INTRODUCTION

Ocular surface squamous neoplasia (OSSN) is the most common neoplasm of the ocular surface. It is a slowly progressive tumor with low potential for metastasis which commonly arises from the limbus. A variety of treatment options has been shown to be successful. Surgical excision combined with cryotherapy has been the standard treatment for OSSN. By complete excision, with or without adjunctive cryotherapy, the recurrence rate is 9% and 33%, respectively. Excision margins are the most important factor in predicting recurrence. If the surgical margin is positive, the recurrence rate can be as high as 53%. In cases of OSSN that involved 360° of the limbus, surgical excision with clear margins is a destructive procedure and might result in severe complications including persistent epithelial defects, corneal haziness and neovascularization, symblepharon formation and limbal stem cell deficiency. In this situation, alternative topical treatments including immune modulators such as interferon alpha-2b (IFNα2b) or chemotherapeutic agents such as mitomycin-C (MMC) and 5-fluorouracil (5-FU) may be used. However, it has been shown that topical MMC and 5-FU are toxic to the ocular surface and might cause limbal stem cell deficiency.
Topical IFNα2b has been shown to be effective as a single-agent therapy or as an adjunct after surgery. As it is not associated with limbal stem cell damage, it could be an excellent alternative treatment for 360° involvement of the limbus.[8,9] In this study we evaluate the efficacy of topical IFNα2b for treatment of 360° limbal OSSN.

METHODS

This prospective study was conducted at Khatam-al-Anbia Eye Institute, Mashhad University of Medical Sciences, Iran. Institutional review board approval was obtained and the study followed the tenets of the declaration of Helsinki. A comprehensive ophthalmic examination was performed in all patients including measurement of uncorrected and best corrected visual acuity, tonometry, slit lamp biomicroscopy, and dilated fundus examination.

The extension of OSSN was determined by slit lamp biomicroscopy with and without Rose Bengal staining. OSSN was classified based on the seventh edition of the American Joint Committee on Cancer (AJCC) classification.[10] All patients who underwent topical IFNα2b medication had primary or recurrent OSSN which had involved 360° of the limbus. The diagnosis was confirmed by small incisional biopsy.

We used IFNα2b at 3 million IU/ml (Interferon alpha-2b 3 Mega Unit Vial, Hejrat Distribution Co, Tehran, Iran) and the volume of three vials of IFNα2b was injected into an empty drop container without dilution. All patients instilled the drop 4 times daily and stored the container in the refrigerator for 2 weeks. After 2 weeks, the patients received another container with IFNα2b.

All patients were examined prior to initiation of IFNα2b and were seen after 1-day, 1-week, 1-month, and then every month thereafter. The medication was continued for 1-month after complete clinical resolution. All systemic and ocular adverse effects were recorded during follow-up.

RESULTS

Five eyes of five patients including four male and one female subject with mean age of 55 (range, 52–73; median, 60) years and 360° limbal OSSN were included in the study. Table 1 shows demographic data, clinical findings and the outcomes of treatment. In terms of lesion morphology, three eyes presented as sessile papilliform (Figure 1a), one as gelatinous (Figure 1b) and the other one as leukoplakic. All patients complained of low visual acuity, itching, foreign body sensation and photophobia.

Mean follow-up duration was 10.2 (range, 8–12, median, 10) months. Complete clinical resolution was achieved in all eyes after a course of topical INF-α2b therapy for 8 weeks. Before treatment all patients had cornea epithelial irregularity and punctate epithelial erosions on slit lamp biomicroscopy [Figure 1b]. After 1-month, corneal epithelial abnormality improved and all patients reported symptomatic improvement. In the 2nd month visit, the corneal involvement resolved completely. The neoplastic mass disappeared and limbal vascularity was also reduced significantly [Figure 1]. Mean best corrected visual acuity increased from 20/200 before treatment to 20/40 at last follow-up.

No patient developed persistent epithelial defect, symblepharon, or any signs indicative of limbal stem deficiency. No recurrence was seen based on the slit lamp biomicroscopy at final follow up. None of the patients experienced systemic adverse effects related to IFNα2b therapy including malaise, flu like symptoms, bone pain and fatigue. Patients’ information was summarized in Table 1.

DISCUSSION

OSSN is a slowly progressing lesion that arises due to mutations in limbal stem cells. In cases of OSSN with 360° limbal involvement, stem cell dysfunction might change the clinical presentation (case #4 was referred to us with a diagnosis of limbal stem cell deficiency) [Figure 1]. In this situation, signs of limbal stem cell deficiency including corneal epithelial irregularity, epithelial erosion and peripheral corneal neovascularization, may be present before treatment. Eradication of neoplastic cell by surgical excision, cryotherapy or antimetabolites or chemotherapeutic agents (MMC and 5-FU) can damage the remaining limbal stem cells and aggravate limbal stem cell deficiency.[3,5-7]

| Case | Gender | Age | VA (before treatment) | Primary/ recurrent | Previous treatment | Clinical morphology | VA (after treatment) | Recurrence after treatment | Follow-up (M) |
|------|--------|-----|-----------------------|-------------------|-------------------|-------------------|---------------------|---------------------------|---------------|
| 1    | Male   | 62  | 20/400                | Primary           | -                 | Sessile papilliform | 20/60               | No                        | 10            |
| 2    | Male   | 60  | 20/200                | Recurrent         | Excision+ cryotherapy | Sessile papilliform | 20/40               | No                        | 11            |
| 3    | Male   | 55  | 20/100                | Primary           | -                 | Leukoplakic        | 20/40               | No                        | 8             |
| 4    | Female | 51  | 20/100                | Primary           | -                 | Gellatinous        | 20/30               | No                        | 12            |
| 5    | Male   | 73  | 20/400                | Primary           | -                 | Sessile papilliform | 20/40               | No                        | 10            |

VA, visual acuity; M, month
Topical chemotherapy using immune modulator agents have gained great attention. Interferons are glycoprotein molecules which have an important role in human natural defense responses. The Food and Drug Administration (FDA) has approved interferon therapy for a variety of diseases including hairy cell leukemia, type-C viral hepatitis and Kaposi’s sarcoma.\cite{11,12} Several studies have shown that topical IFNα2b as a single therapeutic agent is an effective treatment for both primary and recurrent OSSN.\cite{13‑15} Recently, a study used IFNα2b for large OSSNs (tumor diameter ≥15 mm or ≥180° limbal involvement) and achieved 72% success.\cite{16}

To the best of our knowledge, there is no study reporting the treatment of OSSN with 360° limbal involvement. Treatment of this subtype of OSSN differs from others as limbal stem cell deficiency and extensive ocular surface damage may occur before or after treatment. However, in our study, all patients achieved favorable results with no significant systemic or ocular side effect. Extended follow up is needed to determine recurrence after 1-year.

In the current study topical IFNα2b was well tolerated by all patients. The corneal epithelial irregularity and punctate epithelial erosions were a result of partial limbal cell deficiency or dysfunction before treatment. During treatment, all cases showed improved visual acuity and ocular symptoms. We believe such improvements increased their compliance as compared to other OSSN cases with less severe ocular surface problems. We employed a higher dose of topical IFNα2b: 3 million IU/ml instead of 1 million IU/ml. In a recent study, Galor et al\cite{17} compared the effectiveness of these two concentrations of IFNα2b for treatment of OSSN. Although, not statistically significant, their results showed a trend toward increased success rates and faster resolution of the lesion in the 3 million IU/ml group. Our unpublished data showed similar findings and we chose the 3 million IU/ml concentration for extensive OSSN. In addition, continuous follow up of these patients would be necessary to evaluate long term outcomes of treatment. We excluded the patients with invasive OSSN based on clinical examination and histopathology. However, a small incisional biopsy cannot confirm the lack of invasion in other parts of the tumor. In general, in cases of invasive OSSN, topical monotherapy is contraindicated and the ophthalmologist must consider surgical excision and cryotherapy.\cite{18}

In summary, topical IFNα2b appears to be a safe and effective treatment for OSSN with 360° limbal involvement. This noninvasive treatment reduces the risk of limbal stem cell deficiency associated with surgical excision or topical antimetabolite chemotherapeutic agents.

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