Phase 2 Bioadjuvant Study of Interferon Alfa-2a, Isotretinoin, and Vitamin E in Locally Advanced Squamous Cell Carcinoma of the Head and Neck

Long-term Follow-up

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Objective: To evaluate the long-term effects of the combination of isotretinoin, interferon alfa-2a, and vitamin E in locally advanced squamous cell carcinoma of the head and neck.

Design: Phase 2 prospective study.

Setting: Tertiary care academic medical centers.

Patients: Forty-five patients entered this study. All patients had stage III or IV squamous cell carcinoma of the head and neck and had been treated with surgical resection, radiation, or both. All patients were then treated with bioadjuvant chemopreventive treatment for 12 months. We previously reported a 24-month median follow-up of this phase 2 trial of the combination of isotretinoin, interferon alfa-2a, and vitamin E as bioadjuvant therapy after definitive local therapy. In that study, all 45 patients completed treatment, but 1 patient was excluded from analysis of recurrence and development of second primary tumors.

Main Outcome Measure: Longer-term (49.4-month median) follow-up.

Results: Among the 45 patients treated under the protocol, only 7 patients (16%) had died. Nine (20%) of 45 patients experienced progressive disease. Only 1 second primary tumor (acute promyelocytic leukemia) occurred during follow-up, and no aerodigestive second primary tumors occurred among the 45 patients. The 5-year progression-free survival and overall survival percentages were 80% (95% confidence interval, 65.1%-89.1%) and 81.3% (95% confidence interval, 63.7%-90.9%), respectively. These results are significantly better than the historical 5-year overall survival for advanced squamous cell carcinoma of the head and neck (approximately 40%).

Conclusion: The bioadjuvant combination is highly effective in preventing recurrence and second primary tumors, and its role as standard therapy in advanced squamous cell carcinoma of the head and neck is being investigated in a randomized phase 3 study.


Quamous cell carcinoma of the head and neck (SCCHN) accounts for approximately 3% of all malignancies, with an estimated 40000 new cases and 11000 deaths annually in the United States. Despite advanced curative therapy for SCCHN, the outcome of such treatment is poor. Preventive strategies are clearly desirable.

Retinoids, including vitamin A and its synthetic derivatives, have been extensively studied during the past 2 decades. A landmark trial by Hong et al showed that a high dose of isotretinoin was active against oral leukoplakia, although the toxicity was significant. In a subsequent study reported on by Lippman et al, patients with oral leukoplakia were initially treated with isotretinoin at a high dose and randomized to a lower dose of isotretinoin or beta carotene, and the patients treated with the lower dose of isotretinoin had a better response than those treated with beta carotene. Chiesa et al studied the synthetic retinoid fenretinide in patients with oral leukoplakia treated surgically.

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cantly fewer second primary tumors (SPTs). In short-term follow-up, the rate of SPTs was significantly lower in the treated group; however, in long-term follow-up, the SPT rates became much less significant, compared with the initial report. In a similar study conducted by Bolla et al, there was no difference in SPT rates for local or distant recurrence. Khuri et al recently reported data from an intergroup, placebo-controlled, double-blind study evaluating the efficacy of low-dose isotretinoin (30 mg/d) in prevention of SPTs in patients with stage I or II SCCHN. Since 1991, 1190 patients were randomized to receive 30 mg of isotretinoin daily or placebo for 3 years. There were no differences in SPT rates between the 2 groups, and a transient protective effect of isotretinoin on recurrence was lost after cessation of treatment. Therefore, single-agent retinoid therapy does not appear to have any impact on the prevention of SPTs or recurrence in SCCHN.

METHODS

We previously reported on a phase 2 study demonstrating activity and tolerability of the combination of isotretinoin, interferon alfa-2a, and vitamin E as bioadjuvant therapy after definitive local therapy. In the original report, a total of 45 patients with locally advanced (stages III and IV) SCCHN were treated for 12 months with isotretinoin, 50 mg/m² orally daily; interferon alfa-2a, 3 × 10⁶ IU/m² in subcutaneous injections 3 times per week; and vitamin E, 1200 IU orally daily, with dose modifications (Table 1). Toxic effects were manageable, the most frequent being fatigue, influenza-like symptoms, mild to moderate hematologic side effects, and mucocutaneous toxic effects, as well as hypertriglyceridemia. There was only 1 case of a grade 4 toxic effect (infection) (see detailed information in Shin et al). Overall, 84% (38/45) of enrolled patients completed the full 12-month course of treatment.

Length of survival was assessable for all patients. One patient was excluded from analyses of recurrence and SPT development because the patient already had recurrent disease at the time of study entry. At a median of 24 months of follow-up, 4 (9%) of 44 patients had regional recurrences and 2 patients (5%) had local plus distant recurrences. No SPT of the aerodigestive tract was observed in a 24-month follow-up, but 1 case of acute promyelocytic leukemia occurred. The overall 1- and 2-year survival percentages were 93% and 91%, respectively, while the 1-year and 2-year disease-free survival percentages were 91% and 84%, respectively.

RESULTS

The Kaplan-Meier plot of the survival curve for the time to progression is depicted in Figure 1. At a median follow-up of 49.4 months, only 9 (20%) of 44 patients experienced progressive disease, 3 since the last report (Table 2). Two patients had local recurrences, and 1 had local and distant relapse. The progression-free survival percentages at 1 year, 3 years, and 5 years were 88.9% (95% CI, 75.3%-95.2%), 82.2% (95% CI, 67.6%-90.7%), and 80% (95% CI, 65.1%-89.1%), respectively. The current Kaplan-Meier survival curve is shown in Figure 2. Seven (15.6%) of the 45 patients died. The median follow-up among the 38 surviving patients was 49.4 months. The median overall survival had not yet been reached. The overall survival percentages at 1 year, 3 years, and 5 years were 97.8% (95% CI, 85.3%-99.7%), 88.9% (95% CI, 75.3%-95.2%), and 81.3% (95% CI, 63.7%-90.9%), respectively.

Only 1 SPT, a case of acute promyelocytic leukemia, was observed in the whole cohort, including observation from the longer follow-up. No SPT of the aerodigestive tract was observed. No other SPT was seen since the last follow-up.

COMMENT

Results of this extended follow-up for the bioadjuvant therapy in locally advanced SCCHN are highly encouraging. If these results are confirmed in phase 3 randomized trials, this therapy could benefit a large number of patients, since approximately two thirds of patients with SCCHN have developed locally advanced disease at diagnosis. Furthermore, most patients in advanced stages have a poor prognosis, with historical long-term survival around 30%. The 5-year survival percentage in our patient cohort was far superior, at more than 80%. Also, there were no further recurrences after 2 years of follow-up, while historically no plateau in recurrence rates has been evident until at least 4 or 5 years of follow-up. However, the current results should be interpreted cautiously, since the patients who entered this phase 2 study were a relatively select group (ie, relatively young; me-

Table 1. Dosage Modification of Bioadjuvant Therapy

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosage Level</th>
<th>0*</th>
<th>-1</th>
<th>-2</th>
<th>-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isotretinoin, oral, mg/m² per day</td>
<td>50</td>
<td>40</td>
<td>30</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Interferon alfa-2a, subcutaneous, mU/m² 3 times weekly</td>
<td>3.0</td>
<td>2.0</td>
<td>1.5</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Vitamin E, oral, IU/d</td>
<td>1200</td>
<td>1200</td>
<td>1200</td>
<td>1200</td>
<td></td>
</tr>
</tbody>
</table>

*Starting dose.
We demonstrated that bioadjuvant therapy (isotretinoin, interferon alfa-2a, and vitamin E) might offer a long-term effect in regard to prevention of recurrence, which is quite exciting, especially considering that there is no established role for adjuvant chemotherapy in high-risk SCCHN.

A second important finding in this study was the low incidence of SPTs. One large series reported the incidence of SPTs at 3 years, 5 years, and 8 years as 10%, 15%, and 23%, respectively. Other authors have reported the rate of SPT risk to range from 3% to 7% per year. In our cohort of stage III and IV SCCHN, there were no cases of SPT of the aerodigestive tract, despite the high-risk nature of our population of patients. There was only 1 case of acute promyelocytic leukemia, which is not known to be related to SCCHN.

We demonstrated that bioadjuvant therapy (isotretinoin, interferon alfa-2a, and vitamin E) might have a significant role in preventing SPTs and in decreasing the risk of recurrence in advanced SCCHN. The outcome with this combination might represent an advance in comparison with single-agent retinoids. Synthetic and natural retinoids are able to reverse established leukoplakia, with responses as high as 100%. High-dose, single-agent isotretinoin significantly reduces the risk of SPTs compared with placebo in SCCHN. However, no effect on the risk of local or distant recurrences of initial cancer was observed with this regimen. Most recently, 2 randomized placebo-controlled clinical trials were reported in the literature evaluating the role of low-dose single-agent isotretinoin in the prevention of SPTs in patients with stage I or II SCCHN. Neither of these studies showed a decrease in the incidence of SPT in patients treated with low-dose isotretinoin.

The improvement in the outcome observed in our study might be explained by the synergy among interferon alfa-2a, retinoids, and vitamin E. The combination of retinoids and interferon is known to enhance radiation-induced cytotoxicity, synergistically inhibit cell growth, and promote neovascularization in SCCHN. Vitamin E was later added to our regimen because it decreases isotretinoin toxicity and also may have chemopreventive activity. The improved efficacy observed with combination bioadjuvant therapy compared with single-agent retinoids or retinoids plus interferon was mechanistically demonstrated in preclinical models. In our recent study, the 3-drug combination (isotretinoin, interferon alfa-2a, and vitamin E) was more effective in growth inhibition of SCCHN cells than the single agents alone or 2-drug combinations (ie, interferon alfa-2a plus isotretinoin). This is due to increased S-phase arrest, decreased number of cells at G2/M phase, increased apoptosis, and up-regulation of p53 and Fas/CD95 death receptor in combined treated cells vs single-agent or 2-drug combinations.

In fact, the in vitro synergy was confirmed in a trial using this combination in advanced premalignant lesions (ie, moderate to severe dysplasia). In a phase 2 clinical trial the advanced premalignant lesions (eg, moderate to severe dysplasia) of the head and neck, the combination of isotretinoin, interferon alfa-2a, and vitamin E was used. There were major pathologic responses in as many as 50% of cases with advanced premalignant lesions, which is observed with the use of single-agent retinoids only when they are used in early premalignant lesions (ie, hyperplasia or mild dysplasia).

These encouraging data support the investigational use of combination bioadjuvant therapy in high-risk, locally advanced head and neck cancers. This combination regimen is being tested in a randomized fashion in a currently ongoing phase 3 study of bioadjuvant therapy vs observation through the Eastern Cooperative Oncology Group in patients with locally advanced SCCHN. The starting dose of the treated group was reduced to –1 dose level (80% of the phase 2 dose) of the phase 2 study since the reduced dose is expected to be better tolerated. This study is hoped to establish a role for bioadjuvant therapy in this devastating disease.

Table 2. Patterns of Failure in Original Report and Current Report*

<table>
<thead>
<tr>
<th>Patterns of Failure</th>
<th>Original Report</th>
<th>Current Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Locoregional only</td>
<td>4 (9)</td>
<td>6 (14)</td>
</tr>
<tr>
<td>Locoregional plus distant metastasis</td>
<td>2 (5)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>6 (14)</td>
<td>9 (20)</td>
</tr>
<tr>
<td>Second primary tumor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aerodigestive tract</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nonaerodigestive</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

* N = 44. Median follow-up was 24 months in the original report and 49.4 months in the current report.
REFERENCES