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Surgery versus interferon alpha-2b treatment strategies for ocular surface squamous neoplasia: a literature-based decision analysis

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Abstract

Purpose—To compare treatment strategies for ocular surface squamous neoplasia (OSSN), ranging from surgical excision to empiric topical interferon alpha-2b (IFN-α2b).

Methods—A decision model was constructed to determine which of four treatment strategies minimized expected persistence/recurrence of disease in patients with OSSN: excision followed by repeat excision for positive surgical margins, excision followed by IFN-α2b for positive margins, incisional biopsy followed by IFN-α2b for positive biopsies, and empiric treatment with IFN-α2b. Probabilities were estimated from literature published between 1983 and 2015. Expected values for the probability of recurrence could range from 0 (no persistence/recurrence) to 1 (persistence/recurrence). Sensitivity analyses were performed for each variable.

Results—Excision followed by IFN-α2b for positive margins was estimated to minimize persistence/recurrence of OSSN (EV 0.13 versus 0.17 for empiric IFN-α2b, 0.22 for excision-only, and 0.30 for incisional biopsy-directed IFN-α2b). The optimal strategy was sensitive to three variables: efficacy of IFN-α2b, recurrence following negative surgical margins, and accuracy of excisional biopsy.

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Conclusions—In our decision analysis using studies published between 1983 and 2015, surgical excision followed by IFN-α2b for positive margins is the favored strategy for minimizing persistence/recurrence of OSSN. Future prospective studies would add to the certainty of these conclusions.

MeSH

Eye Neoplasms; Decision Analysis

Other

Ocular Surface Squamous Neoplasia; Interferon-alpha 2b

Introduction

Ocular surface squamous neoplasia (OSSN) is the most common non-pigmented malignancy of the conjunctiva and the third most common of all ocular tumors in elderly patients[1,2]. Von Graefe first reported these tumors in 1860, and the terminology used to identify them has evolved since that time. OSSN currently refers to a spectrum of epithelial abnormalities that ranges from dysplasia of the corneal and/or conjunctival epithelium to frankly invasive squamous cell carcinoma[1]. While most reports of OSSN in the United States are among elderly males of European origin with significant ultraviolet B (UVB) exposure, the tumor occurs in both sexes and across all ages and regions of the world[3,4]. The incidence has been estimated at 0.08–0.18 per 100,000 per year worldwide, and as high as 3.4 per 100,000 per year in countries such as Zimbabwe[1,5]. Higher rates of OSSN are seen in patients with human immunodeficiency virus (HIV) infection and xeroderma pigmentosum[6–8]. An association between OSSN and human papilloma virus has also been postulated[1,9–11].

In the past, treatment of OSSN was primarily surgical with wide excision of the tumor and cryotherapy to tissues at the surgical margins with the intent of destroying adjacent but clinically unapparent malignant cells. In the last decade however, there has been a trend toward the use of topical chemotherapeutic agents to complement or replace surgical management of OSSN. Topical interferon-alpha 2b (IFN-α2b) is of particular interest because of its apparent efficacy and low toxicity[12]. Proposed advantages of IFN-α2b therapy include treatment of the entire ocular surface rather than solely tissue within the surgical field, less damage to fragile limbal stem cells, and the convenience of outpatient management[12]. However, there has not been a randomized trial comparing IFN-α2b therapy to surgical management in order to confirm that these putative benefits are associated with comparable rates of success. In addition, efforts to indirectly compare the strategies have been limited by widely varying estimates for recurrence rates, ranging from 5% to 66% for surgical treatment[13–15] and from 0 to 28% with IFN-α2b treatment [16–22], depending on the surgical technique, IFN-α2b regimen, and length of follow up.

The majority of OSSN-related morbidity accrues from multiple rounds of surgical intervention, causing repeated damage to the ocular surface. This can result in corneal and conjunctival scarring, loss of limbal stem cells, and potentially exenteration in severe cases;

therefore, resolution of primary disease and prevention of recurrence are the principal goals of therapy. In the absence of randomized trials or other prospective comparative studies to direct clinical practice, we used a decision analysis informed by a systematic review of the literature to compare four strategies for treating OSSN, ranging from surgical excision alone to empiric topical IFN-α2b.

Materials and Methods

The Model

We developed a decision-analytic model to evaluate the expected value (EV) of four treatment strategies aimed at minimizing the persistence/recurrence of disease in patients with OSSN: 1) traditional surgical excision with cryotherapy followed by repeat excision for cases with positive margins (excision-only), 2) surgical excision with cryotherapy followed by topical IFN-α2b for cases with positive margins (excision-directed IFN), 3) incisional biopsy followed by topical IFN-α2b for cases with positive biopsies (incisional biopsy-directed IFN), and 4) empiric treatment with topical IFN-α2b (empiric IFN) (Figure 1).

Model Parameters

The base-case population was a multiracial, generally immunocompetent group over the age of 50 years. As the length of treatment was highly variable in our review of the literature, the model was evaluated over a single treatment course. Variables used in the model are listed in Table 1 and included test characteristics of excisional and incisional biopsies, rate of positive surgical margins following excision, recurrence rate for positive and negative margins, rate of successful treatment with IFN-α2b, and recurrence following clinical resolution after IFN-α2b treatment. The end points for each strategy were dichotomized as either complete clinical resolution, or disease persistence or recurrence.

Model Assumptions

For the excision-only strategy, a patient with a positive biopsy and positive margins underwent a second intervention (re-excision) prior to facing the probability of recurrence. If the excisional biopsy was positive but with negative margins, the patient faced a probability of recurrence associated with negative margins. We assumed that all patients entering the decision tree had OSSN; therefore, if the excision biopsy was negative, the diagnosis was considered missed and the patient continued to have OSSN. The excision-directed IFN-α2b strategy is identical to the excision-only strategy except that a patient with a positive biopsy and positive margins received IFN-α2b as the second intervention. Prior to this additional intervention, the appropriate proportion of individuals who would have not recurred despite positive margin status was removed. If IFN-α2b was successful, the patient went on to face a chance of recurrence following IFN-α2b treatment. If IFN-α2b was not successful the patient assumed the risk of recurrence associated with positive margins. For the incisional biopsy-directed IFN-α2b strategy, a patient with a positive incisional biopsy received IFN-α2b. If the IFN-α2b was unsuccessful or if the incisional biopsy was negative, the patient continued to have OSSN. For the empiric IFN-α2b strategy, the patient was treated with IFN-α2b then followed the same path of probabilities as those with a positive biopsy in the incisional biopsy-directed IFN strategy.

Model Endpoints and Analysis

To model the expected probability of persistent disease or recurrence, we assigned an outcome value of 0 for complete resolution with no recurrence or a value of 1 for persistence or recurrence. In the base case analysis, intermediate probabilities were used for all chance nodes. We identified the strategies that minimized the expected probability of missed/persistent disease or recurrence. Sensitivity analyses were conducted using the range of reported values in the literature. An additional analysis was performed to determine the preferred strategy when avoidance of a missed diagnosis was considered the optimal outcome.

Model Probabilities

We performed a systematic review of the literature to obtain values and ranges for each variable used in the model. We searched Medline (via Ovid), Web of Science, and the Cochrane Library, each from inception to January 2015. Known relevant articles were used to identify appropriate MeSH terms, which were combined with key words to maximize the sensitivity of the search. Combining the three databases produced 2,049 results, of which 1,162 duplicates and unrelated articles were excluded by initial screening. The remaining 887 abstracts were further screened, excluding those that were non-English, non-human, published prior to 1983, case reports or studies with uncertain methods, or focused on populations with HIV or xeroderma pigmentosum. The resulting 36 studies were then acquired and various data were extracted, including patient demographics (age, sex, and race), length of disease course, treatment strategy implemented, accuracy of clinical suspicion, accuracies of incisional and excisional biopsies, rates of positive and negative margins, success rates, time to resolution, recurrence rates, and time to recurrence[13–48]. For each variable used in the decision and sensitivity analyses, the number of contributing studies, the range of reported findings, the calculated weighted means used for the base case, and the ranges used can be found in Table 1. Ranges used in sensitivity analyses were extended beyond the most extreme values observed in the literature in order to ensure that potential threshold values were not overlooked.

Results

Model Probabilities

The mean accuracies of clinical and pathologic diagnosis were 0.84 and 0.98, respectively[13,15,16,27,38,40,45]. The risk of positive margins following excision was estimated at 0.42[13,15,27,34,45,48]. The mean rates of recurrence with positive and negative margin status were 0.52 and 0.11, respectively[13–16,26,34,36,44,45]. The rate of successful treatment with IFN-α2b was estimated to be 0.88 and subsequent risk of recurrence was 0.06[16–25,29–30,32–34,37,39,41–43,47]. Incisional biopsy accuracy rate was difficult to estimate as the literature contained a mixture of minimally invasive testing including true incisional biopsy, impression cytology, optical coherence tomography, and confocal microscopy.

Base Case Analysis

Based on expected value analysis of the decision tree, excision-directed IFN-α2b emerged as the optimal strategy with the lowest expected value of persisting or recurrent disease (EV 0.13). Other strategies, ordered from lowest to highest disease burden, were empiric IFN-α2b (EV 0.17), excision-only (EV 0.22), and incisional biopsy-directed IFN-α2b (EV 0.30).

Sensitivity Analyses

Sensitivity analyses identified three variables that would cause a shift in the decision when certain threshold values within their estimated range were applied. Empiric IFN-α2b would become the optimal strategy in the following situations: the probability of successful treatment with IFN-α2b increases from 0.88 to 0.94, the probability of recurrence for excised lesions with negative surgical margins increases from 0.11 to 0.20, or the accuracy excisional histopathologic diagnosis decreases from 0.98 to 0.92. When avoidance of a missed diagnosis was assigned as the primary endpoint, empiric treatment with topical IFN-α2b was superior to other strategies as all patients with suspected OSSN were treated.

Discussion

Currently, many options exist for the treatment of OSSN. Among the four strategies we explored, our analyses demonstrate that the optimal approach for minimizing the likelihood of disease persistence or recurrence is surgical excision followed by topical IFN-α2b for cases with positive surgical margins. Presumably, this combination of both surgical and chemotherapeutic strategies produces the lowest risk of recurrence because it combines the strengths of both arms; however, it also confers the risks and expenses associated with both modalities, which are factors not considered in this analysis. Similar conclusions regarding the benefits of topical IFN-α2b following surgical excision were found in a recent retrospective analysis of 389 OSSN patients[49]. The success rates of other modes of treatment were only slightly less effective in this model and remain reasonable alternatives given the individual needs and challenges of particular patients. A recent case control study of 98 OSSN patients treated with either surgery or topical IFN-α2b, which found no significant difference in recurrence rates[34]. With avoidance of a missed diagnosis as the primary endpoint, empiric treatment with IFN-α2b was naturally superior since it presumes disease in all patients with suspected OSSN. In this regard, it is important to reiterate that our model assumes that all patients entering the decision have OSSN. While our review of the literature estimates the accuracy of OSSN diagnosis on clinical grounds alone to be approximately 84%, the analysis does not take into account that some cases will be misdiagnosed as pterygia, pinguecula, papillomata, dyskeratoses, and nevi[11,13,14,21,28]. Surgical approaches have higher diagnostic power, but will produce some missed diagnoses due to false negative biopsies. Additionally, the decision to proceed with surgical excision depends on a preoperative clinical diagnosis and subsequently conveys all the risks associated with excision mentioned earlier. Patients treated empirically with IFN-α2b without biopsy will have a number of false positive empiric diagnoses, but without the same surgical risks.

Sensitivity analyses to detect variables exerting the most influence on our outcome identified that the optimal decision was sensitive to three variables: success rate of IFN-α2b therapy,

recurrence rates of excised tumors with negative surgical margins, and accuracy of excisional biopsy histopathology. While the accuracy of excisional biopsy histopathology, was well above 92% in all studies examined, the other variables show considerable variation among reports, some of which readily meet threshold values required for a change in the decision. The identification of key variables in the sensitivity analysis has important clinical implications. First, it points clinicians' attention to factors that may determine success or failure of different treatment strategies in their practices. Furthermore, the paucity of prospective randomized trials in the OSSN literature highlights the need for such trials and identifies these variables as important areas of investigation in such a study.

Our excision-only strategy is somewhat problematic due to challenges in the literature, as the management of cases with positive margins is uncertain in many reports. The majority of these reports are retrospective pathology reviews in which a correlation with the initial treatment and pathologic findings are correlated with recurrence. The details of the management of positive margins are not well described, and can involve an amalgam of simple excisional techniques, additional cryotherapy, and adjunct radiation or chemotherapeutic therapies; moreover, the efficacies of these interventions are highly variable and difficult to estimate. Whether clinicians just observed these patients hoping that marginal tumor had been cleared by cryotherapy or if additional surgery, cryotherapy, or topical therapy was performed is difficult to extract from most of these reports. The rate of recurrence after surgery with negative margins may also be driven by variation in clinical practice. Since topical IFN-α2b therapy requires months of outpatient administration of eye drops, patient variation in compliance with these medications over long periods of time plays a considerable role in selection of the optimal treatment strategy. Furthermore, many clinicians do not use IFN-α2b monotherapy for large thick tumors. Inclusion or exclusion of such patients in case series may also explain the variation in the success rates with interferon. Finally, reports varied widely in their treatment regimen, definitions of success and failure, and length of follow up.

Several limitations of our study should be noted. The heterogeneous nature of the reports from which the data was extracted creates challenges in making comparisons among different studies. Articles varied significantly in IFN-α2b dosing, duration of treatment, and length of follow up. In addition, we did not include other topical treatments such as mitomycin C (MMC) and 5-flurouricil (5-FU). We chose to focus on IFN-α2b for several reasons. First, IFN-α2b treatment has the least toxicity of these different modalities, and despite the lack of a randomized prospective trial, IFN-α2b has been the focus of the most reports in recent years. A recent survey of cornea specialists reported that 56% used IFN-α2b as first line therapy over MMC and 5FU[50]. Another survey of 81 ophthalmologists who treat OSSN showed that approximately five-times more likely to treat with IFN-α2b monotherapy over MMC or 5FU for localized disease[50]. Furthermore, while efficacy and treatment regimens of MMC and 5-FU differ from IFN-α2b, analogous variables would be expected to influence their efficacy in comparison to surgical approaches. Like IFN-α2b, there is also a similar need for prospective randomized data to provide reliable data regarding the comparative efficacy and side effects of these medications in the treatment of OSSN to better inform their use in relation to surgical management.

In summary, our study identified surgical excision followed by topical IFN-α2b for cases with positive surgical margins as the most effective strategy for minimizing persistence or recurrence of OSSN. We also identified efficacy of topical IFN-α2b, recurrence risk with negative surgical margins and IFN-α2b treatment, and accuracy of pathologic diagnosis as important drivers of clinical outcomes. Until additional data from a prospective trial is available, ophthalmologists hoping to improve the outcomes of OSSN patients should strive to find ways to optimize these variables within their practices.

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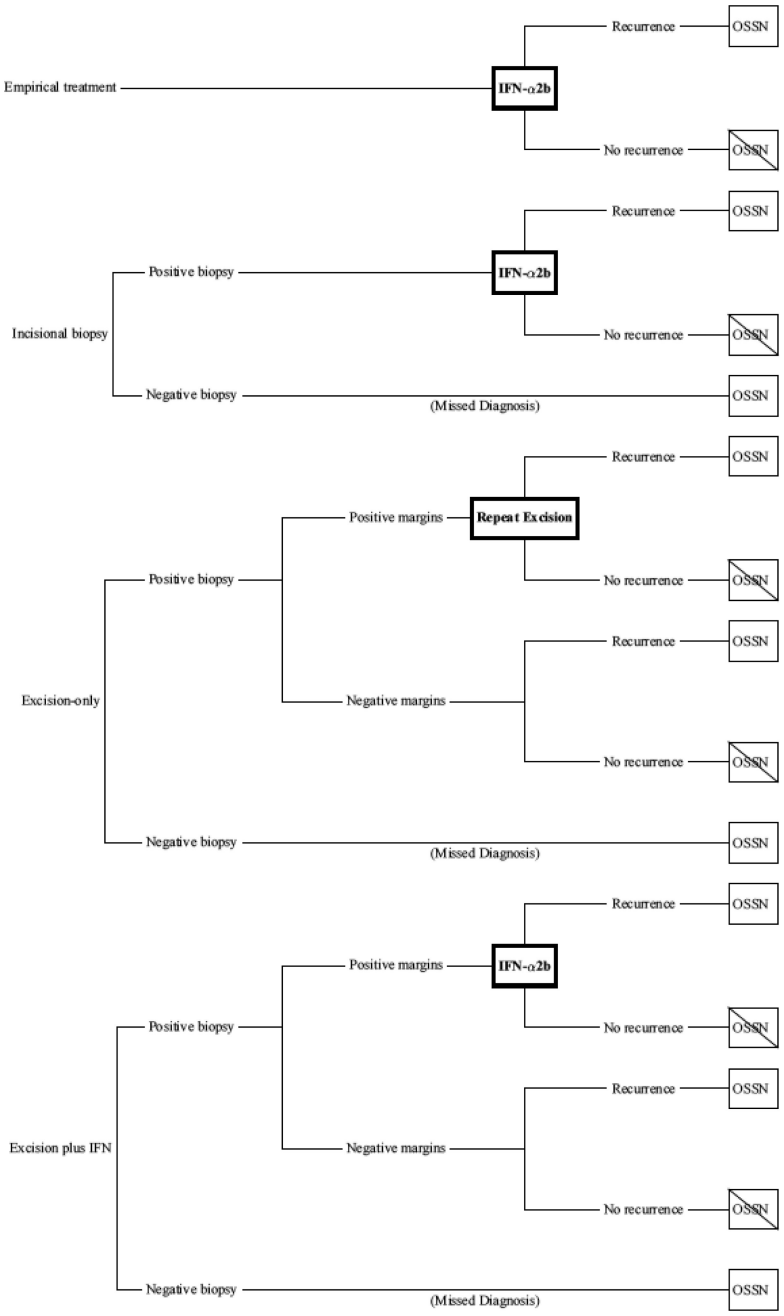

Figure 1.

Decision tree comparing ocular surface squamous neoplasia (OSSN) treatment models of surgery combined with topical interferon-α2b (IFN-α2b) for cases with positive surgical margins (excision-directed IFN-α2b), excision followed by re-excision for cases with positive surgical margins (excision-only), incisional biopsy with topical IFN-α2b for biopsy confirmed OSSN (incisional biopsy-directed IFN-α2b), and empiric topical IFN-α2b for all cases of suspected OSSN (empiric IFN-α2b). Outcomes for a single course of treatment were either successful resolution or unsuccessful treatment/recurrence.

Table 1

Summary of literature review, decision analysis, and sensitivity analyses.

Variable	Studies providing data	Total # of subjects range (mean)	Range of values from literature	Weighted mean used for base case	Range used in sensitivity analyses	Threshold Value (competing strategy)
Accuracy of clinical diagnosis[13,15,16,38,45]	5	26 – 145 (79.8)	0.73 – 1.00	0.84	0.5 – 1.0	none
Accuracy of excisional biopsy[13,27,40]	3	40 – 612 (257.33)	0.97 – 0.98	0.98	0.90 – 1.00	0.92 (Empiric IFN)
Probability of positive margins after simple excision[13,15,27,34,45,48]	6	10 – 478 (141)	0.18 – 0.47	0.42	0.00 – 1.00	none
Probability of recurrence with positive surgical margins[13,15,45]	4	26 – 120 (75)	0.00 – 0.67	0.52	0.00 – 1.00	none
Probability of recurrence with negative surgical margins[13,14,16,26,34,36,44,45]	7	10 – 120 (54.7)	0.00 – 0.33	0.11	0.00 – 0.50	0.20 (Empiric IFN)
Accuracy of incisional/in-clinic biopsy[15,18,19,29–31,35,40,46,47]	10	2 – 46 (15.7)	unclear	unclear	0.50 – 1.00	none
Probability of success for IFN treatment[16–25,28–30,32–34,37,39,41–43,47]	22	2 – 49 (10.05)	0.54 – 1.00	0.88	0.50 – 1.00	0.94 (Empiric IFN)
Probability of recurrence after IFN treatment[16–23,25,28–30,32–34,39,41–43,47]	20	2 – 49 (12)	0.00 – 0.29	0.06	0.00 – 0.50	none