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Chemoprevention in the Management of Oral Cancer: EUROSCAN and Other Studies

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INTRODUCTION

SECOND PRIMARY tumours constitute a major problem in patients with squamous cell cancer of the head and neck. They occur in 15–30%, mainly in the upper aerodigestive tract [1–3]. The majority occurs more than 6 months after the index tumour and are called "metachronous"; when they occur within 6 months "synchronous." They occur more in males than in females and usually have a bad prognosis because they often occur at bad sites (lung/oesophagus) or in already treated areas rendering curative treatment difficult or impossible. In certain early stage diseases such as T1NO laryngeal cancer the risk of death from a later lung cancer is greater than from the primary disease. For this reason second primary tumours are regarded as the "overshadowing threat" to early stage head and neck cancer patients [4]. Second tumours are one of the main reasons that despite many advances in the treatment of head and neck cancer (e.g. in reconstructive surgery or combined treatment modalities), long time survival has only marginally increased in the past decades. Interest in the phenomenon has increased. During the past 10 years much has become known of their aetiology and pathogenesis, frequency and preferred sites. Research on the value of screening and (chemo)prevention has taken place and is still in progress. Next to many similarities, important differences are present for the four sites: oral cavity, oro- and hypopharynx and larynx, with regard to site relationships, frequency and geographic differences in it and clinical differences. For example, in laryngeal cancer, many patients present with early stage disease and have higher than 90% 5 year survival rates, making early detection or prevention measures relatively more important than in oral cancer, oro- and hypopharyngeal cancer in which many patients present with advanced disease. In addition, preferred sites have been documented; in laryngeal cancer more than half of all second tumours occur in the lung, whereas in the three other sites they occur spread over the whole of the upper aerodigestive tract. In this paper, we will focus on the problem of second tumours in oral cancer with emphasis on the role of chemoprevention.

AETIOLOGY AND PATHOGENESIS

The pathogenesis of oral cancer is multifactorial determined and the same factors that caused the first tumour, such as tobacco and alcohol, influence the development of a second tumour as well [5–10]. In addition, genetic susceptibility [11–14] plays a role. It is very likely that these same factors play a role in the aetiology of a second and subsequent tumours as well.

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FREQUENCY OF MULTIPLE PRIMARY TUMOURS IN ORAL CANCER

The frequency of second tumours in oral cancer is comparable with that of oro- and hypopharyngeal cancer but definitively higher than in laryngeal cancer. Few studies are devoted to second tumours of index tumours of the oral cavity alone. The reported frequencies for oral cancer is 7.1–30.0% (Table 1, refs 1, 2, 15–21). In one series in oral cancer, a division was made of the location of the index-tumour within the oral cavity [19]. The series showed that more second tumours occur in index-tumours of the floor of the mouth, inferior alveolar process and retromolar trigone, than in the rest of the oral cavity. These findings have as yet not been confirmed by others.

MANAGEMENT OF SECOND PRIMARY TUMOURS

As an adjunct to changes in life style (cessation of smoking and drinking, dietary habits), two approaches will be discussed: early detection and (chemo-)prevention.

Early detection

In many centres panendoscopy is performed routinely during the initial work-up of oral malignancy [22–28]. Although in some studies high frequencies of synchronous tumours were found, meta-analysis has shown that only a maximum 2% was detected by panendoscopy only; implying that its cost-effectiveness has to be kept constantly in mind. It is rational to perform panendoscopy only in the highest risk groups, whereas it is irrational in patients of old age, with advanced disease, in poor general condition or with large tumours with risk of airway obstruction.

To complicate the problem, the majority of second tumours occurs metachronously. Since biannual panendoscopy is unfeasible, restricting screening to lung cancer could be considered. The usual screening during follow-up is a once or twice yearly chest X-ray, but its value is questionable [29–33]. Biannual bronchoscopy and sputum cytology is possibly more effective. In oral cancer, such studies have yet to be performed. However, data on laryngeal cancer can possibly shed light on whether this kind of follow-up could be useful in oral cancer.

In a multicentre study in the Netherlands, the effectiveness of bronchoscopy twice a year in patients with laryngeal cancer as an adjunct to routine follow-up was investigated [34]. In 170 selected patients 500 bronchoscopies were performed. 5 (2.8%) male patients developed lung cancer after a follow-up of 34 months. In only 2 of them was the diagnosis made by bronchoscopy. After treatment, both developed a recurrent lung cancer. Rodriquez *et al.* [35] performed twice yearly bronchoscopy in 286 patients with laryngectomy for laryngeal cancer. In 36 patients (12.5%) lung cancer was found after a

Table 1. Oral cancer: frequency, site and time sequence of second primary tumours

Reference	n	SPT n (%)	UADT n (%)	SYN %	META %
15	3443	248 (7.1)	110 (3.2)	—	—
1	158	28 (17.7)	24 (15.1)	—	—
16	337	101 (30.0)	82 (24.3)	—	—
2	152	26 (17.1)	22 (14.4)	—	—
17	138	17 (12.5)	—	5.6	8.7
18	1551	287 (18.5)	135 (8.7)	7.9	10.5
19	210	38 (18.0)	23 (11.0)	1.9	16.1
20	437	57 (13.0)	46 (10.5)	6.1	6.9
21	728	127 (17.4)	97 (13.3)	7.4	10.0

SPT = second primary tumour; UADT = upper aerodigestive tract; SYN = synchronous; META = metachronous.

3-year follow-up. In 6 of the 36 patients the diagnosis of lung cancer was based on bronchoscopy only.

In conclusion, the extra burden for patient and personnel and the cost-effectiveness does not justify routine bronchoscopy in the follow-up of laryngeal cancer. In oral cancer the total frequency of second primary tumours is higher than in laryngeal cancer, but the percentage of secondary tumours in the lung is lower. Therefore, periodic bronchoscopy in oral cancer is unjustified.

Since screening in the follow-up is not useful in the total group of patients, it is to be investigated whether in the future a better identification of patients "at risk" may justify endoscopy in subgroups. Such risk factors could be based on gender, smoking and drinking habits, differences in HLA antigens, immunoglobulin allotypes, vitamin A and beta-carotene serum levels and DNA damage repair deficiencies [11–14, 36, 37]. Research into markers of mucosa at risk is also of importance [38].

Chemoprevention

Chemoprevention, defined as intervention in the process of carcinogenesis with dietary or chemical agents with the aim to prevent or delay the development of cancer, offers an attractive alternative. Several clinical chemoprevention trials with beta-carotene, vitamin A and other retinoids or with agents working along other mechanisms are at present being carried out (ref. 39, Table 2). Curatively treated early stage head and neck cancer patients form an ideal population to test chemopreventive medication because of the extremely high risk. Three studies will be discussed. In two of these studies all sites within the head and neck were eligible, in one (EUROSCAN) only the oral cavity and larynx were eligible.

M.D. Anderson study

Hong *et al.* [39] at M.D. Anderson published the results of the use of 13-*cis*-retinoic acid (isotretinoin) 50–100 mg/m^2 of body surface area during 12 months in cured head and neck cancer patients. All stages and all the four sites (oral cavity, oro- and hypopharynx and larynx) were eligible. Of the 103 patients, only 2 (4%) second tumours occurred after a follow-up period of 32 months in the isotretinoin group ($n = 49$), as compared with 12 (24%) in the placebo group ($n = 51$). After 42 months these frequencies have increased to 6 (3/49) vs. 28% (14/51). These data showed for the first time that chemoprevention of second tumours in head and neck cancer is possible. However, the series was limited and the number of second tumours in the placebo group (24%) was exceptionally high (5–10% was expected after 32 months), whereas the number of second tumours (4%) in the treated patients was exceptionally low. These encouraging data need to be confirmed by other studies. In addition, the toxicity of 13-*cis*-retinoic acid 50–100 mg/m^2 was considerable. Hong and coworkers activated a new trial in November 1991, with low dose (30 mg) 13-*cis*-retinoic acid, in which 1000 early stage patients will be included.

Gettec study

In France the Gettec is performing a chemoprevention study in 323 patients (260 oral cavity and 62 oropharyngeal cancers), randomised between standard follow-up or follow-up and Etrenitate (beta-all-*trans* retinoic-acid, Tigason) in a dose of 50 mg in the first month and 25 mg in the following 23 months. Patients were entered from 1985 and entrance was stopped in December 1991.

EUROSCAN

The by far largest chemoprevention study in early stage head and neck cancer is EUROSCAN [40, 41]. This European study will be discussed in detail. EUROSCAN is an EORTC chemoprevention study in curatively treated patients with oral cancer, laryngeal cancer and lung cancer which started in June, 1988. As chemopreventive drugs retinyl palmitate 300 000 IU daily during 1 year and half this dose during the second year, or *N*-acetylcysteine 600 mg for 2 years, or both the drugs or neither of them are being used, in a 2 × 2 factorial design. The rationale for the choice of these two drugs will be discussed.

Vitamin A

In vivo, in vitro and in nutritional epidemiological studies, vitamin A and its precursor beta-carotene have been found to protect against epithelial cancer [42–44]. A higher risk of lung cancer has been found in individuals with low intake and/or

Table 2. Chemoprevention trials in head and neck cancer

Institute	Year	Stage	Site*	Drug/dose	n	Result
MD Anderson	1984–1990	All	All	13-*cis*-RA 50–100 mg/m^2	103	+
Gettec	1985–1991	Early	Oral cavity, oropharynx	Etrenitate 50 → 25 mg	323	Awaited
EUROSCAN	1988–1993	Early	Oral cavity, larynx, lung	Retinol 300 000 IU	1500 of 2000	
				NAC 600 mg	entered	Awaited
Connecticut	1990 →	Early	All	beta-carotene 50 mg	600 planned	Awaited
MD Anderson	1991 →	Early	All	13-*cis*-RA 30 mg/m^2	1000 planned	Awaited
EUROSCAN II	1993 →	Early	All	To be announced	4000 planned	

*All sites: oral cavity, oro- and hypopharynx and larynx.

serum levels of retinol or beta-carotene [45–48]. In several studies low serum levels of vitamin A and/or beta-carotene were correlated to with head and neck squamous cell cancer and/or lung cancer [49–51]. Serum levels of vitamin A showed to be lower in patients with head and neck cancer with ($n=24$) than without ($n=71$) second primary tumours [36].

Vitamin A has proven to be a relatively safe, non-toxic drug, even when given in high doses and for long periods [52, 53]. Retinol palmitate (EUROSCAN) has been used for many years for skin diseases with acceptable side effects and the dose of 300.00 IU daily is partly based on this experience, and in part on its efficacy in the treatment of oral leucoplakia [53]. This dose yields justifiable side effects with comparable response rates as higher doses.

N-Acetylcysteine

N-Acetylcysteine (NAC)—a precursor of glutathione [54]—has attracted attention as a possible chemopreventive agent. It has potent anti-oxidant/detoxificant properties. *In vitro*, NAC inhibits mutagens such as aflatoxin, benzpyrene and cigarette-smoke condensate [55–57]. It prevents chemically induced lung and colon tumours in experimental animals. NAC added before and after the carcinogen exposure significantly reduced the incidence and multiplicity of lung tumours in mice and of colon tumours in the rat [58, 59]. NAC is safe and does not have major side effects.

Vitamin A and N-acetylcysteine

NAC is supposed to act in early stages of carcinogenesis: before and possibly shortly after the occurrence of DNA damage; vitamin A later: in the promotion and progression phases. NAC as well as vitamin A could be active as single drug, while the combination theoretically cover almost the whole carcinogenic process, whereas no interaction with regard to side effects is expected.

End points in chemoprevention trials

The normal endpoints in trials are malignancy: the number of local/regional recurrences, distant metastases and second primary tumours. In chemoprevention trials not only the frequency of malignant events but also when they occur (has chemoprevention led to delay of the development of malignancy?) is of importance. With larger series, survival can be taken as the endpoint. However, as compared with standard phase III chemotherapy trials, in chemoprevention trials many more patients are needed, with more costs and longer follow-up, because, depending on the population under study, only a very small minority will eventually develop malignancy in the study period. Even when a positive effect has been found with a given drug in a certain dose administered during a certain period, it is not known if this drug, dosage and time period of administration, are optimal with the least possible side-effects and toxicity. Although malignancy is without doubt the "hardest" endpoint in chemoprevention trials, there is a need for a process to test more drugs (or combinations), doses and schedules in small effective trials.

In the USA, much effort at present therefore is devoted to the development of so-called biomarkers as intermediate endpoints in chemoprevention trials [60]. It is hoped that biomarkers eventually will be identified which are related to epithelial carcinogenesis and which can serve as "surrogate" endpoint in the conduct of future chemoprevention trials. They would enable us to perform more chemoprevention studies with fewer patients, less costs and in a shorter time, than studies that use malignancy as the endpoint.

End points in EUROSCAN

The endpoints of EUROSCAN are the number and time of occurrence of second tumours, local/regional recurrence and distant metastases. In addition, long term survival rates are included. For this latter reason, 2000 patients are needed.

In EUROSCAN, the study of biomarkers as intermediate endpoints is as yet not included routinely in all patients. However, in subgroups the feasibility of panels of markers is being tested. Although from a research point of view it appears attractive to incorporate biomarker research in all EUROSCAN patients, however, it has to be realised that it is uncertain whether valid biomarkers will ever be found. EUROSCAN has in addition a logistic problem. Collection, transport and analysis from material for research into biomarkers as intermediate endpoints from all patients brought in from 63 institutes out of 14 countries would cost an enormous amount of money and effort.

Accrual as per 1 June 1992

The study started on 1 June 1988. The following data were as on 1 June 1992. On 1 June 1992, 1487 of the planned 2000 patients had entered the study. On average, 40–50 new patients are entered per month. The accrual of the last 500 patients will end in early 1993. There are 63 cancer centres from 14 European countries entering patients.

Centres for the Netherlands (535 patients), Italy (468), Germany (98), Spain (74), Yugoslavia (66), Belgium (56), Czechoslovakia (48), Turkey (34), France (32), Poland (28), Portugal (17), Hungary (9), Great Britain (17) and Norway (1) brought patients into the trial. Of the patients 39% had lung cancer, 61% had head and neck cancer, 70% with laryngeal cancer and 30% with oral cancer.

In 1115 patients with sufficient follow-up per 1 June 1992, there was no evidence of disease in 960 patients, local/regional recurrence in 82 patients, distant metastases in 47 patients, local and distant metastases in 7 patients, whereas second primaries were found in 19 patients.

Side effects and toxicity of retinyl palmitate

Pastorino *et al.* [61, 62] reported on the side-effects of retinyl palmitate (300000 IU daily for at least 12 months, the same dose as in the first year of EUROSCAN) administration as adjuvant treatment for resected stage Ia lung cancer. After a median follow-up of 28 months, 283 patients could be evaluated: 138 allocated to treatment with retinyl palmitate and 145 to standard treatment. The clinical results available justify a continuation of this dose of vitamin A. Skin dryness and desquamation were the most frequent symptoms, affecting 60% of the treated patients. Other symptoms such as dyspepsia, headache, nose-bleeds and mild hair-loss occurred in less than 10% of patients and were self terminating. Only in 4 (3%) patients the treatment had to be interrupted because of symptoms potentially related to vitamin A administration. It was concluded that high dose retinyl palmitate administration is a well-tolerated and safe treatment.

Side effects and toxicity in EUROSCAN

The following reporting of side-effects is preliminary; the majority of patients have not reached the end of the intervention period. At all follow-up visits a questionnaire regarding

the side-effects dryness, desquamation, itching, headache, dyspepsia, nose-bleeds, hair-loss or others is filled in. All side-effects even mentioned only once, are then fed into the computer. Side-effects noted in this manner in 1115 patients with sufficient follow-up as per 1 June 1992 for the three treatment arms of the total of four arms [(1) vitamin A and NAC ($n=286$); (2) vitamin A ($n=288$); (3) NAC ($n=279$) and (4) no drugs ($n=262$)] were as follows: No side effects were found for the three treatment arms in 53.5, 58.7 and 79.1%, respectively. Present, but well tolerated side effects were found in 28.7, 26.0 and 13.4%, respectively. Poorly tolerated side-effects were noted in 5.6, 5.9 and 3.6%, respectively. Unbearable side-effects were noted in 12.2, 9.4 and 4.0%, respectively. The most common side-effects were mucocutaneous complaints, headache and dyspepsia. It can be concluded from this intermediate analysis of side-effects and toxicity that both the single drugs, as well as the combination treatment is well tolerated and that the toxicity is mild as compared with the earlier mentioned intervention scheme as used by Hong *et al.* [39].

CONCLUSION

In the management of second primary tumours in head and neck cancer chemoprevention is more promising than intensified screening. It is gradually developing from an interesting experimental model to a realistic adjuvant treatment. The data from Hong *et al.* [39] need confirmation by larger studies using less toxic but hopefully equally effective drugs. In Europe, the EUROSCAN study is running successfully and it might confirm that this still experimental treatment is becoming a realistic intervention in cured head and neck cancer patients. Results of this study and of the GETTEC study are awaited in the coming years. When positive results are obtained, in the future chemopreventive agents might be routinely applied in these extremely high risk patients. The ideal drug or drug combination, the dose and the duration have still to be established.

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