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Progressive 13-*cis*-Retinoic Acid Dosage in the Treatment of Oral Leukoplakia

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16 patients with oral leukoplakia were treated with oral 13-*cis*-retinoic acid. The initial dose, given for 3 months, was 0.2 mg/kg/day, increasing by a further 0.2 mg/kg/day in successive 3 month cycles. The maximum dosage reached at 1.0 mg/kg/day, was given to only 2 patients (who received a total of 15 months treatment). However, 10 patients completed the cycle at 0.8 mg/kg/day (12 months treatment in total), but treatment could not continue due to toxicity (grade I and II), which was cutaneous, mucosal, and haematological (hypertriglyceridemia and hypercholesterolemia). There was grade III toxicity in the skin and mucosa in only 1 case, a patient treated at a dose of 1.0 mg/kg/day. The toxicity was reversible in all cases. 14 of the patients completed the trial. In 4 there were improvements graded as partial responses (PR) obtained at 0.2 mg/kg/day (3PR) and 0.6 (1PR) and there was one complete response (CR) obtained at 0.4 mg/kg/day. Overall there was thus an objective response rate of 36% who showed 50% or more reduction in lesion size. After the retinoic acid treatment was stopped, patients were followed-up for 12 months; 2 patients showed regression of the responses obtained after 6 and 9 months. This study shows that oral treatment with 13-*cis*-retinoic acid at low dosages is efficacious and with minimal toxicity. It also shows that it is not feasible to treat these patients at doses above 0.8 mg/kg/day for long periods—mainly due to poor compliance.
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INTRODUCTION

BOTH RANDOM and non-random clinical studies, have shown that oral leukoplakia can regress during the administration of 13-*cis*-retinoic acid [1]. However, 13-*cis*-retinoic acid can cause undesirable, adverse effects, especially at doses of 1 to 2 mg/kg of body weight [2]. There are no published results of treatment using lower dosages. We have therefore carried out a study in which the compliance, toxic effects, and responses to treatment using 13-*cis*-retinoic acid in progressively larger dosages were evaluated in a group of 16 patients with oral leukoplakia.

PATIENTS AND METHODS

Patients were included in the study if, first, they had leukoplakia confirmed histologically; second, if the lesion could be measured; third, if hepatic and renal functions were normal, with a normal lipid profile; fourth, if they had no previous neoplasia; and fifth, if the leukoplakia had not been treated during the 6 months prior to the commencement of the study. The objectives of the study were fully discussed with each patient, including the characteristics of the drugs to be used, particularly their toxic nature, and also the importance of continuing the treatment for as long as possible. Patients in whom risk factors such as alcohol, tobacco smoking and poor oral hygiene were found, were given appropriate advice to reduce these habits. All were given a thorough oral examination. The lesion, or lesions, were recorded on measurable and photographable record cards.

The 13-*cis*-retinoic acid (Hoffmann-La Roche) was administered orally starting with a dosage of 0.2 mg/kg per day, given in divided doses twice a day, for 3 months. The dosage was then increased by 0.2 mg/kg in a second 3 month phase, that is, to 0.4 mg/kg, and then to 0.6 mg/kg in a third 3 month phase, followed by 0.8 mg/kg in the fourth 3 month period and so on. No specific reduction in the dosage of 13-*cis*-retinoic acid was planned but a temporary 1 or 2 week break in treatment was introduced if there was toxicity. If a second period of toxicity occurred, or if the treatment became intolerable, the treatment was stopped completely and not recommended. Similarly, for cases in which there was progression of the lesion, where there was grade III cutaneous toxicity, or grade II increase in transaminases, bilirubin, alkaline phosphatase or increase of cholesterol or triglycerides; or grade I nausea lasting more than 2 weeks the treatment was stopped.

The patients were followed-up at the end of each month during the first 3 month cycle (that is, the cycle of 0.2 mg/kg/day). The aim of these follow-ups was to verify the regularity and the manner in which the patients took the drugs, and how the patients' attitudes towards the treatment changed, along with the motivation of the patient for continuing treatment, and also to evaluate the toxicity and the response caused by this treatment. After the first cycle the patients were visited at least every 3 months. Patients were visited more frequently if there were signs of toxicity.

The results were clinically assessed and classified as follows: (1) complete response (CR) when inspection revealed no evidence of a lesion; (2) partial response (PR) defined as a reduction of the lesion by 50% or more of its initial size; (3) minor response (MR), a response of between 25% and 50% in reduction of the initial area; (4) stable condition (SD), where there

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was less than reduction of 25%; (5) progression (P)—for all increases in the lesions' size and/or the appearance of new lesions. These results had to last for at least 1 month from the initiation of the changes during the treatment. The haematological status was monitored at the same monthly and 3-monthly intervals as the clinical examination. Blood count, liver function, coagulation tests, and lipid profiles were monitored. All the patients were followed-up for at least another 12 months after the cessation of the retinoic acid treatment.

RESULTS

16 patients (10 women) aged between 44 and 79 years (mean 57) were studied. In 12 of the patients there were multiple lesions of leukoplakia. 8 of the patients were tobacco smokers; 4 were both tobacco smokers and alcohol drinkers; 4 neither smoked nor drank alcohol. Oral hygiene was considered poor in 10 patients. 8 of the patients had dental protheses. The leukoplakias in 3 of the patients had been treated previously—2 with surgery and the other with a vitamin-based treatment 2 years before entering the study.

Of the 16 patients starting the study 2 had to be excluded, because of toxicity from the retinoic acid. This modest skin or mucous toxicity occurred only 1 and 3 weeks after the initiation of the first cycle of 0.2 mg.

Table 1 shows the dose of retinoic acid and results achieved, and also shows the maximum dose which each patient was able to tolerate, and the variation of the results after the end of treatment. Overall, there were 10 improvements (considering minor, partial and complete responses) out of a possible 14 (71%) but only 5 (35%) were major responses (CR + PR).

Of these 5 objective responses (OR), 3 were obtained after the first cycle at 0.2 mg/kg of 13-*cis*-retinoic acid and were PR, whilst the other two were obtained at the end of the second cycle with 0.4 mg/kg of 13-*cis*-retinoic acid (the only one CR), and with 0.6 mg/kg of 13-*cis*-retinoic acid (the fourth PR), respectively. No case progressed during the treatment, but in 2 there was eventual regression of a positive response: 1 case regressed from PR to MR, and the other went from MR to SD, in 6 and 9 months, respectively after the cessation of treatment. The results of the treatment were maintained for all other patients over the extra 12-month follow-up.

Table 1. *Results of treatment of oral leukoplakia with* 13-cis-*retinoic acid*

Patient number	Results while on retinoic acid	Min dose at which result obtained	Max dose tolerated	Result 12 months after cessation of treatment
1	PR	0.2	0.4	MR
2	—*	—	—	—
3	MR	0.8	0.8	NC
4	MR	0.2	0.4	SD
5	—	—	—	—
6	PR	0.2	1.0	NC
7	SD	0.2	0.8	NC
8	PR	0.6	0.8	NC
9	SD	0.2	0.8	NC
10	MR	0.2	1.0	NC
11	MR	0.2	0.8	NC
12	MR	0.2	0.8	NC
13	SD	0.2	0.2	NC
14	SD	0.2	0.2	NC
15	PR	0.2	0.6	NC
16	SD	0.2	0.8	NC

*Not evaluated; NC = no change; PR = partial response; MR = minor response, SD = stable disease.

Table 2 shows the momentary and definitive interruptions as well as the toxicity verified for the various dosages of 13-*cis*-retinoic acid. Toxicity clearly increased with the rising dosage of 13-*cis*-retinoic acid, and mainly affected the skin and the mucosa (grades I and II).

The tolerated upper limit of the dose of retinoic acid was found to be 0.8 mg/kg. In fact, at a dose of 1.0 mg/kg of 13-*cis*-retinoic acid, 8 out of 10 rejected further treatment. In addition, for all doses of 13-*cis*-retinoic acid, there was a modest increase, less than 20% of the base value, in the serum level of cholesterol and a triglyceridemia (range 12–50%). Conjunctivitis was frequent at all doses (range 25–60%). 1 case of grade III toxicity in the skin and mucosal was observed at the 1.0 mg/kg dose of 13-*cis*-retinoic acid: this occurred after 2 weeks of treatment.

DISCUSSION

The aim of this study was to verify the acceptability and the effectiveness of treatment using 13-*cis*-retinoic acid in patients in good general health, who had oral leukoplakia and who were treated with 13-*cis*-retinoic acid in progressively increasing dosages starting with 0.2 mg/kg per day.

The results indicate an upper limit to the dosage of 13-*cis*-retinoic acid that can be tolerated, at 0.8 mg/kg per day. Only 10 of the 16 patients (62.5%) managed to complete a 3 month cycle at 0.8 mg/kg, and of these, only 2 managed to undergo the treatment at 1.0 mg/kg per day.

However, compared with the toxicity found in other studies, which usually used higher doses of retinoids, the toxicity found in the patients in this study was only of a modest nature—grade I and II for skin, mucosal and haematology, except in the case of 1 patient treated with 1.0 mg/kg in whom the cutaneous toxicity was grade III. Furthermore, the toxicity in all cases reversed in a small number of days after the suspension of treatment. Despite considerable time and attention given to discussion, the percentage of definitive interruptions, caused by problems with patient compliance, was high. As many as 6 out of the 16 patients (37%) interrupted the treatment at doses below 0.8 mg/kg/day.

The percentage of major objective responses (CR + PR) to the retinoid (36%) was the lowest yet reported in the literature. However, a general improvement in the lesions was obtained in 70% of the patients. These results were obtained with doses of 13-*cis*-retinoic acid considerably lower than those used by other authors (who have used doses varying from 1 to 2 mg/kg [1]). In the present study three responses (3 PR) out of 5 (4 PR + 1 CR) were obtained during the first 3 month cycle at low doses of 0.2 mg/kg per day. In addition, it has to be pointed out that the responses increased with rising dosage: in 1 case the MR in the first cycle became a PR in the third cycle (0.6 mg/kg), and in another case of MR in the first cycle, it became a CR in the second cycle (0.4 mg/kg).

The 14 patients completing the study were followed-up for a further 12 months when only two changes were found: at 6 and 9 months, there was a regression of the responses obtained. This is in contrast with the results reported by Hong *et al.* [2] who in a random study in which patients with leukoplakia were treated for 3 months by using 1–2 mg of 13-*cis*-retinoic acid found regression of the positive responses 2–3 months after the cessation of the treatment in all patients. Perhaps, the more lasting results obtained in the present study

Table 2. Adverse effects and doses of 13-cis-*retinoic acid*

	Dose of 13-*cis*-retinoic acid				
	0.2 (16)*	0.4 (14)*	0.6 (12)*	0.8 (11)	1.0 (10)*
Skin dryness and cheilitis (grade I–II)	8	6	6	7	7
Skin dryness and cheilitis (grade III)	—†	—	—	—	1
Conjunctivitis	4	5	6	6	6
Nausea and/or vomiting (grade I)	2	1	2	2	2
Headache and irritability	1	—	—	1	1
Increase in serum transaminases (grade 1)	1	—	—	1	—
Hypertriglyceridemia and/or Hypercholesterolemia	2	3	3	3	5
Treatment temporarily discontinued	3	3	2	2	1
Treatment abandoned	2	2	1	1	8

( )*Total number of patients treated at this dosage in mg/kg/day.
†No patients.

can be attributed to the longer duration of the treatment even though the dosages were lower than those used in Hong's study. Indeed, in a second random study by the same author it was pointed out that it is possible to maintain the responses obtained with 13-*cis*-retinoic acid, using small doses (0.5 mg/kg/day) of the drug for 3 months [5]. Therefore, in terms of an objective response in oral leukoplakia patients, it would seem that there is no appreciable difference between 1, 1.5 and 2 mg/kg/day [1].

This study shows therefore, that 13-*cis*-retinoic acid can be considered to be a valid long-term clinical treatment for patients with oral leukoplakia using doses up to and not over, 0.8 mg/kg/day. Compliance, rather than toxicity remains the main problem.

1. Hong WK. The biology and chemoprevention of head and neck cancer. *Educational Book* 1991, 99–103.
2. Hong WK, Endicott J, Itri ML, *et al.* 13-*cis*-retinoic acid in the treatment of oral leukoplakia. *N Engl J Med* 1986, **315**, 1501–1505.
3. Slaughter DP, Southwick HW, Smejkal W. "Field cancerization" in oral stratified squamous epithelium: clinical implications of multicentric origin. *Cancer* 1953, **6**, 963–968.
4. Strong MS, Incze J, Vaughan CW. Field cancerization in the aerodigestive tract—its etiology, manifestation, and significance. *J Otolaryngol* 1984, **13**, 1–6.
5. Lippman SM, Toth BB, Batsakis JG, *et al.* Low-dose 13-*cis*-retinoic acid (13cRA) maintains remission in oral premalignancy: more effective than Beta-carotene in randomized trial. *Proc Ann Meet Am Soc Clin Oncol* 1990, **9**, A225.
6. Stich HF, Rosin MP, Hornby AP, Mathew B, Samaranayake R, Nair MK. Remission of oral leukoplakias and micronuclei in tobacco/betel quid chewers treated with beta-caroten and with beta-carotene plus vitamin A. *Int J Cancer* 1988, **42**, 195–199.
7. Bollag W. Retinoids and interferon—a new promising combination. *Int Symposium on Interferon Alpha Therapy in Malignant Diseases* ISIT, Athens, 1990, 56.
8. Malone WF, Kelloff GJ. Chemioprevention strategies utilizing combinations of inhibitors of carcinogenesis. *J Natl Cancer Inst* 1989, **81**, 824.
9. Pluygers E, Baldewijns P, Beauduin M. Markers of promotion in carcinogenesis as intermediate endpoints for monitoring the efficacy of cancer prevention. *CM Cancer* 1991, 219–224.
10. Malone WF, Kelloff G, Boone C. Ongoing preclinical and initial clinical studies in chemoprevention. *CM Cancer* 1991, 111–123.
11. Toma S, Albanese E, Palumbo R, Nicolo G, Morerio C, Mangiante PE. *In vitro* effects of beta-carotene on human oral keratinocytes from precancerous lesions and squamous carcinoma. *Anticancer Drugs* 1991, **2**, 581–589.