Pergamon

Oral Oncol, Eur J Cancer Vol. 32B, No. 6, pp. 373–376, 1996

Printed in Great Britain
0964-1955/96 $15.00 + 0.00

PII: S0964-1955(96)00010-3

Papers

Efficacy of Vitamin A in the Prevention of Loco-regional Recurrence and Second Primaries in Head and Neck Cancer

R. Jyothirmayi,[1] K. Ramadas,[1] C. Varghese,[1] R. Jacob,[1] M.K. Nair[1] and R. Sankaranarayanan[2]

[1]Regional Cancer Centre, P.O. Box 2417, Trivandrum 695011, India; [2]Unit of Descriptive Epidemiology, International Agency for Research on Cancer (IARC), 150 cours Albert Thomas, 69372 Lyon Cedex 08, France

Chemoprevention with retinoids is currently an experimental approach to prevent local relapses and second primaries in treated head and neck cancer patients. We evaluated the effectiveness of vitamin A in preventing the above events in a randomised trial involving 106 head and neck cancer patients who had achieved complete regression of their disease with radiotherapy and/or surgery. They were randomised to receive retinyl palmitate (200,000 IU per week for 1 year) or placebo. 50 subjects on vitamin A and 43 on placebo completed 1 year supplementation; 49 in the former group and 42 in the latter could be evaluated over a 3 year period from the initiation of the study. One fifth (11/56) of patients in the vitamin A group and one tenth (5/50) in the placebo group had loco-regional recurrence. The frequency of recurrences in stage I patients in the vitamin A group was higher compared to the placebo group, although it was not statistically significant. No second primaries were observed in the vitamin A group; 2 patients in the placebo group had second primaries. No clinically obvious side effects were observed with vitamin A. The higher frequency of recurrences in the vitamin A group is of concern although it may be a chance finding given the small size of the trial. The effect on second primaries is consistent with other observations reported in literature.

Key words: oral cancer, head and neck cancer, local recurrence, prevention, chemoprevention, second primaries, vitamin A

Oral Oncol, Eur J Cancer, Vol. 32B, No. 6, pp. 373–376, 1996

INTRODUCTION

Head and neck epithelial cancers are among the most common cancers in both sexes in southern India [1]. A third of incident cancers in males and female cancers occur in head and neck sites. The causal role of tobacco and alcohol in these cancers has been well established [2–5]. They are locally infiltrating tumours, metastasising to regional lymph nodes and seldom spreading to distant sites. Loco-regional recurrence is a major problem in the vast majority of treated head and neck cancers [6–8]. Second primaries are also frequently reported in long-term survivors of head and neck cancer [9, 10]. Prevention of the above two phenomena are challenging tasks in the long-term control of head and neck cancers. Chemoprevention with retinoids is one of the current experimental approaches. In this paper, we describe our experience with vitamin A in the prevention of local recurrences and second primaries in treated head and neck cancer (HNC) patients in Kerala, India.

MATERIALS AND METHODS

119 patients with HNC, who revealed complete clinical regression of lesions on follow-up after therapy, were invited to participate in this trial. These subjects had either radical radiotherapy or surgery or both during the earlier half of 1991. They were evaluated for disease status during March 1992; 106 patients with no clinical evidence of disease, nor-

Correspondence to R. Sankaranarayanan.
Received 20 Dec. 1995; provisionally accepted 21 Dec. 1995; revised manuscript received 12 Feb. 1996.

Table 1. Subject characteristics

Factor	Placebo ($n = 50$)	Vitamin A ($n = 56$)
Mean age (years)	58.2	56.3
Sex		
Male	36	37
Female	14	19
Tobacco habits		
Chewing	33	32
Smoking	35	26
Primary site		
Oral cavity	37	45
Oropharynx	2	3
Hypopharynx	2	1
Larynx	9	7
Histology		
Well differentiated squamous cell carcinoma	32	40
Moderately differentiated squamous cell carcinoma	13	9
Poorly differentiated squamous cell carcinoma	2	2
Others	3	5
Stage		
I	17	18
II	19	20
III and IV	14	18
Treatment		
Radiotherapy	44	47
Surgery	3	5
Radiotherapy + Surgery	3	4

mal liver and kidney function were selected for inclusion in the trial. Informed consent was obtained from all the participants before randomisation. The characteristics of these patients are given in Table 1. The recruited subjects underwent evaluation of tobacco chewing and smoking, as well as alcohol drinking habits at baseline as well as during reviews.

The subjects were randomised to receive either oral vitamin A ($n = 56$) 200,000 IU per week, as chewable tablets of retinyl palmitate, or placebo ($n = 50$) for 1 year beginning from 25 March 1992. The placebo consisted of capsules of tapioca powder. The subjects were provided with supplies lasting for 2 months and followed up once in 2 months. Their compliance was assessed during reviews when residual capsules were counted. 50 (89%) subjects on vitamin A and 43 (86%) subjects completed supplementation for 1 year. Blood was collected at baseline and at exit after completion of supplementation during March 1993 for measurement of haemoglobin, proteins, retinol and for liver and kidney function tests.

The subjects were examined by three clinical oncologists, blind to the treatment groups, once in 2 months for detailed clinical assessment regarding disease status and toxic symptoms due to supplements. Patients with clinical suspicion of recurrences or second primaries were subjected to biopsy and histopathological examination. The results are presented on the intention to treat basis involving all subjects randomised to receive the treatment. The differences in the proportion of responses between the placebo and intervention groups were tested by the chi-square test after the arcsin transformation. All tests were two-tailed and a P value of less than 0.05 was considered to indicate a statistically significant difference.

Table 2. Details of outcome

Outcome	Placebo ($n = 50$)	Vitamin A ($n = 56$)
Local recurrence at primary site	3	7
Regional node recurrence	2	3
Recurrence at primary site and regional nodes	0	1
Second primary	2	0

RESULTS

The results of responses as of March 1995 when subjects had completed 3 years on follow-up are given in Table 2. 49 subjects on vitamin A and 42 subjects on placebo could be evaluated during the above 3 year period.

One fifth of subjects (11/56) in the vitamin A group had loco-regional recurrence as compared to one tenth (5/50) in the placebo group. Although the frequency of loco-regional recurrence was high in the vitamin A group, it did not reach statistical significance. Table 3 reveals the frequency of loco-regional recurrences by clinical stage at presentation. The frequency of relapses in stage I patients in the vitamin A group was not significantly higher than that in the placebo group. 6 of the 11 recurrences in the vitamin A group and 2 of 5 in the placebo group occurred in the first year of follow-up.

No second primaries were observed in subjects in the vitamin A group as opposed to 2 subjects developing second primaries (1 case of tongue cancer and 1 of floor of mouth cancer) in the placebo group.

The mean serum retinol level increased from 0.6 μg/ml at baseline to 0.78 μg/ml at exit in the vitamin A group; the corresponding values were 0.55 μg/ml both at baseline and exit in the placebo group.

No clinically obvious side effects of vitamin A were observed during and after supplementation, except for dryness of the tongue in two subjects. Administration was not interrupted in any subject due to toxicity. The liver and renal functions remained within the normal range in all subjects during and after supplementation.

DISCUSSION

Chemoprevention with retinoids is currently an experimental approach to prevent the progression of precancerous lesions to cancer and to reduce the risk of second primary cancers in treated head and neck cancer patients. Retinoids are believed to act at the cellular and molecular level to reverse or suppress the carcinogenic process. Although the risk of loco-regional recurrence in HNC is predominantly a

Table 3. Loco-regional recurrence by stage

Clinical stage	Placebo	Vitamin A
I	2/17 (12%)	6/18 (33%)
II	1/19 (5%)	2/20 (10%)
III and IV	2/14 (14%)	3/18 (17%)

Table 4.

Author	Agent	*n*	Disease progression			Second primary	
			Local	Regional	Distant	Head and neck	Other sites
Bolla *et al.* [14]	Etretinate	156	12	7	19	12	16
	Placebo	160	11	8	10	13	16
Benner *et al.* [15]	Isotretinoin	49	5	8	8	3	4
	Placebo	51	7	7	5	13	3

function of the extent of disease and treatment, the role of on-going carcinogenic processes due to field cancerisation and the influence of continuing exposure to tobacco and alcohol, if any, may be contributory factors. The risk of second primaries in the exposed head and neck epithelium is likely to be a direct outcome of the field cancerisation phenomenon. Hence, logically chemoprevention with anti-initiators and promoters may contribute to the control of the above factors.

Vitamin A compounds have been widely studied in the prevention of head and neck carcinogenesis [11–13]. Synthetic retinoids have been evaluated in preventing second primaries and loco-regional recurrences in treated head and neck cancer patients [14, 15]. Beta carotene has not been evaluated for its efficacy in the control of local recurrences and second primaries in HNC patients. Table 4 shows the results of two trials with etretinate and 13-*cis* retinoic acid (isotretinoin). In the study by Bolla *et al.* [14] supplementation was started no later than 5 days after initiation of therapy; 156 patients were randomised to receive oral etretinate (50 mg/day in the first month followed by 25 mg/day for 23 months) and 160 subjects to the placebo group. The 5-year survival was 64% in the etretinate group and 75% in the placebo group. There were no significant differences in loco-regional and distant relapses or in the frequency of second primaries in either of the groups. Toxic side effects were observed in half of the subjects on etretinate.

The effect of isotretinoin was evaluated at a median follow-up of 54.5 months [15]. It was administered to 49 subjects (50–100 mg/m^2/day for 12 months) and 51 subjects were in the placebo group. There was no difference in the frequency of loco-regional and distant relapses in either group, but there was a significant reduction in the frequency of second primaries in those on isotretinoin (14% versus 32%). However, a significant proportion of subjects experienced moderate to severe toxicities from isotretinoin: skin dryness 63%; cheilitis 24%; hypertriglyceridaemia 26%; and conjunctivitis in 18%.

Another trial that evaluated retinyl palmitate (300,000 IU/day for 12 months) in resected stage I lung cancer patients reported a one third reduction in the frequency of second primaries in the treated group as opposed to the placebo group [16]. A large European trial has now accrued almost 2500 treated HNC patients to evaluate the efficacy of retinyl palmitate (300,000 IU/day in year 1 followed by 200,000 IU/day in the second year) to prevent loco-regional recurrences and second primaries [17]. A large trial is now evaluating the effectiveness of reduced doses of 13-*cis* retinoic acid [18].

Our investigation, which involved a small number of subjects, was mainly conducted as a pilot study to evaluate patient compliance, acceptability of supplements and the feasibility of adequate follow-up in our setting. We have evaluated vitamin A for its efficacy in reversing oral leucoplakia and we found that half of the subjects supplemented with vitamin A had complete regression of lesions [19, 20]. The present study has also shown that chemoprevention with vitamin A is an acceptable treatment with no troublesome side effects, and that it is possible to achieve compliance with supplementation and follow-up in the hospital setting. The higher frequency of loco-regional recurrences observed in the vitamin A group, particularly in stage I patients, is of concern. However, it might be a chance observation given the small sample size. The observation in relation to second primaries seems to be consistent with the reported effectiveness of retinoids in preventing second primaries. However, the number of events are small.

Synthetic retinoids, such as isotretinoin [14, 15, 21, 22] have been reportedly associated with considerable toxicity as opposed to natural analogues of vitamin A like retinyl palmitate [16, 17, 23–25]. Our experience in this study and in our previous studies [19, 20] indicate that vitamin A is a well accepted and a safe supplement. Based on our findings, we have now initiated long-term studies with large sample sizes to investigate whether vitamin A can reduce the incidence of cancers in subjects with oral precancerous lesions and second primaries in treated HNC patients.

1. ICMR. *National Cancer Registry Programme. Biennial Report 1988–1989.* New Delhi, Indian Council of Medical Research, 1992.
2. Sankaranarayanan R, Duffy SW, Padmakumari G, Day NE, Padmanabhan TK. Tobacco chewing, alcohol and nasal snuff in cancer in the gingiva in Kerala, India. *Br J Cancer* 1989, **60**, 638–643.
3. Sankaranarayanan R, Duffy SW, Day NE, Krishnan Nair M, Padmakumary G. A case control investigation of cancer of the oral tongue and the floor of the mouth in southern India. *Int J Cancer* 1989, **44**, 617–621.
4. Sankaranarayanan R, Duffy SW, Krishnan Nair M, Padmakumary G, Day NE. Tobacco and alcohol as risk factors in cancer of the larynx in Kerala, India. *Int J Cancer* 1990, **45**, 879–882.
5. Sankaranarayanan R, Duffy SW, Padmakumary G, Day NE, Krishnan Nair M. Risk factors for cancer of the buccal and labial mucosa in Kerala, India. *J Epidemiol Comm Health* 1990, **44**, 286–292.
6. Krishnan Nair M, Sankaranarayanan R, Padmanabhan TK. Evaluation of the role of radiotherapy in the management of carcinoma of the buccal mucosa. *Cancer* 1988, **61**, 1326–1331.
7. Padmanabhan TK, Sankaranarayanan R, Krishnan Nair M. Evaluation of local control, survival and pattern of failure with radiotherapy in cancer of the oral tongue. *Oncology* 1990, **47**, 121–123.
8. Krishnan Nair M, Sankaranarayanan R, Krishnan E, Padmanabhan TK, Mayadevi S. Aleyamma M. Independent predictors of response and disease free survival in oral cancer treated with radical radiotherapy. *Cancer* 1992, **69**, 2221–2227.
9. Haughey BH, Gates GA, Arfken CL, Harvey J. Meta-analysis of second malignant tumours in head and neck cancer: the case

for an endoscopic screening protocol. *Ann Otol Rhin Laryngol* 1992, **101**, 105–112.
10. Day GL, Blot WJ. Second primary tumours in patients with oral cancer. *Cancer* 1992, **70**, 14–19.
11. Sankaranarayanan R, Mathew B, Nair PP, *et al.* Chemoprevention of the cancers of the oral cavity and head and neck. In: Hakama M, Beral V, Buiatti E, Faivre J, Parkin DM, Eds. *Chemoprevention in Cancer Control.* IARC Scientific Publications No. 136. Lyon, IARC, 1996, 13–25.
12. Tanaka T. Chemoprevention of oral carcinogenesis. *Oral Oncol, Eur J Cancer* 1995, **31B**, 3–15.
13. Scully C. Oral precancer: preventive and medical approaches to management. *Oral Oncol, Eur J Cancer* 1995, **31B**, 16–26.
14. Bolla M, Lefur R, Ton Van C, *et al.* Prevention of second primary tumours with etretinate in squamous cell carcinoma of the oral cavity and oropharynx. Results of a multicentric double blind randomised study. *Eur J Cancer* 1994, **30A**, 767–772.
15. Benner SE, Pajak TF, Lippman SM, Earley C, Hong WK. Prevention of second primary tumours with isotretinoin in patients with squamous cell carcinoma of the head and neck: long term follow-up. *J Natl Cancer Inst* 1994, **86**, 140–141.
16. Pastorino U, Infante M, Maiola M. Adjuvant treatment of stage I lung cancer with high dose vitamin A. *J Clin Oncol* 1993, **11**, 1216–1222.
17. Vries N de, Pastorino U, Zandwijk N van. Chemoprevention of second primary tumours in head and neck cancer in Europe: EUROSCAN. *Oral Oncol, Eur J Cancer* 1994, **30B**, 367–368.
18. Lippman SM, Benner SE, Hong WK. Retinoid chemoprevention studies in upper aerodigestive tract and lung carcinogenesis. *Cancer Res* 1994, **54** (Suppl.), 205s–208s.
19. Stich HF, Hornby AP, Mathew B, Sankaranarayanan R, Krishnan Nair M. Response of oral leukoplakias to the administration of vitamin A. *Cancer Lett* 1988, **40**, 93–101.
20. Sankaranarayanan R, Mathew B, Varghese C, *et al.* Chemoprevention of oral leukoplakia with vitamin A and beta carotene: an assessment. *Oral Oncol, Eur J Cancer* (to appear).
21. Hong WK, Endicott J, Itri LM,, *et al.* 13-cis retinoic acid in the treatment of oral leukoplakia. *N Engl J Med* 1986, **315**, 1501–1505.
22. Lippman SM, Batsakis JG, Toth BB,, *et al.* Comparison of low-dose isotretinoin with beta-carotene to prevent oral carcinogenesis. *N Engl J Med* 1993, **328**, 15–20.
23. Pastorino U, Chisea G, Infante M,, *et al.* Safety of high-dose vitamin A. *Oncology* 1991, **48**, 131–137.
24. Omenn GS, Goodman GE, Thornquist M,, *et al.* The B-carotene and retinol efficacy trial (CARET) for chemoprevention of lung cancer in high risk populations: smokers and asbestos exposed workers. *Cancer Res* 1994, **54**, 2038s–2043s.
25. Omenn GS, Goodman GE, Thornquist M, *et al.* Long term vitamin A does not produce clinically significant hypertriglyceridaemia: Results from CARET, the B-carotene and retinol efficacy trial. *Cancer Epidemiol Biomarkers Prevention* 1994, **3**, 711–713.

Acknowledgements—The authors gratefully acknowledge Dr Padmanabhan P. Nair, Beltsville Human Nutrition Research Centre, Beltsville, U.S.A. for his help in analysing serum retinol and Dr D. M. Parkin for his constructive comments. Our thanks are due to Mrs E. Bayle who prepared this manuscript.