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Chemoprevention of Second Primary Tumours in Head and Neck Cancer in Europe: EUROSCAN

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INTRODUCTION

In 1988 the European chemoprevention study EUROSCAN on the prevention of second primary tumours in patients with head and neck, or lung cancer, began. The end of the accrual phase is in 1994. It, therefore, seems appropriate to comment on the past, the present status and future expectations of the trial.

EUROSCAN is a study by the European Organization of Research and Treatment of Cancer (EORTC), of curatively treated patients with oral cancer, laryngeal cancer or lung cancer, which started in June 1988 [1]. Retinol palmitate 300 000 IU daily for 1 year and half this dose for a second year, or *N*-acetylcysteine (NAC) 600 mg for 2 years, or both drugs are being used as chemopreventive drugs, in a 2×2 factorial design with controls receiving neither agent. More than 60 cancer centers from 14 European countries participate in the study. In the original protocol, 2000 evaluable patients were calculated to be needed in the trial for it to have sufficient power. The compliance (pill intake) has been checked and is around 70%, instead of the anticipated 80%. In addition, a few poorly performing centers, with regard to quality of follow-up, had to be excluded from analysis. This implies that the definite target has been raised to 2600 patients. The number of patients included in January 1994 is over 2300. With the present accrual it is expected that randomisation will end around September 1994, and thus the end of the intervention period is around September 1996.

A first analysis of EUROSCAN will not be performed before the end of the intervention period. With constant pressure to publish preliminary results, it is important to stress that no interim analysis will be performed. Although a substantial number of events (second primary tumours, recurrences, metastases) has already occurred, the majority of them have taken place within the intervention period. Around September 1996, the median follow-up will be more than 3 years, hopefully allowing conclusions to be drawn.

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WHAT CAN BE EXPECTED?

Although no data will be available before 1996, we believe that some optimism is justified, based on the experimental and clinical data on the two drugs used.

NAC

The use of NAC as a possible chemopreventive agent is based on its anti-oxidative/detoxifying properties. Most of the properties of prophylactically used NAC are linked to its capacity to either: (1) reduce extracellular cystine to cysteine or (2) be de-acetylated and be presented to utilising cells either as cysteine or cystine. NAC can exercise anti-oxidant action through two mechanisms: the first, at the intracellular level, as a precursor of glutathione (GSH) synthesis. NAC easily penetrates the cell where it is de-acetylated to form L-cysteine, thus supporting the biosynthesis of GSH. The second mechanism lies at the extracellular level, by acting directly on oxidant radicals through properties of NAC. NAC also enhances glutathione-S-transferase [2].

Evidence for the chemopreventive effect of NAC in animal models came initially from the work by De Flora *et al.* (1986). NAC added to the food of mice prevented the formation of urethane-induced lung tumours. NAC decreased the induction of lung tumours in Swiss albino mice, when added to the diet over 15 days before and 4 months after an intraperitoneal injection of the carcinogen [3]. The use of NAC in EUROSCAN was, among others, based on this finding. Since the start of EUROSCAN, NAC has been tested in similar animal studies by others, with similar results.

In mice, the formation of skin papillomas by 7,12 dimethylbenzathracene + 12-*O*-tetradecanoylphorbol-13-acetate could be prevented [4]. In Wistar rats treated with 2-acetylaminofluorene according to the Teebor and Becker protocol [5], GSH and NAC added to the diet delayed the development of γ-glutamyl transpeptidase-positive foci in the liver and prevented 2AAF-induced sebaceous squamous cell carcinomas of Zymbal glands [6]. In a rat colon carcinogenesis model using 1, 2-dimethyl hydrazine, NAC also exerted a protective effect [7]. In the NCI test program, NAC was tested in two animal test systems [8]. In male Syrian golden hamsters, methylnitrosurea (MNU) was instilled intratracheally and NAC was administered in the feed. Tracheal tumours were assessed after 6 months. In groups received 6400 mg/kg from 1 week following carcinogen treatment until the end of the experiment, the carcinoma incidence was statistically significantly

decreased from 58.6 to 24%. In the second experiment, virgin female Sprague–Dawley rats were treated with MNU by intravenous injection and were fed either 8000 or 4000 mg/kg NAC. This study lasted for 180 days. The tumour multiplicity was reduced from 12.1 tumours/rat in MNU controls to 8.6 tumours/rat in animals treated with 8000 mg/kg NAC during carcinogen treatment, to 9.25 tumours/rat in animals fed 8000 mg/kg after MNU treatment, and 8.9 tumours/rat in animals fed 8000 mg/kg during the whole period. In animals fed 4000 mg/kg, the tumour multiplicity was 10.7 tumours/rat [8].

In addition to these convincing animal data, NAC has shown in a variety of experimental data to exert protective effects, such as the extracellular inhibition of mutagenic agents from exogenous and endogenous sources, inhibition of genotoxicity of reactive oxygen species, modulation of metabolism coordinated with blocking of reactive metabolites, protection of DNA and nuclear enzymes and prevention of the formation of carginogen–DNA adducts (for review, see [9]). At the chemoprevention branch of the NCI, NAC is regarded as one of the most promising chemopreventive agents. In addition, preliminary data from the EUROSCAN show a low frequency of side-effects.

Retinol palmitate

That 13-*cis*-retinoic acid is active in the prevention of second primary tumours in head and neck cancer is well recorded [10]. Retinoids are also active in prevention of oral leukoplakia (for review, see [11]). But what is known about retinol palmitate, the drug used in EUROSCAN? Pastorino *et al.* recently published their results of adjuvant treatment of stage I lung cancer with retinol palmitate 300 000 IU daily for 12 months [12]. After curative surgery, patients were randomly assigned to either a group given retinol palmitate or no treatment. After a median follow-up of 46 months, the number of patients with either recurrences or new primary tumours was 56 (37%) in the treated arm and 75 (48%) in the control arm. 18 patients in the treated group developed a second primary tumour and 29 patients in the control arm developed 33 second primary tumours, which is a reduction of 33% in the group treated with retinol palmitate.

Based on these findings, we believe that some optimism on the outcome of EUROSCAN is justified. With this in mind, there is consensus that it may be unethical to embark on a new European large scale chemoprevention trial ("EUROSCAN II") without knowing the outcome of the current EUROSCAN study. EUROSCAN II must be based on the result of EUROSCAN I. This is in agreement with a recent statement by U.S. and European experts in the field of lung cancer indicating that there is no room for new large phase III studies until the results of the ongoing studies (EUROSCAN and the American chemoprevention studies) have become available. Neither retinoids nor NAC are yet standard treatments against second primary tumours in head and neck or lung cancer [13].

NEAR FUTURE

What can and will be done with patients in EUROSCAN, and with patients with early stage head and neck cancer suitable for chemoprevention between the end of the accrual phase of EUROSCAN I and the start of EUROSCAN II? In the coming years, the power and quality of the study will be increased in several ways. An independent committee of European and U.S. experts in the field of chemoprevention and second primary tumours will check the quality of the data. Blinded revision of reported events takes place by another independent committee of experts (is an event reported as a second primary or recurrence equally regarded as such by the committee?). Analysis of risk factors, in particular smoking habits, will start in 1994 in close collaboration with the EORTC Data Center and the IARC. Use of comedication (are patients using other medication with possible chemopreventive activity?) is presently already under analysis.

Awaiting EUROSCAN II, small phase I trials with modulation of biomarkers as the endpoint are strongly encourged by the EUROSCAN Steering Committee, in agreement with the NCI Chemoprevention Branch guidelines. A few small biomarker studies are already in progress. In order to avoid duplication of research in this field, and to use the most promising chemopreventive agents becoming available, the EUROSCAN Coordinating Committee urges potential investigators not to embark on such studies without contacting the EUROSCAN Steering Committee via the authors of this paper.

CONCLUSION

Although EUROSCAN results will not become available before 1996, some optimism that chemoprevention with retinoids, scavengers of free radicals (as NAC) or combinations will become a realistic adjuvant treatment in early stage head and neck cancer is justified.

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