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Treatment of unresectable recurrent head and neck carcinoma with 13-cis-retinoic acid and interferon-α. A phase II study

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Abstract

Sixteen patients with unresectable recurrent head and neck carcinomas were treated with 13-cis-retinoic acid and interferon-α. All patients had presented with recurrences after having been treated primarily with surgery and radiotherapy, while two of them had also received induction chemotherapy. The site of relapse was strictly locoregional in all cases (only at the primary site in three cases, at the cervical lymph nodes only in four cases and both at the primary site and the neck in the remaining nine cases. Two patients were female, and 14 male, with an age range of 47–72 years (median 61 years). Interferon-α was administered subcutaneously at a dose of 3×10^6 IU every second day. The dose of retinoids was 40 mg per os every day. The duration of treatment was two to 14 months (median seven months). There were two cases of partial response (tumour regression >50 per cent), eight cases of stable disease lasting for three to seven months (median four months) and six cases presented with progressive disease. All patients died after a survival of three to 17 months (median 9.5 months). Toxicity was generally minimal. We believe that the results are not encouraging, but also not disappointing. The fact that toxicity was indeed mild, with not a single case of life-threatening sequellae even after prolonged administration of the two agents, allows us to conclude that an increase of the dose of IFN-α might be more beneficial. Selection of patients with more 'favourable' recurrences will give a better chance to the treatment combination to prove its real efficacy. Larger numbers of patients have to be treated and evaluated before definite conclusions can be reached.

Key words: Head and neck neoplasms; Carcinoma; Interferon-alpha; Retinoids

Introduction

Patients with squamous cell carcinoma of the head and neck (SCCHN) that have been treated with surgery and radiotherapy and sometimes with chemotherapy as well, are totally hopeless when they present with unresectable local recurrences. The skin of the neck is often infiltrated by the tumour and most patients eventually die from local tumour extension, without developing distant metastases. The median survival of these patients is approximately five months (Clark and Frei, 1989). During this period they live an uncomfortable life, having unimpaired consciousness, pain, discomfort, difficulties in swallowing and very often odour due to ulceration, necrosis and infection of the infiltrated tissues.

Standard chemotherapy regimens used over the last decades for palliation have proved to be totally unsuccessful, failing to prolong survival or even to reduce the severity of the symptoms (Tannock and Browman, 1986; Taylor, 1987).

Since SCCHN has been associated with an impairment of the immune system responses, therapy with an immunomodulator such as interferon-α (IFN-α) seems to offer a reasonable alternative therapeutic approach. During the last five years interferons α, β, and δ have been administered both in vitro and in vivo in SCC and other tumours as well, in order to estimate the antitumour activity of these agents. Some investigators have also used additionally interleukin-2 (IL-2), tumour necrosis factor (TNF) or vitamin A (Richtsmeier *et al.*, 1990, Schantz *et al.*, 1990; Clayman *et al.*, 1992a; Clayman *et al.*, 1992b).

Retinoids have recently established their role as chemoprevention agents in the development of true carcinoma from premalignant lesions. The significant reduction of incidence of second primaries in patients treated successfully for primary SCCHN who received retinoids post-therapeutically, also enhanced their role in the management of SCC (Fountzilas, 1994).

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TABLE I
CLINICAL DETAILS OF PATIENTS

Patient	Age	PS	Primary site	Site of recurrence	Previous treatments	Survival (months)	Response
1	52	50	larynx	neck	TL, RND, Ro	5	PD
2	58	40	larynx	stoma	TL, Ro	3	PD
3	59	60	larynx	neck	TL, RND, Ro	10	SD
4	63	80	larynx	stoma	TL, Ro	17	PR
5	72	40	larynx	larynx-neck	Vertical laryng., Ro	5	PD
6	54	40	larynx	neck	ICH, Ro, TL	16	SD
7	71	50	hypopharynx	hypopharynx-neck	ICH, Ro	10	SD
8	65	60	hypopharynx	hypopharynx-neck	Ro	11	SD
9	62	70	larynx-nasopharynx	trachea-neck	Horizontal laryng., RND, Ro	9	PR
10	47	60	larynx	stoma	TL, RND, Ro	5	PD
11	51	70	larynx	stoma-neck	Vertical laryng., Ro	3	PD
12	57	50	larynx	stoma-neck	TL	6	PD
13	62	40	larynx	stoma-neck	TL, Ro	8	SD
14	59	60	larynx	stoma-neck	TL, Ro	8	SD
15	57	60	larynx	stoma-neck	TL, Ro, RND	7	SD
16	63	70	larynx	neck	TL, Ro	9	SD

TL = Total laryngectomy; RND = Radical neck dissection; Ro = Radiotherapy; ICH = Induction chemotherapy; PD = Progressive disease; SD = Stable disease; PR = Partial response; PS = Performance status (Karnofsky scale).

Both interferon-α and retinoids have been used as single-agent therapy in the treatment of several advanced solid tumours, including SCCHN but they proved to be of limited activity (Fierro *et al.*, 1988; Smith *et al.*, 1992).

The encouraging results published recently, after the use of IFN-α plus retinoids in advanced cases of cervical carcinoma and cancer of the skin in the USA (Lippman *et al.*, 1992a), led us to the thought that this regimen might be of some benefit in hopeless cases of recurrent SCCHN.

Materials and methods

Between April, 1992 and November, 1993, 16 patients with unresectable recurrent head and neck carcinomas entered the study. Fourteen patients were treated for laryngeal, and two for hypopharyngeal carcinomas, primarily with surgery and radiotherapy (Table I). Two of them had also received platinum-based induction chemotherapy. All presented locoregional recurrences after a period ranging from six to 52 months (median 14 months). The site of recurrence was at the primary site only in three cases, at the cervical lymph nodes only in four cases, and at both the primary site and the neck in the remaining nine cases. Two patients were female and 14 male with an age range of 47–72 years (median 61 years).

All the lesions were far advanced with skin infiltration in most cases and/or fixation of the tumour to the deep structures of the neck (Figures 1–3). There was histological confirmation of recurrent SCCHN in all cases. Laboratory examinations included complete blood counts and extended serum chemistries, which were repeated at monthly intervals for the first three months and every two months thereafter. Before the initiation of treatment all patients also underwent physical examination, chest X-ray, endoscopy with a flexible endoscope and computer tomography.

Patients received 13 cis-retinoic acid orally at a dose of 40–60 mg per day and interferon-α subcutaneously at a dose of 3×10^6 units three times a week.

Evaluation of response and toxicity was recorded every month. Complete response was defined as the disappearance of all evidence of tumour. Partial response as a decrease of 50 per cent or more in tumour size, stable disease as a decrease of less than 50 per cent, progressive disease as an increase of 25 per cent or more in tumour size, or the appearance of new lesions.

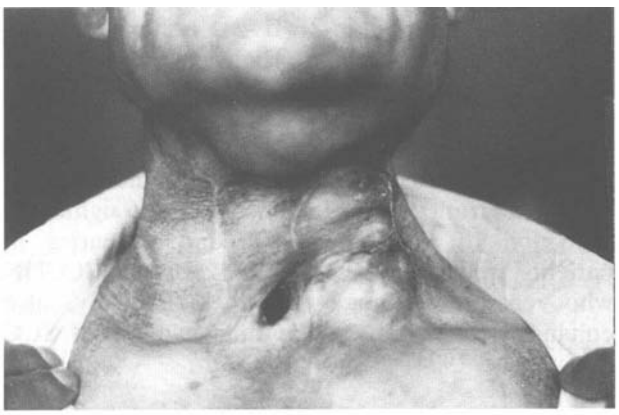

FIG. 1
Patient No. 1 (see Table).

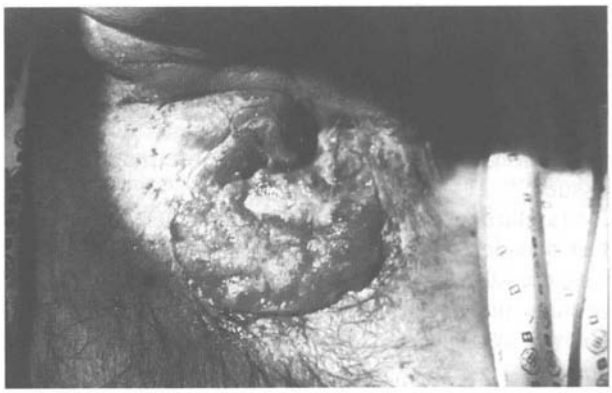

FIG. 2
Patient No. 2 (see Table).

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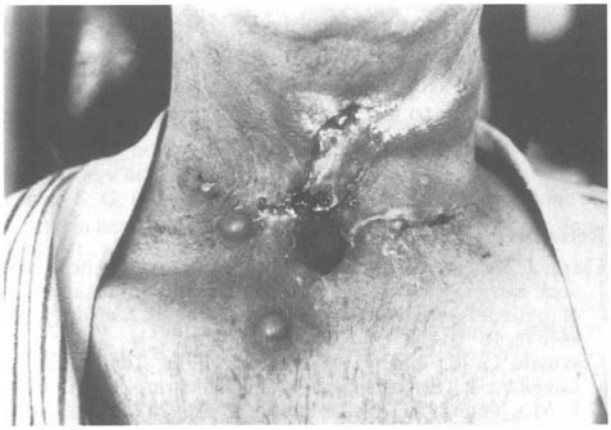

FIG. 3
Patient No. 13 (see Table).

Results

All patients received the treatment for at least two months. The duration of treatment was between two to 14 months (median seven months). There were two cases of partial response (tumour regression >50 per cent), eight cases of stable disease lasting for three to seven months (median four months) and six cases presented progressive disease.

The first patient who presented a partial response was a female patient who underwent total laryngectomy in May 1991 and post-operative radiotherapy in July 1991 for a T4N0M0 laryngeal G3 carcinoma. In April 1992 she presented an ulcerated recurrence at the stoma and the treatment with roaccutan-interferon started (Figure 4). Two months later the size of the tumour was less than half its original size and it remained stable until April 1993 (Figure 5). Thereafter, in spite of the continuation of treatment for two more months, rapid progression of the tumour was noticed and the patient died in September of the same year.

The second patient who presented a partial response was male and had a very interesting course

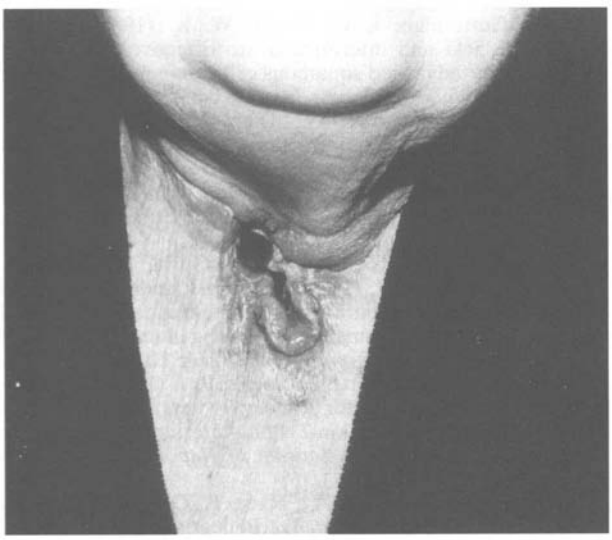

FIG. 4
Patient No. 4 (see Table) before treatment with interferon-retinoids.

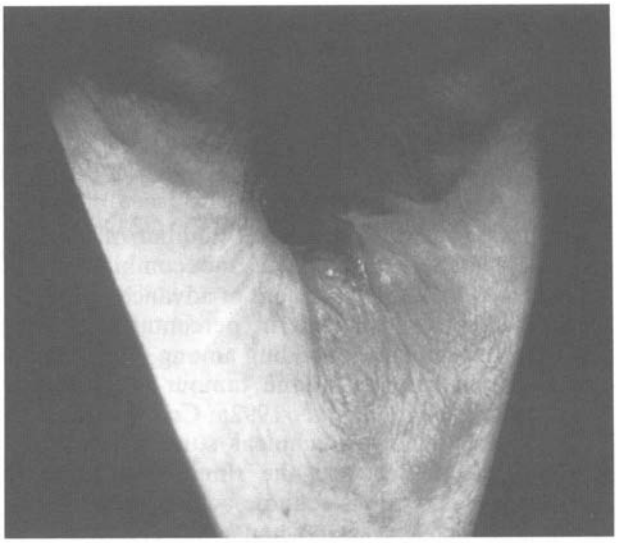

FIG. 5
The same patient after treatment.

of the disease. In January 1991 he presented a T2N0M0 supraglottic G2 carcinoma and was treated primarily with a full course of radiotherapy. Due to remaining tumour in May of the same year he underwent a horizontal laryngectomy. In April 1992, he developed a metastatic lymph node and was treated surgically with a radical neck dissection on the left side. In December 1993, he presented a second primary tumour at the posterior part of the nasal cavity. It was a T2N0M0 G1 carcinoma which was treated successfully with radiotherapy. In September 1994, he was admitted to our department with dyspnoea due to a G3 carcinoma occupying the trachea and the supraclavicular lymph nodes of the neck with skin infiltration. A tracheostomy was performed and he started the 13-cis-retinoic acid plus interferon-α treatment. Within two months the tumour showed significant reduction in size (>50 per cent) which lasted for four months but then the tumour progressed. Death occurred three months later.

Toxicity was generally minimal. Mild fever (Grade 1) was observed at the beginning of the treatment in six patients and was easily controlled with paracetamol. Skin dryness Grades 1 and 2 was noted in eight patients and Grade 3 in two, some of whom developed red skin patches and that is the reason why in almost half of the patients the initial dose of retinoids was reduced from 60 mg to 40 mg daily. There were two cases of mild hypertriglyceridaemia (Grade 1). Mild to moderate fatigue (Grade 1–2) was noted in five patients.

All patients died after a survival time of three to 17 months (median 9.5 months).

Discussion

The clinical application of recombinant cytokines in cancer treatment has achieved some success and several trials employing various cytokines are currently under trial. Initial studies on the efficacy

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of IFN-α plus IL-2, IFN-γ and IFN-α plus TNG-α in the treatment of SCCHN have indicated that this form of immunotherapy may result in tumour regression in some patients with advanced malignancies (Rosenberg *et al.,* 1988; Richtsmeier *et al.,* 1990; Schantz *et al.,* 1990; Clayman *et al.,* 1992a, Clayman *et al.,* 1992b).

Preliminary results in a small number of patients published recently show that the combination of cytokines used in the treatment of advanced SCCHN leads to clinical responses in percentages ranging from 10–50 per cent depending among other factors upon the resectability of the tumour (Richtsmeier *et al.,* 1990; Clayman *et al.,* 1992a; Crispino, 1993).

There are a few preclinical studies published, supporting the idea that the simultaneous use of interferon-α and 13-cis-retinoic acid accelerates the antitumour activity seen when each agent is used alone (Knobler *et al.,* 1991; Dmitrovsky and Bosl, 1992). Based on these findings, two phase II trials of this combination of drugs were undertaken aiming to cure SCC of different origins. The first trial achieved a striking overall response rate of 68 per cent in 28 patients with advanced SCC of the skin (Lippman *et al.,* 1992a). The second study was addressed to a population of young women suffering from locally advanced cervical cancer and achieved a 50 per cent overall response (Lippman *et al.,* 1992b).

There have been only two phase II trials until now using this regimen in recurrent head and neck cancer. One is from the University of Texas (Voravud *et al.,* 1993) and the other is ours (Nikolaou *et al.,* 1993). The authors of the first study have treated 21 patients, 10 of whom had distant metastases and nine were treated with platinum-based chemotherapy for recurrent disease before entering the study. The results were disappointing as only one patient presented a partial response and the overall survival four to 95 weeks only (median 25.5 weeks). The median number of cycles that these patients received was only two and it is not clear what the exact extent of each cycle was.

The population of our patients included only far advanced unresectable recurrences and the treatment resulted in two major responses and eight cases of stabilisation of the disease for a short period. We believe that the slightly better results seen in our patients are due to the fact that in our study there was not a single case presenting distant metastases and also the longer duration of therapy. We observed that in most cases the first signs of benefit were noted after at least two months of continuous therapy.

We believe that the results are not encouraging, but also not disappointing. The fact that toxicity was indeed mild, with not a single case of life-threatening sequellae even after prolonged administration of the two agents, allow us to conclude that an increase of the dose of IFN-α might be more beneficial. Selection of patients with more 'favourable' recurrences will give a better chance for the treatment combination to prove its real efficacy. This hypothesis is supported by the fact that both partial responders had considerably less tumour bulk than the other patients and their performance status was >70 on the Karnofsky scale. Larger numbers of patients have to be treated and evaluated before definite conclusions can be reached.

References

Clark, J. R., Frei, E. III. (1989) Chemotherapy for head and neck cancer: Progress and controversy in the management of patients with Mo disease. *Seminars of Oncology* **16:** 44–57.

Clayman, G. L., Liu, F. J., Savage, H. E., Taylor, D. L., Lavedan, P., Buchsbaum, R. M., Pellegrino, C., Trujillo, J. M., Young, G., Schantz, S. P. (1992a) Acute-phase proteins in patients with head and neck cancer treated with interleukin 2/interferon alfa. *Archives of Otolaryngology, Head and Neck Surgery* **118:** 41–47.

Clayman, G. L., Young, G., Taylor, D. L., Savage, H. E., Lavedan, P., Schantz, S. P. (1992b) Detection of regulatory factors of lymphokine-activated killer cell activity in head and neck cancer patients treated with interleukin-2 and interferon-α. *Annals of Otology, Rhinology and Laryngology* **101:** 909–915.

Crispino, S. (1993) The use of interferon in head and neck cancer: A clinical review. *Forum* **34:** 384–392.

Dmitrovsky, E., Bosl, G. J. (1992) Active cancer therapy combining 13-cis-retinoic acid with interferon-α. *Journal of National Cancer Institute* **84:** 218–219.

Fierro, R., Johnson, J., Myers, E., Colao, D., Pelch, K., Rust, D., Wagner, R., Whiteside, T., Vlock, D. (1988) Phase-II trial of non-recombinant interferon-α (IFN) in recurrent squamous cell carcinoma of the head and neck (Abstract). *Proceedings of the American Society of Clinical Oncology* **7:** 156.

Fountzilas, G. (1994) Retinoids in the management of head and neck cancer. An update. *Journal of Chemotherapy* **6(2):** 127–138.

Knobler, R. M., Trautinger, F., Radaszkiewicz, T. (1991). Treatment of cutaneous T cell lymphoma with a combination of low-dose interferon alfa-2b and retinoids. *Journal of the American Academy of Dermatology* **24:** 247–252.

Lippman, S. M., Kavanagh, J. J., Paredes-Espinoza, M., Delgadillo-Madrueno, F., Paredes-Casillas, P., Hong, W. K., Holdener, E., Krakoff, I. H., (1992a) 13-cis-Retinoic acid and interferon-alfa 2a: High activity systemic therapy for squamous cell carcinoma of the cervix. *Journal of National Cancer Institute* **84:** 241–245.

Lippman, S. M., Parkinson, D. R., Itri, L. M., Weber, R. S., Schantz, S. P., Ota, D. M., Schusterman, M. A., Krakoff, I. H., Gutterman, J. U., Hong, W. K. (1992b). 13-cis-Retinoic acid and interferon-α 2a: Effective combination therapy for advanced squamous cell carcinoma of the skin. *Journal of National Cancer Institute* **84:** 235–241.

Nikolaou, A., Fountzilas, G., Themelis, C., Daniilidis, J. (1993). Treatment of unresectable recurrences of the head and neck carcinomas with interferon-α and retinoids (Abstract). Proceedings of the 15th World Congress of Otorhinolaryngology – Head and Neck Surgery, Istanbul, pp. 360.

Richtsmeier, W. J., Koch, W. M., McGuire, W. P., Poole, M. E., Chang, E. H. (1990) Phase I-II study of advanced head and neck squamous cell carcinoma patients treated with recombinant human interferon gamma. *Archives of Otolaryngology, Head and Neck Surgery* **116:** 1271–1277.

Rosenberg, S. A., Schwartz, S., Speiss, P. J. (1988) Combination immunotherapy for cancer: synergistic antitumour interactions of interleukin-2 alpha-interferon, and tumour infiltrating lymphocytes. *Journal of National Cancer Institute* **80:** 1393–1397.

Schantz, S. P., Clayman, G. L., Racz, T., Grimm, E. A., Liu, F. J., Lavedan, P., Taylor, D., Pellegrino, C., Savage, H. (1990) The in vivo biologic effect on interleukin 2 and interferon alfa on natural immunity in patients with head and neck cancer. *Archives of Otolaryngology, Head and Neck Surgery* **116:** 1302–1308.

Smith, M. A., Parkinson, D. R., Cheson, B. D., Friedman, M. A. (1992) Retinoids in cancer therapy. *Journal of Clinical Oncology* **10:** 839–864.

Tannock, I. F., Browman, G. (1986) Lack of evidence for a role of chemotherapy in the routine management of locally advanced head and neck cancer? *Journal of Clinical Oncology* **4(7):** 1121–1126.

Taylor, S. G. (1987) Why has so much chemotherapy done so little in head and neck cancer? *Journal of Clinical Oncology* **5(1):** 1–3.

Voravud, N., Lippman, S. M., Weber, R. S., Rodriquez, G. I., Yee, D., Dimery, I. W., Earley, C. L., Von Hoff, D. D., Ki Hong, W. (1993) Phase II trial of 13-cis-retinoic acid plus interferon-α in recurrent head and neck cancer. *Investigational New Drugs* **11:** 57–60.

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