeated biopsy, namely being negative for malignancy. The concentration of topical IFNα-2b was set to 106 IU/ml according to a previous report (6). The Institutional Review Board of Hokkaido University Hospital waived the approval of this study as a clinical trial because of a non-invasive study and the limited number of cases examined. No patient with OSSN initially underwent enucleation or orbital exenteration during the designated study period. The presence of distant metastases was assessed by systemic computed tomography 6 to 12 months after surgery.

Results

Table I summarizes the clinicopathological findings in this study. All of the cases were male, and the mean age was 62.3 years. Figure 1 shows the slit-lamp findings at their first visit for cases 1 to 3, with OSSN arising in the bulbar conjunctiva (Figure 1A, C and E). In case 1, the whitish nodule with marked conjunctival hyperemia was located in the nasal bulbar conjunctiva (Figure 1A). A reddish sessile papillomatous tumor located in the bulbar conjunctiva in case 2 (Figure 1C). In case 3, the patient presented with a whitish tumor in the bulbar conjunctiva and cornea. In case 4, the slit-lamp examination showed marked lower eyelid swelling with irregular whitish conjunctival tumor and congestion (Figure 2A). In cases 1 to 3, the patients were treated with local pedunculated conjunctival flaps and cryotherapy combined with free conjunctival flaps following local resection. Histopathology of the resected tumor tissues revealed malignant tumor cells.
differentiating from squamous cells, consistent with OSSN. The tumors were diagnosed as SCC and carcinoma in situ in cases 1, 2, and 4 (Figure 3A, B and D), and case 3 (Figure 3C), respectively. Histopathology of the resected tumor tissues suggested positive surgical margin at the corneal side in all cases. Topical IFNα-2 b was administered to patients for 4 to 12 months. The mean follow-up duration was 37.8 months. All patients are well without local recurrence (Figure 1B, D and F; Figure 2E) or distant metastasis.

Representative Case Report

The patient was a 39-year-old male complaining of irritation and continuous discharge from his right eye; he had a medical history of atopic dermatitis. He was diagnosed with allergic conjunctivitis and treated with topical anti-allergic agents at a nearby clinic. However, since his symptoms did not improve and proliferative changes were observed in the conjunctiva, he was referred to Hokkaido University Hospital. Slit-lamp examination demonstrated marked lower eyelid swelling with an irregular massive conjunctival mass (Figure 2A). Magnetic resonance imaging revealed anterior orbital invasion of the tumor (Figure 2B). At this time, the patient withdrew informed consent and refused orbital exenteration, instead hoping to preserve the eyeball. Therefore, we decided to conduct local resection of the tumor tissues with lower eyelid reconstruction (Hughes flap) and used adjuvant topical IFNα-2b eye drops. One month

Table 1. Clinicopathological features of patients with ocular surface squamous neoplasia. All patients were males and had no evidence of recurrence or metastasis.

| Case | Age, years | Eye   | TNM classification* | Surgical margin | Duration of IFN (months) | Follow-up period (months) |
|------|------------|-------|----------------------|-----------------|--------------------------|---------------------------|
| 1    | 50         | Right | pT1N0M0              | +               | 6                        | 40                        |
| 2    | 80         | Left  | pTisN0M0             | +               | 2                        | 42                        |
| 3    | 81         | Right | pTisN0M0             | +/-             | 3                        | 35                        |
| 4    | 39         | Right | pT2N0M0              | +               | 8                        | 34                        |

IFN: Interferon-α-2b. *TNM classification was based on AJCC Cancer Staging Manual, 8th edition (10).
after resection, the reconstructed lower eyelid presented with favorable granulation-like tissue (Figure 2-C). The lower eyelid had undergone epithelialization, maintaining a smooth ocular surface (Figure 2D). The patient’s best corrected visual acuity (BCVA) was 0.2 OD due to atopic posterior capsular cataract. There was no recurrence of the tumor in the ocular adnexa at 1 year after treatment. Since the biopsy was conducted from the lower bulbar conjunctiva and histology demonstrated no remaining tumor cells, he underwent cataract extraction with implantation of posterior chamber intraocular lens 18 months after the initial surgery (Figure 2E). BCVA recovered from 0.2 to 1.2 OD. Furthermore, the patient remains well without local recurrence, or intraocular or orbital invasion (Figure 2F) of the tumor 1.5 years after cataract surgery.

Discussion

Topical IFN-α2b plays an important role in immunotherapy, immunoreduction, and immunoprevention (6). In our four cases with OSSN, histopathology of the resected tumor tissues suggested a positive surgical margin in the corneal side. Shields et al. showed that topical IFNα-2b was effective for reducing the risk of recurrence after surgery (6). We have shown IFNα-2b to be useful as an adjunctive treatment in conjunctival melanoma, thereby possibly promoting the host innate immune system (7). By adding IFNα-2b eye drops, activation of the local immune system might have led to attack of potential residual tumor cells after tumor resection and prevented tumor recurrence in this study. These results suggest that topical IFNα-2b is also effective in OSSN treatment as immunoprevention in this study.

As we show in a representative case, we for the first time successfully carried out cataract surgery in a case with conjunctival SCC arising in atopic dermatitis. OSSN can develop in the corneal tissues and invade intraocular tissues following intraocular surgery (8, 9), unless preoperative OSSN was appropriately managed before the surgery. Therefore, before intraocular surgery in patients having a history of OSSN, it is mandatory to ensure no tumor cells are left on the ocular surface based on repeated biopsies. Topical IFNα-2b not only can save a patient’s life, but also contribute to favorable QOV following cataract surgery.

In conclusion, Topical IFNα-2b treatment contributed to suppression of tumor recurrence and improvement of quality of vision in patients after local resection of OSSN.
Conflicts of Interest

The Authors declare no conflicts of interest.

Authors’ Contributions

LK wrote the article. LK and SK collected the clinical and pathological data and evaluated those for patients in this study. KI and SI reviewed and critically revised the article.

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