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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

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Patients who are cured from head and neck carcinomas remain at high risk for developing a second primary in the head and neck area. It is now clear that retinoids exert a prophylactic action on the development of epithelial cancers when tested on laboratory animals and on human premalignant lesions. They are now used in the chemoprevention of epithelial cancers in randomised trials evaluating their efficacy. We prospectively studied 316 patients who developed squamous cell carcinoma of the head and neck, classified as T1/T2, N0/N1 ≤ 3 cm, M0 according to the UICC TNM classification. Patients were randomly assigned to receive orally, either etretinate (a loading dose of 50 mg/day for the first month, followed by a dose of 25 mg/day in the following months) or a placebo for 24 months. Adjuvant treatment began no later than 15 days after surgery and/or the initiation of radiotherapy. The 5-year survival rate and disease-free survival rate are similar in the two groups. There are no significant differences regarding either local, regional and distant relapses. After a median follow-up of 41 months (range 0–81), 28 patients in the etretinate group and 29 in the placebo group developed a second cancer with, respectively, 12 and 13 in the head and neck region. Adjuvant treatment was definitively discontinued mainly due to toxicity in 33% of patients in the etretinate group versus 23% in the placebo group ($P < 0.05$). Etretinate, a second-generation retinoid, does not prevent second primary tumours in patients who have been treated for squamous cell carcinoma of the oral cavity and oropharynx.
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INTRODUCTION

In France, head and neck carcinoma is expected to account for 8% of carcinomas in adults [1]. All these carcinomas are linked to tobacco use and alcohol, and they constitute a major national health problem. Until now, neither primary prevention nor individual screening have succeeded in modifying either the incidence or the poor outcome of these carcinomas. If surgery and/or radiotherapy continue to be the corner-stone of local treatment, chemotherapy has failed to reduce distant metastases or obviate second primaries and thus improve overall survival. According to the tumour site, clinical stage, clinical work-up and modalities of follow-up, 30–50% of patients develop local or regional recurrence, 20–30% distant metastases, and 10–40% a second primary tumour [2]. Moreover, for patients who are thought to be cured from the primary, the emergence of metachronous tumours is the chief cause of treatment failure and death, particularly for patients who present with early stage disease, for they appear to be at higher risk [3].

It has been suggested that retinoids (retinol and its synthetic analogues) might be used in the pharmacological approach to chemoprevention of cancer because of their ability to exert hormone-like control on normal cellular differentiation and proliferation, which may be the basis of neoplastic development [4, 5]. Several retinoids do not necessarily bind to cytosolic receptors, but can bind directly to nuclear retinoic acid receptors and, thereby, influence the genome [6, 7].

Since 1983, retinoids, such as the synthetic retinoid isotretinoin (13-*cis*-retinoic acid) [8], have been used in different trials related to premalignant [9, 10] or invasive lesions of the head and neck. We chose etretinate, a second generation retinoid [11], because of its superior papilloma therapeutic index as assessed by Bollag, with the chemically induced skin papilloma model in mice [12]. In addition, a preventive effect was described on bronchial metaplasia in heavy smokers [13] and on recurrence of superficial bladder tumours [14], but at that time we had no

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data concerning head and neck cancer or oral leukoplakia. As to the molecular mechanism of etretinate action, etretinate and its metabolite acitretin do not bind to nuclear retinoid acid receptor α (RARα) and nuclear retinoid acid receptor β (RARβ); however, RARα and RARβ are activated slightly by etretinate and to a greater degree by acitretin [15]. We report here the results of etretinate in a double-blind randomised study focused on T1/T2, N0/N1 ≤ 3 cm, M0, clinical stage carcinoma or oral cavity and oropharynx.

MATERIALS AND METHODS

The trial was started under the auspices of a French Study Group on Head and Neck Tumors (GETTEC). The statistics department of the Institut Gustave Roussy was responsible for centralised data management and statistical analysis.

Eligibility criteria

Eligibility criteria were histologically confirmed primary squamous cell carcinoma of the oral cavity and oropharynx, classified as T1/T2, N0/N1 ≤ 3 cm, M0, according to the TNM clinical classification of the UICC; there was no central review of pathology in patients at trial entry (and at relapse). The aims of the study and its design were fully discussed with all the patients in order to obtain their informed consent.

The clinical work-up included a thorough history study and physical examination with determination of weight and WHO performance status. It should be mentioned that histories of smoking (current or former smoker) and alcohol consumption (level of quantity) were not assessed in the on-study forms. An endoscopy of the pharynx, larynx, tracheo-bronchial tree and the oesophagus was mandatory as well as chest X-ray, blood count, electrolytogram, triglyceridaemia, transaminases, alkaline phosphatases and retinolaemia.

Patients were excluded from the study if they were older than 75 years and if they had one of the following characteristics: WHO performance status > 2, synchronous carcinoma, previous carcinoma other than basal cell carcinoma or *in situ* carcinoma of the cervix, serum creatinine concentration > 130 μmol/l, serum bilirubin concentration > 35 μmol/l, previous chemotherapy. Females of reproductive capacity were also excluded, because of the well-known teratogenicity of etretinate.

Study design

Patients were randomly assigned to receive orally either etretinate (a loading dose of 50 mg/day for the first month, followed by a dose of 25 mg/day for the following months) or placebo for 24 months. Randomisation was performed at the Institut Gustave Roussy by means of a computer-generated list balanced for every 4 patients and stratified by centre. Both the drug and the placebo were provided in identical opaque gelatin capsules (Roche Laboratory, Basel, Switzerland), and similarly packaged, so that neither the patients nor the physicians were aware of the treatment assigned.

Adjuvant treatment was begun no later than 15 days after surgery or the initiation of radiotherapy. Compliance was assessed by simply asking the patients at each consultation if they had regularly taken their capsules, and the number of omitted capsules was recorded on the follow-up forms; there was no count of remaining pills by clinic staff. Local and regional control after treatment were evaluated 6 to 8 weeks after the completion of treatment, and included physical examination with a biopsy if the patient exhibited clinical symptoms. Patient follow-up comprised chest X-ray films, obtained every 6 months, and laboratory tests (triglyceridaemia, transaminases and alkaline phosphatases) every 4 months. Plasma etretinate levels were not monitored to assess compliance.

Statistical analysis

The main end-points were overall and disease-free survival. The second end-point was the development of second primary tumours which were not limited to the head and neck, oesophagus or lungs. Biopsies were performed in all sites when failure of primary treatment was suspected. Second primary tumours were all documented by a biopsy, whatever the site. By definition, a second primary tumour of the head and neck had to be separated from the first by more than two centimetres, if it was occuring on the same anatomical site, and had to occur at least 6 months after the onset of the treatment. Survival was measured from the date of randomisation to the date of death or the most recent follow-up. Time to distant metastasis or a local recurrence (after the disappearence of the tumour from the initial site) was measured from the date of randomisation to the date of the occurrence of either event or to the date to the most recent follow-up. A sample of 330 patients was planned so that an improvement in the 5-year survival rate from 50 to 65% could be detected with a type I error of 0.05 and a type II error of 0.15. Comparisons were tested by the χ^2 test and Student's *t*-test. Survival curves were estimated by the Kaplan–Meier method [16]; 95% confidence intervals were calculated by Rothman's method [17] and survival curves were compared using the logrank test [18]. All *P* values are two tailed.

RESULTS

Demographic data

Between March 1985 and December 1991, 324 patients from eight centres were enrolled in the study: 161 in the etretinate group and 163 in the control group. Two small centres were ruled out because of a lack of follow-up of the 8 patients they entered. Thus, the analysis is based on 316 patients (156 etretinate and 160 placebo). The percentage of patients included per centre was: Rouen 30%, Lille 26%, Institut Gustave Roussy 20%, Grenoble 16%, Besançon 6%, Poissy 2%. Patients' characteristics in the two groups before treatment were similar (Table 1), as were local treatment modalities (Table 2).

Survival and disease-free survival

As of January 1992, the duration of follow-up ranged from 0 to 82 months (median 41 months). 4 patients (2 in each treatment group) were lost to follow-up The actuarial survival curves are shown in Figure 1. No significant difference was noted between them. The 5-year survival rate (95% confidence interval) in the etretinate group was 64% (53–74%) versus 75% (66–82%) in the placebo group. No significant difference was noted in disease-free survival curves between the two groups.

Patterns of failure are shown in Table 3. There are no differences regarding local or regional relapses (logrank NS) or for distant relapses (logrank NS).

Second primary tumours

28 patients in the etretinate group and 29 in the placebo group developed a second tumour. The actuarial survival curves for second tumour are shown in Figure 2 (difference NS). Table 4 shows the site of second primaries. The 3- and 5-year rates were 18 and 38% in the etretinate group versus 20 and 24% in the placebo group, respectively.

Table 1. Patients' characteristics

Characteristic	Etretinate group (n = 156)	Placebo group (n = 160)
Sex		
Male	147 (94%)	152 (95%)
Female	9 (6%)	8 (5%)
Age, years*	53 (10)	54 (8)
WHO performance status		
0	124 (79%)	124 (78%)
1	31 (20%)	35 (22%)
2	1 (1%)	1†
Weight, kg*	67 (11)	66 (12)
Primary tumour site		
Oral cavity	131 (84%)	129 (81%)
Tongue	63 (40%)	60 (38%)
Floor of the mouth	42 (27%)	47 (29%)
Gum	6 (4%)	3 (2%)
Other	20 (13%)	19 (12%)
Oropharynx	25 (16%)	30 (19%)
Other localisation	0	1 (1%)
Tumour stage		
T0	0	1 (1%)
T1b	59 (38%)	59 (37%)
T2c	94 (60%)	98 (61%)
T4d	1 (1%)	0
TXe	2 (1%)	2 (1%)
Node stage		
N0	133 (85%)	126 (79%)
N1 ≤ 3 cm	21 (13%)	31 (19%)
N2 ≤ 3 cm	2 (1%)	2 (1%)
		1†
Histology‖		
In situ	2‡ (1%)	1§ (1%)
Differentiated or moderately differentiated	127 (84%)	131 (82%)
Poorly differentiated	2 (1%)	8 (5%)
Differentiation cannot be assessed	19 (13%)	19 (12%)
Miscellaneous	2 (1%)	0
Retinol (mmol/l)*	3 (1.4)	2.9 (1.4)
	48†	49†

* Mean (S.D.). †Could not be assessed. ‡T0 Tumour stage with an edge biopsy. §T2 tumour stage.
‖Data for 4 patients in the etretinate group and 1 patient in the placebo group were not available.

Table 2. Characteristics of patients according to local treatment

Characteristics	Etretinate group (n = 156)	Placebo group (n = 160)
Surgery alone	16 (10%)	16 (10%)
External irradiation alone	23 (15%)	33 (21%)
Brachytherapy	15 (10%)	9 (6%)
External irradiation combined with surgery	30 (19%)	24 (15%)
Brachytherapy combined with surgery	36 (23%)	39 (24%)
External irradiation + brachytherapy	27 (17%)	22 (14%)
Surgery + external irradiation + brachytherapy	9 (6%)	17 (11%)

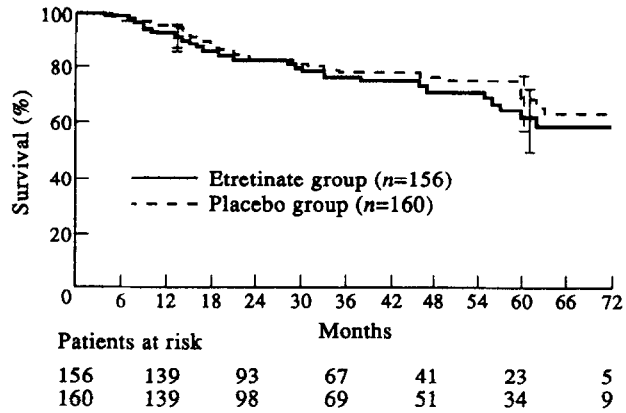

Figure 1. Kaplan–Meier survival estimation (95% confidence interval).

Table 3. Incidence of primary treatment failure

	Etretinate group (n = 156)	Placebo group (n = 160)
Disease progression		
Local	11	8
Regional	6	5
Local and regional	1	3
Distant	19	10
Lymph nodes	2	0
Lung	3	4
Liver	4	2
Bone	5	3
Skin	5	0
Brain	0	1
Miscellaneous	2	0

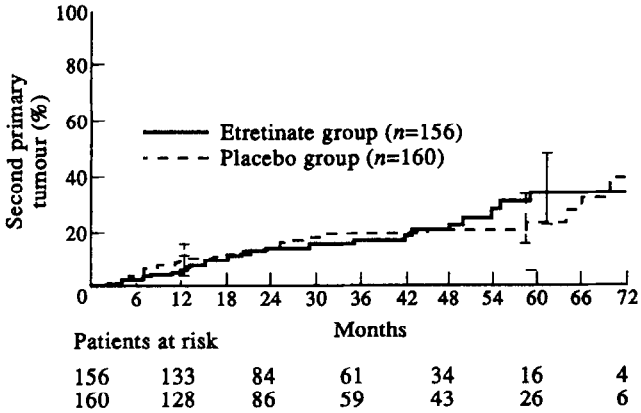

Figure 2. Kaplan–Meier second primary tumour estimation (95% confidence interval).

Toxicity and compliance

Seventeen per cent of the patients in the etretinate group have stopped their treatment temporarily versus 16% in the placebo group (NS). Adjuvant treatment was definitively discontinued in 33% of the patients in the etretinate group versus 23% for the placebo group ($P < 0.05$); the breakdown according to centres ranges from 6 to 50%. Twenty-five per cent of the patients in the etretinate group stopped taking the medication at 12 months versus 17% for the placebo group and, respectively, 33 versus 23% at 24 months.

Table 4. Site of second primary

	Etretinate group (n = 156)	Placebo group (n = 160)
Total number	28	29
Oesophagus	6	5
Stomach	0	1
Head and neck*	12	13
Colon–rectum	4	1
Lung	5	4
Pancreas	1	1
Bladder	0	2
Skin	0	2

*2 patients of 25 developed a second primary which appeared 2 cm or less from the primary at 10 months (T1 N0 of anterior pilar of the tonsil) and 17 months (T2 N0 of the tonsil). All the other second primaries occurred later than 6 months from the primary and were distant more than 2 cm.

The causes, as shown in Table 5, were due to biological or clinical toxicity, local or distant relapse, a second primary, intercurrent disease, lack of discipline. When the causes of toxicity were analysed (Table 6), significant differences were found for labial (19 versus 7%; $P < 0.001$), cutaneous (26 versus 7%; $P < 0.001$), ocular (7 versus 2%; $P < 0.03$), capilar (8 versus 3%; $P < 0.05$) and onycholysis (12 versus 1%; $P < 0.001$) toxicity of etretinate treatment. However, no difference was found between alkaline phosphatases, transaminases and triglyceridaemia with respect to biological toxicity.

DISCUSSION

This randomised, placebo-controlled study was launched to investigate the activity of etretinate, administered as adjuvant therapy, for improving overall survival and decreasing the occurrence of second primary after treatment of T1/T2, N0/1 < 3 cm squamous cell carcinoma of the oral cavity and oropharynx. Eighty-two per cent of the tumours were located in the oral cavity. Five per cent of the patients in the etretinate group (8/156) and 3% in the placebo group were given the adjuvant treatment, although they were not controlled after the completion of the primary treatment. In addition, 51 patients in the etretinate group (33%) and 36 in the placebo group (23%) did not complete the 24-month course of treatment because of clinical or biological toxicity, a relapse or other reasons. Finally, after a median follow-up of 41 months, neither the overall survival, nor the number of second primaries had altered. Overall survival curves were similar, and the percentage of second primaries at 3 years was 18% in both groups. In more than 75% of the cases, the second primary tumour occurred in the head and neck, oesophagus or lung, which is in keeping with the concept that the occurrence of neoplastic disease in these areas is tobacco-related [3].

These results are different from those of Hong who used a different retinoid [8]. In Hong's study, 103 patients who were disease free after primary treatment of stage I, II, III or IV squamous cell cancers of the larynx, pharynx or oral cavity were included. Only 49 patients were stage I or II, 20 in the isotretinoin group and 29 in the placebo group. They received either isotretinoine at 50–100 mg/m^2 surface area or placebo, prescribed for 12 months. The percentage of second primaries was, respectively, 4 and 24% ($P = 0.005$) after a median follow-up of 32 months. Thirty-three per cent of the patients in the isotretinoin group stopped their treatment because of drug toxicity compared with only 6% in the placebo group. Hong's study recorded whether patients had stopped smoking or not. This was not the case in our study, but the patients were asked to stop smoking in all the centres, and it is likely that the proportion of patients who continued to smoke was similar in the two groups; it is questionable that the discontinuation of smoking had an impact on the occurrence of second primary with such a short follow-up time. The percentage of patients with disease progression, either local, regional or distant was similar in the two groups. The percentage of patients who developed a second primary in the placebo group was also comparable at 24%. The percentage of patients who definitively discontinued their treatment was identical (33%), as was the pattern of clinical toxicity. The power of our trial is reasonable:

Table 5. Patients for whom adjuvant treatment was definitively discontinued according to study group

	Etretinate group (n = 156)	Placebo group (n = 160)	P value
Total	51 (33%)	36 (23%)	< 0.05
Cause			
Clinical biological toxicity	14	5	
Metastases relapse	13	5	
Second primary	8	10	
Local progression	5	5	
Complication of local treatment	3	1	
Intercurrent disease	5	4	
Lack of discipline	2	6	
Unknown	1	0	
Delay with date of randomisation			
0 months	2	0	
≤ 6 months	18	15	
≤ 12 months	39	27	
≤ 18 months	48	32	
≤ 24 months	51	36	

*$P < 0.05$.

Table 6. Incidence of toxic effects

	Etretinate group (n = 156)	Placebo group (n = 160)	P value
Toxic effect*	79 (51%)	42 (26%)	< 0.001
Cheilitis	(19%)	(4%)	< 0.001
Cutaneous†	(26%)	(7%)	< 0.001
Conjunctivitis	(7%)	(2%)	< 0.03
Oral‡	(12%)	(12%)	NS
Digestive§	(4%)	(3%)	NS
Alopecia	(8%)	(3%)	< 0.05
Onycholysis	(12%)	(1%)	< 0.001
Rhinorrhoea	(2%)	(0%)	NS
Miscellaneous	(2%)	(3%)	NS

*The most severe effect in each patient is listed. The percentage of the different types of toxicity is higher than the percentage reported in each group of patients, since different types of toxicity may occur in the same patient. †Cutaneous toxicity includes cutaneous rash, pruritis, erythema, skin dryness, squamous skin. ‡Oral toxicity includes mucositis, glossitis, gingivitis. §Digestive toxicity includes gastralgia, oesophagitis, dysphagia, vomiting.

with 150 patients per group, the probability of detecting a decrease of the 3-year second-rate tumour from 20 to 15% is 25%, and respectively, 73% from 20 to 10% with a 5% alpha value, and 98% from 20 to 5% with the same alpha value, which corresponds to the difference observed by Hong.

Despite its presumed superior therapeutic index, the efficiency of etretinate has to be questioned in relation to that of *trans*-retinoic acid which is thought to be the most useful retinoids [19]. All *trans*-retinoic acid is a ligand for nuclear receptors that regulate gene function [20, 21], as is etretinate, but its binding to RARα measured by competition is higher than etretinate [22].

Thus, the long-term results of other trials including retinoids or natural vitamin A (retinyl palmitate) are awaited with interest before promoting chemoprevention in daily practice, as adjuvant treatment of cured head and neck cancer patients, since no other trials have been published [23, 24]. A new trial is ongoing in Houston, with low dose 13-*cis*-retinoic acid. Its aim is to prevent second primary tumours in patients presenting with early stage head and neck carcinoma; 1000 patients are needed. In Europe, a joint venture of the EORTC Lung Cancer and Head and Neck Cancer Cooperative Groups was set up in 1988 [25]. Eligibility criteria include being previously treated for squamous cell cancer of the larynx (Tis, T1-2-3, N0-1), squamous cell cancer of the oral cavity (T1-2, N0-1), or non-small cell lung cancer (pT1-2, N0-1 and T3N0). Four treatment arms are planned in a 2 × 2 factorial design, to increase efficiency and power: retinyl palmitate and *n*-acetyl-cysteine, retinol palmitate, *n*-acetyl cysteine and no treatment. As of June 1992, 1507 patients were entered out of the 2000 required. In order to develop effective chemo-

prevention strategies for patients who had a first cancer, other trials will have to answer other questions regarding the choice of retinoid, the optimal dose (high versus low dose), the optimal schedule, the optimal schedule and duration of treatment and, particularly, the type of combined modality (single agent versus combination with cytokines).

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