Head and neck and lung cancer

Approximately 5% of all cancers develop in the mucosa of the head and neck area (Boyle et al., 1990). A substantial number of these patients present at a moment that curative treatment is possible, due to the fact that many head and neck cancers cause complaints in an early stage. The prognosis of T1N0 and T2N0 glottic laryngeal cancer, for instance, is in the order of 90 and 70% 5 year survival respectively.

It is very likely that the pathogenesis of head and neck cancer is multifactorial. Both tobacco and alcohol are important risk factors in oral, oropharyngeal, hypopharyngeal and laryngeal cancer (Wynder et al., 1956, 1976; Williams & Horn, 1977; Tuyns, 1979; Rothman et al., 1980). In addition, it is very likely that an individual genetic susceptibility (de Vries et al., 1987a, 1987b; Schantz & Hsu, 1989; Spitz et al., 1989) is important if only because so many individuals have been and are being exposed to tobacco and alcohol, whereas only relatively few actually develop cancer in the upper air- and food passages. Patients with head and neck cancers are prone to develop multiple primary cancers (see further), probably because the mucosa of the upper air and food passages is being exposed to the same carcinogens.

The situation in lung cancer patients is different from that of head and neck cancer patients. Lung cancer is the leading cause of cancer deaths in men and the second leading cause of cancer deaths in women, after cancer of the breast. The major factor in the development of lung cancer is the inhalation of tobacco smoke, by susceptible hosts. In contrast to head and neck cancer patients, most lung cancer patients already have a poor prognosis at the time of diagnosis. The 5 year survival rate for all stages of lung cancer has been about 9% for the last 20 years. This small subpopulation of patients that will be cured from their lung cancer are unfortunately prone to develop second primary cancers as well.

Multiple primary tumours occurs in 10–30% of all patients with head and neck cancer and in 10% of patients with lung cancer (Vrabec, 1979; Gluckman & Crissman, 1983; Pepperman & Fitzpatrick, 1981; Gluckman, 1983; Wagenfeld et al., 1981; Hordijk & de Jong, 1983; de Vries & Snow, 1986; de Vries et al., 1986; De Vries, 1990, and many others). The great majority of these second primary cancers occur metachronously in the respiratory tract and upper digestive tract.

These second primary tumours usually carry a bad prognosis because they often occur either at notoriously bad sites, like (again in) the lung or esophagus, or within primarily treated areas within the head and neck, defying curative treatment. Improvements in local/regional control rates in head and neck cancer patients have not resulted in a proportional increase in survival rates in these patients. The reason for this is that as fewer patients die from uncontrolled disease in the head and neck, more patients are exposed to the risk of second primary tumours (and distant metastases) (Goepfert, 1984). Second tumours are the most important cause of death in cured (early stage) head and neck cancer patients.

In principle, two approaches are possible to combat the problem of second tumours in head and neck and lung cancer patients: early detection and (chemo-)prevention. Regarding early detection, it has become common practice at many centres to perform panendoscopy during the initial work-up of head and neck cancer patients. However, most second tumours occur metachronously. Regular, e.g. half yearly panendoscopy has been shown to be not feasible. As a result many second tumours are still being detected beyond a curable stage during follow-up.

Chemoprevention

Chemoprevention offers a more attractive approach. Many animal, in vitro and epidemiological studies have shown a protective effect of Vitamin A and the other retinoids (the synthetic and natural analogs of Vitamin A). Several clinical chemoprevention trials with beta-carotene, Vitamin A and other retinoids are at present being carried out. Chemopreventive agents working along other mechanisms are also currently being tested.

In general, two different approaches are used in chemoprevention trials. In many trials in the United States, relative low doses of retinoids, or vitamin A, beta-carotene or both are administered, aiming at restoration to normal levels. This approach is used in persons at relatively low risk, with high compliance, and has little risk of side effects or serious toxicity. The other approach is to use high doses, in which more activity at promotion/progression phases of cancer development is to be expected. This approach is better suited for high risk groups. Side-effects can be expected, but doses are kept below the threshold above which serious toxicity can be expected.

Curatively treated and early stage head and neck cancer and lung cancer patients form an ideal population to test the value of chemopreventive medication because of the extremely high risk to develop second tumours. In these high risk groups, three interesting chemopreventive studies were initiated several years ago, which will be discussed.

M D Anderson study

Hong et al. (1990) from the M D Anderson Institute recently published the results of their study in cured head and neck cancer patients in which 13-cis-retinoic acid (isotretinoin) 50–100 mg m⁻² of body surface area during 12 months was
used. In this study in which 103 patients were entered, only two second tumours occurred in the isotretinoin group, as compared to 12 (24%) in the placebo group. These data showed for the first time that chemoprevention of second tumours in head and neck cancer patients is possible. In spite of these exciting results, a word of caution is warranted for four reasons:

(a) The toxicity of 13-cis-retinoic acid in the dose used, was considerable and defies further treatment with 13-cis-retinoic acid in this dose. One of the conclusions of the authors was that further research into the use of lower doses of 13-cis-retinoic acid or other less toxic medication (such as Vitamin A) is needed.

(b) The number of patients in the study was limited.

(c) The number of second tumours in the untreated group (24%) after 32 months is exceptionally high (one would expect 5–10% after 30 months), whereas the number of second tumours (2%) in the untreated patients is exceptionally low. These results are almost too good to be true and one wonders whether the results are due to the treatment effect only, or whether a coincidental factor—especially in the placebo group—is playing a role. The encouraging data from this study therefore need to be confirmed by other studies.

(d) All stages of head and neck cancer patients were eligible instead of early stage patients only. In general, chemoprevention is especially indicated in early stage head and neck cancer patients since these patients have the best prognosis with regard to their ‘index’-tumour, whereas the prognosis is advanced stage cancer patients is relatively more dependent on the primary tumour itself.

The Milan Trial

A randomised chemoprevention trial in lung cancer patients was initiated in 1984 at the National Cancer Institute of Milan, and started in July 1985 (Pastorino et al., 1991b). Patients with pathological diagnosis of stage 1 (T1-T2, N0, M0) non-small cell lung carcinoma after complete surgical resection were selected for entry. Aims of the trial were (a) to investigate the tolerability of high dose retinol palmitate (vitamin A) administered for a long period of time; (b) evaluate the effect of retinol palmitate on the frequency of recurrences of initial lung cancer; (c) evaluate the efficacy of retinol palmitate to prevent or delay the occurrence of second primary cancers. Patients were randomly assigned to either vitamin A treatment or control without treatment, stratified according to histological cell type (squamous vs non-squamous) and previous cancer at another site (absent vs present). The accrual was closed in 1989, and follow-up of all patients was updated in July 1990. Between July 1985 and October 1989, 313 patients entered the trial and 307 were evaluable for the analysis: 150 in the treatment arm and 157 in the control arm. At a median follow-up of 29 months, a total of 113 (37%) patients failed after treatment: 47 (31%) in the treated arm and 66 (42%) in the control arm (P = 0.051). A total of 35 second primary cancers were detected in 32 patients: 14 (9%) in the treatment arm and 21 (13%) in the control arm. Three patients in the control arm developed more than one second primary tumour and another patient had both a recurrence and a second primary tumour. Excluding those second primary tumours which were clearly unrelated to the chemoprevention target (colon, prostate, melanoma), the total number of patients who failed was 43 vs 63 (P = 0.035). The probability of disease-free survival (time to recurrence or second primary cancer) at 5 years resulted in 61 vs 48% in favour of the treatment arm (P < 0.05) and the overall estimated survival at 5 years was 66% vs 57% (P = 0.3). The authors concluded from this preliminary analysis that daily oral administration of retinol palmitate was effective in reducing the number of cancer failures and improving the disease-free survival in patients curatively resected for stage I lung cancer, although it did not significantly reduce the incidence of second primary tumours. A longer follow-up will be necessary to provide a clearcut demonstration of the chemopreventive potential of high-dose vitamin A in this patient population.

Euroscan

A further, much larger chemoprevention study in head and neck cancer and lung cancer patients is EUROSCAN (EUROSCAN Steering Committee, 1990; de Vries et al., 1990). EUROSCAN is an European chemoprevention study in curatively treated patients with oral cancer, laryngeal cancer and lung cancer which started in June 1988 under the responsibility of the European Organisation of Research and Treatment of Cancer (EORTC). In contrast to Hong’s et al. (1990) study, in EUROSCAN only early stage patients are eligible. As chemopreventive drugs Retinyl Palmitate 300,000 IU daily during 1 year and half this dose during a second year, or N-acetyl-cysteine 600 mg during 2 years, or both drugs or neither are being used, in a 2 x 2 factorial design (Stampfer, et al., 1985). 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 be protective against the development of epithelial cancers (Peto et al., 1981; Colditz et al., 1987; Byers, 1988).

Epidemiological studies have shown a higher risk of lung cancer in individuals with low intake and/or serum levels of retinol, or beta-carotene (Ziegler et al., 1984; Byers et al., 1984; Menkes et al., 1986; Middleton et al., 1986).

Several serum studies have found that low serum levels of vitamin A and/or beta-carotene are correlated with head and neck squamous cell cancer and/or lung cancer (Bichler & Daxenbichler, 1982; Fex et al., 1986; Friedman et al., 1986). We recently compared serum levels of vitamin A, vitamin E and beta-carotene in patients with head and neck cancer with and without second primary tumours (SPT’s) (de Vries & Snow, 1990) and it was found that in 24 head and neck cancer patients with SPT’s the serum levels of vitamin A were lower than in 71 patients with single head and neck cancers.

It was felt that safe drugs were needed in an experimental, large scale study as EUROSCAN was meant to be. Vitamin A has proven to be a relatively safe and non-toxic drug, even when given in high doses and for a long period (Silverman et al., 1963; Bendich et al., 1989). Retinol Palmitate in an emulsified form has optimal features with regard to intestinal absorption, availability from the tissue, with limited liver toxicity. It has been used for many years for skin diseases with acceptable side effects. Based on experience in skin diseases such as psoriasis, ichthyosis and skin cancer, the dose of 300,000 IU daily yields justifiable side effects with comparable response rates as in higher doses.

N-Acetylcysteine

N-Acetylcysteine (NAC) has attracted attention as a possible chemopreventive agent (van Zandwijk, 1991). NAC is a precursor of extracellular and intracellular glutathione (GSN) (de Flora et al., 1985; Cotgreave et al., 1986) and it is widely used in the treatment of patients with chronic bronchitis and emphysema. It has become popular for its potent anti-oxidant/de-toxicant properties. NAC is for instance effective treatment for preventing fatal oxidative liver damage in paracetamol poisoning (Prescott et al., 1979). NAC has also been shown to give local protection of the urinary tract against phosphamide and cyclophosphamide induced toxicity (Fuchs et al., oral, palmitate-NAC, E). NAC is able to inhibit mutagens such as aflatoxin, benzpyrene and cigarette smoke condensate (de Flora, 1984, de Flora et al., 1984, 1989). It prevents chemically induced lung and colon tumours in experimental animals. NAC added before and after the car-
cinogen exposure significantly reduced the incidence and 
multiplicity of lung tumours in mice and of colon tumours in 
the rat (de Flora et al., 1986; Wilpart et al., 1986). Evidence 
has also been provided for the ability of NAC to inhibit 
DNA adduct formation by either ingested or inhaled carcino-
gens (de Flora et al., 1991). The results suggest that it is 
possible to prevent chemically induced cancers by drugs that 
raise the levels of physiologically trapping agents such as 
GSH and that NAC should at least be effective at the 
initiation stage of carcinogenesis. The significance of anti-
oxidant protection is also underlined by the confirmation of 
an association between low levels of serum vitamin E and the 
risk of lung cancer (Byers et al., 1984). Thus, the restoration 
of physiological levels of trapping agents in patients who 
have already had a tumour seems to be an important first 
step in the prevention of a second tumour. The anticarci-
ogenic effect of NAC is of particular interest since as men-
tioned earlier, the drug is safe, without major side effects at 
the dose of 600 mg/daily and it had been widely used in the 
treatment of patients with chronic lung disease (Ferrari, 1980).

Vitamin A and N-acetylcysteine

The combination of the two drugs was chosen for the follow-
ing reasons. NAC is supposed to be active in early stages of 
carcinogenesis: before and possibly shortly after the occur-
rence of DNA damage. Vitamin A is thought to act late in 
carcinogenesis: in the promotion and progression phases. 
NAC as single drug could be active as well as vitamin A, 
while the combination theoretically covers almost the whole 
carcinogenic process. No interaction with regard to side 
effects are expected from the combination.

End points

In total 2,000 patients are planned because the endpoints of 
EUROSCAN do not only consist of the number of second 
tumours, local/regional recurrence and distant metastases, 
but also include long term survival rates.

In the United States of America, much effort at present is 
devoted to the development of so-called biomarkers as inter-
mediate endpoints in chemoprevention trials (Lippman et al., 
1990; Schatzkin et al., 1990). 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 much more chemoprevention studies 
with less patients, less costs and in less time, than studies that 
use malignancy as the endpoint.

In EUROSCAN study of biomarkers as intermediate end-
points is as yet not included. Although from a research point 
of view it appears attractive to incorporate research into 
biomarkers as intermediate endpoints in EUROSCAN, it has 
to be realised that it is uncertain whether valid biomarkers 
will ever be found. Until that time, trials using malignancy as 
endpoint will provide the most valuable information.

Accrual per June 1990

The study started on 1 June 1988. The following data were as 
on 1 June 1991. Eight hundred and fifty-three of the 2,000 
patients planned had entered the study at that time. The 
mean accrual at present is 40 new patients per month. The 
accrual is still rising: in 1988, 31 patients; in 1989, 135 
patients; in 1990, 461 patients and in 1991 until 1 June, 226 
patients were entered. It is estimated that the accrual of 
the next 1,150 patients will take another 2–3 years.

More than 30 cancer centres from 13 European countries 
are entering patients. Centres from The Netherlands (313 
patients), Italy (290), Germany (62), Spain (51), Belgium 
(34), Yugoslavia (29), Poland (20), Czechoslovakia (17), 
Turkey (12), Hungary (9), Portugal (8), France (5) and Great 
Britain (3) had brought patients in the trial.

The division in the head and neck cancer patients (n = 506) 
for the different sites was as follows: glottic laryngeal cancer, 
227 patients; subglottic laryngeal cancer, 4 patients; supra-
glottic cancer, 84 patients and oral cancer, 141 patients. Of 
the lung cancer patients (n = 347), there were 210 squamous 
cell cancer and 137 non-squamous cell carcinomas.

In 554 patients with sufficient follow-up per 1 June 1991, 
no evidence of disease in 476 patients, local recurrence in 46 
patients, distant metastases in 19 patients, local and distant 
metastases in two patients and second primaries in 11 
patients were found.

Side effects and toxicity

Retinyl Palmitate

Pastorino et al. (1991a) reported on the side-effects of Retinyl 
Palmitate (300,000 IU daily for at least 12 months, the same 
dose as in the first year of EUROSCAN) administration as 
adjvant treatment for resected stage I lung cancer. After a 
median follow-up of 28 months, 283 patients could be evalu-
ated: 138 allocated to treatment with Retinyl Palmitate and 
145 to standard treatment. The clinical results available do 
well justify a continuation of vitamin A in this dose. Skin 
dryness and desquamation were the most frequent symptoms, 
affecting 60% of the treated patients. Other symptoms such 
as dyspepsia, headache, nosebleeds and mild hairloss occur-
red in less than 10% of patients and were self terminating. 
Only in four (3%) patients the treatment had to be inter-
rupted because of symptoms potentially related to vitamin A 
administration. It was concluded that high dose Retinyl Pal-
mitate administration is a well-tolerated and safe treatment.

EUROSCAN

The side-effects in the 554 patients with sufficient follow-up 
as preliminary noted per 1 June 1991 for the four treatment 
arms [(1) Vitamin A and NAC (n = 135); (2) Vitamin A 
(n = 143); (3) NAC (n = 140) and (4) no drugs (n = 136)] 
were as follows:

No side effects were found for the four treatment arms in 
55, 64, 82 and 99 patients, respectively.

Present, but well tolerated side-effects were found in 25, 21, 
12 and 0 patients, respectively.

Poorly tolerated side-effects were noted in 14, 9, 2 and 0 
patients, respectively.

Unbearable side-effects were noted in 14, 9, 2 and 0 
patients, respectively. The most common side-effects were 
dryness, desquamation and itching of the skin, headache and 
dyspepsia.

It can be concluded that this intermediate analysis of side-
effects and toxicity in the first 554 patients of EURO-
SCAN has shown that both the single drugs, as well as the 
combination treatment is well tolerated and that the toxicity 
is mild and compares favourably with the earlier mentioned 
treatment scheme as was used by Hong et al. (1990).

Conclusion

Chemoprevention of second primary tumours in head and 
neck cancer patients and in lung cancer patients (Pastorino 
et al., 1988) respectively, is developed from an interesting theo-
retical model into a realistic adjuvant treatment. The exciting 
data from the study performed by Hong et al. (1990) need 
confirmation by larger studies, using drugs less toxic while 
hopefully equally effective.

The EUROSCAN study is until now running successfully
throughout Europe. It is to be hoped that it will give an answer whether this at present still experimental treatment modality will eventually develop into a realistic intervention in cured head and neck cancer and lung cancer patients. When this will be so, it might be that in the future chemopreventive agents will be routinely applied in these extremely high risk patients. At present however, the ideal drug or drug combination, the dose and the duration of administration, have still to be established.

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