

SHORT COMMUNICATIONS AND CASE REPORTS

Rapid improvement of extensive non-melanoma skin cancers with combination of 13-cis-retinoic acid and radiotherapy: report of three cases

I. Danopoulou¹, C. Korfitis¹, N. Koliarakis², D.T. Trafalis³

¹Department of Dermatology, and ²Department of Radiotherapy, "A. Sygros" Hospital, University of Athens; ³Department of Medical Oncology-A, "Metaxa" Cancer Hospital, Piraeus, Greece

Summary

Extensive non-melanoma skin cancer (NMSC) constitutes a therapeutic challenge especially in old and debilitated patients. Applied treatments include surgical excision, MOHS micrographic surgery, cryosurgery, electrodesiccation, and radiotherapy. We present 3 elderly patients with extensive basal or squamous cell carcinomas and poor general condi-

tion who were treated with a combination of 13-cis-retinoic acid 1 mg/kg daily and radiotherapy 2.5 Gy daily. The treatment resulted in rapid improvement of the tumors with significant reduction of their size.

Key words: basal cell carcinoma, 13-cis-retinoic acid, isotretinoin, non-melanoma skin cancer, radiotherapy, squamous cell carcinoma

Introduction

Despite the very good results of conventional methods in the treatment of skin carcinomas, some cases, and especially extensive and/ or recurrent lesions in very old patients with poor general condition, constitute a therapeutic problem. On the other hand, the constantly growing incidence of NMSC worldwide makes it more than ever necessary to apply new therapeutic modalities with less toxicity and easier to apply. Retinoids have been reported to exhibit beneficial results concerning the prevention of NMSCs, especially in immunocompromised patients [1].

We report herein on 3 elderly and debilitated NM-SCs patients with very large tumors, treated with isotretinoin in combination with radiotherapy because any extensive surgical procedure was impossible and also because with radiotherapy alone it seemed highly improbable to bring these huge lesions in complete remission. All 3 patients responded well and the tumors diminished in size rapidly.

Case presentations

Case 1

An 89-year-old woman was admitted to our clinic because of a very large tumor with a diameter of 12.5 cm, involving completely her lower eyelid and canthal area, extending to the nose, temporal area and the right cheek (Figure 1a). The patient's eyesight was obstructed and the surface of the tumor was purulent. Biopsy showed basal cell carcinoma. The patient's general condition was poor and she was bed-ridden for the last 6 years because of a stroke. Any aggressive treatment in this patient, such as surgical excision, was out of question. It was therefore decided to treat her with a combination of radiotherapy and isotretinoin.

The patient started radiotherapy and 13-cis-retinoic acid (1 mg/kg/24 h) on the same day and her tumor started regressing within the first week. Twenty-five days from the onset of treatment the tumor had regressed completely, leaving behind only some small lesions

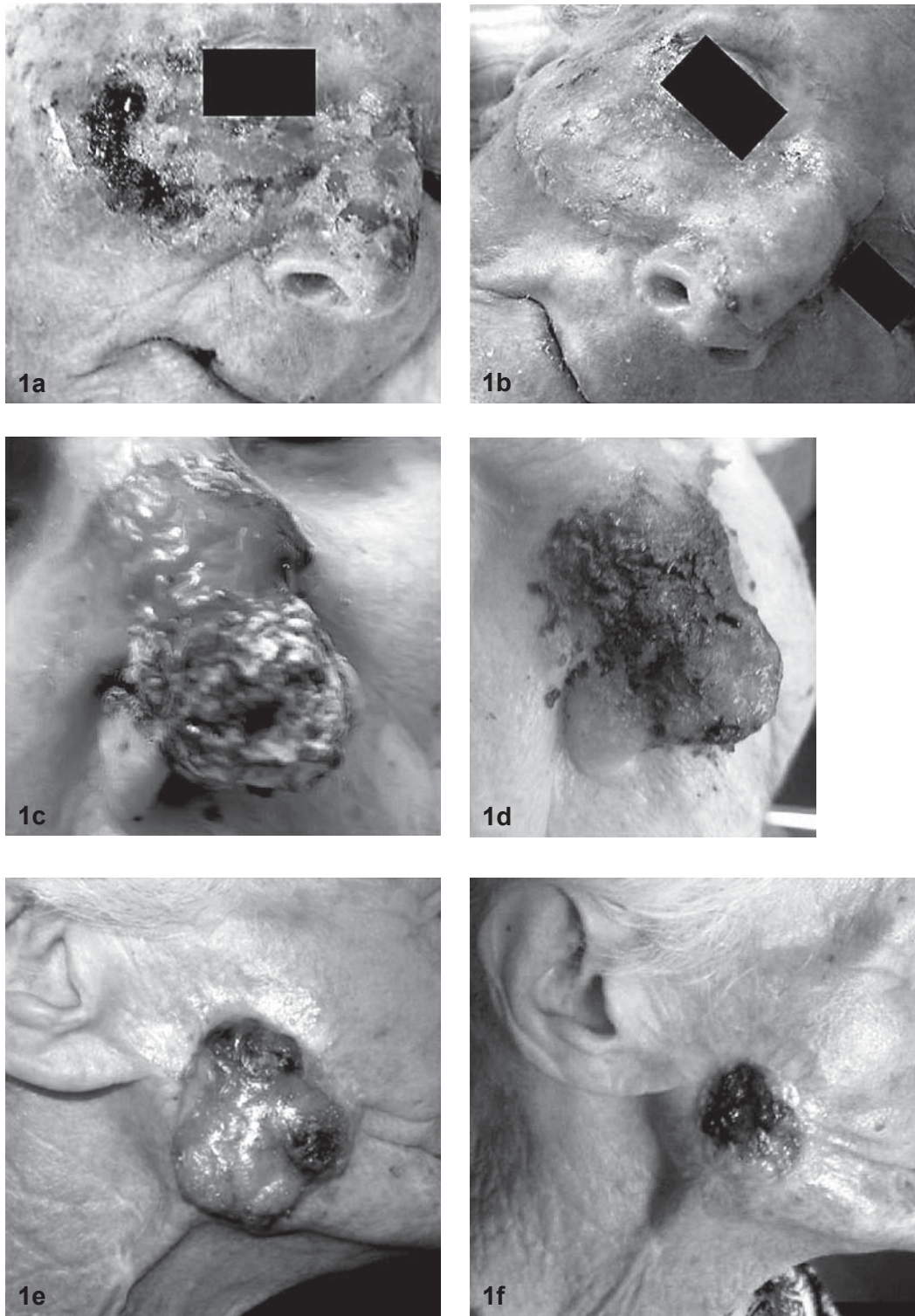


Figure 1. Patients 1, 2 and 3 before (1a, 1c, 1e) and after treatment (1b, 1d, 1f) showing improvement of their tumors.

with erosions without evidence of malignancy (Figure 1b). All the area of the preexisting tumor had completely reepithelized. The daily dose of radiotherapy was 2.5 Gy, administered in 22 sessions. A follow up visit 3 months later did not reveal any sign of recurrence.

Case 2

An 85-year-old female presented with a very extensive ulcerative and hemorrhagic tumor, involving the whole surface of the nose (Figure 1c). Laboratory

work-up including complete blood cell count and serum biochemistry were within normal range. Chest radiography as well as computerized tomography did not reveal any systemic involvement. Biopsy showed squamous cell carcinoma. Radiotherapy was commenced with daily dose of 2.5 Gy on the same day with isotretinoin 1 mg/kg/24 h. After almost 2 weeks of treatment there was a noticeable improvement and after a month the tumor had dramatically diminished in size, leaving behind erosions and hemorrhagic crusts (Figure 1d). However, at that time the patient preferred to discontinue treatment, partly because of the discomfort caused by the frequent bleeding of the lesion. The patient did not return for follow up.

Case 3

A 92-year-old debilitated female patient presented with multiple squamous and basal cell carcinomas as well as actinic keratoses on her face. Some of the lesions had been previously excised. However, a large, histologically confirmed ulcerative squamous cell carcinoma was still located on her right cheek (Figure 1e). Unfortunately the tumor was too large to be excised, considering also the patient's poor general condition. Therefore we decided to administer 13-cis-retinoic acid at a daily dose of 1 mg/kg in combination with radiotherapy. The latter was introduced 3 days later and consisted of 2.5 Gy/day (total dose 60 Gy) for 24 sessions. Rapid improvement was noted starting from the first 3 days of the combined treatment. By the time treatment was completed the size of the tumor had significantly decreased (Figure 1f). Both radiotherapy and isotretinoin were well-tolerated. Three months later a small-sized tumor still remained on her right cheek, however the patient refused further treatment.

Discussion

Retinoids affect cell differentiation and the growth of malignant tumors in several ways. Their interference with genes, and especially proto-oncogenes, growth factors and cell adhesion are some of the mechanisms by which these substances exhibit this activity [2]. Despite their side effects, retinoids are by far less toxic than cytotoxic drugs but also less effective when applied as a single treatment [3]. They have been reported to be more effective in the prevention of skin carcinomas rather than in their remission. Partial remissions have been mentioned but complete remissions are rare [4]. Therefore, 13-cis-retinoic acid has been tried in combi-

nation with interferons in order to intensify its anticancer activity. The combination has been reported to have a synergistic effect and has been applied in cell lines of squamous cell carcinomas resulting in the enhancement of their sensitivity to radiation [5]. To our knowledge the combination of 13-cis-retinoic acid with radiation has not been yet applied in the treatment of patients with NMSC, although a synergistic action of isotretinoin and radiotherapy in combination with interferon- α or after chemotherapy has been reported in other forms of malignancy [6,7].

The surprisingly quick remission of the tumors in our patients indicates that this combination treatment may be useful for such advanced cases, especially in very old patients with poor general condition because of its minimal side effects. The only undesirable event was the frequent bleeding in the second patient, although the follow-up period was rather short in order to conclude on the safety and efficacy of this regime, including the possibility of recurrences. Nevertheless, it seems likely that it could become a useful option at least in the palliative treatment of such debilitated patients with NMSC. Based on this preliminary experience we are now planning a clinical trial with a sufficient number of patients and follow up in order to elucidate the full benefit of this regime.

References

1. Chen K, Craig JC, Shumack S. Oral retinoids for the prevention of skin cancers in solid organ transplant recipients: a systematic review of randomized controlled trials. *Br J Dermatol* 2005; 152: 518-523.
2. Levine N. Role of retinoids in skin cancer treatment and prevention. *J Am Acad Dermatol* 1998; 39: S62-S66.
3. Recchia F, Lalli A, Lombardo M, et al. Ifosfamide, cisplatin, and 13-cis retinoic acid for patients with advanced or recurrent squamous cell carcinoma of the head and neck: a phase I-II study. *Cancer* 2001; 92: 814-821.
4. Campbell RM, DiGiovanna JJ. Skin cancer chemoprevention with systemic retinoids: an adjunct in the management of selected high-risk patients. *Dermatol Ther* 2006; 19: 306-314.
5. Bläse M, Zaruba MM, Santo-Hoeltje L, Bamberg M, Hoffmann W, Rodemann HP. 13-cis retinoic acid in combination with interferon- α enhances radiation sensitivity of human squamous cell carcinoma cells of the oral cavity. *Strahlenther Onkol* 1999; 175: 563-568.
6. Basu P, Biswas J, Mandal R, Choudhury P. Is interferon- α and retinoic acid combination along with radiation superior to chemo-radiation in the treatment of advanced carcinoma of cervix? *Indian J Cancer* 2006; 43: 54-59.
7. Matthay KK, Villablanca JG, Seeger RC, et al. Children's Cancer Group. Treatment of high-risk neuroblastoma with intensive chemotherapy, radiotherapy, autologous bone marrow transplantation, and 13-cis-retinoic acid. *N Engl J Med* 1999; 341: 1165-1173.