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Chemoprevention of Second Primary Tumours: A Model for Intervention Trials

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CANCERS OF the head and neck and lung remain a worldwide threat to public health. Widespread use of tobacco guarantees that a sharp drop in incidence rates is not likely. For clinicians, treatment of these cancers has remained frustrating. There has been no recent significant progress in the treatment of advanced disease. In addition, these patients, identified by an initial head and neck or lung cancer, have a tremendously increased risk for developing second primary tumours. These second primary tumours develop predominantly in the upper aerodigestive tract and lungs. Following a head and neck cancer, the lifetime risk of developing a second primary tumour is between 20 and 40% [1–3]. The risk of primary disease, local-regional recurrence or distant metastases declines after 2 years, but the risk of developing a second primary tumour remains constant and becomes the major threat to survival for these patients [4]. Chemoprevention, the use of drugs to block or reverse carcinogenesis, before the development of invasive cancer, is now being actively studied as a strategy to prevent second primary tumours. It is hoped that if the strategy is effective in this setting, the findings could be used in developing primary prevention regimens as well. Bolla and colleagues, reporting for the French Study Group on Head and Neck Tumours, have studied this approach, and present here the findings of their randomised trial using the synthetic retinoid etretinate (pp. 767–772).

The concepts which have guided the development of intervention strategies for these patients are the presence of a field defect and the multi-step nature of epithelial carcinogenesis. The hypothesis of field carcinogenesis asserts that as a result of diffuse carcinogen exposure, such as in tobacco smoke, the entire epithelial lining of the upper aerodigestive tract is damaged and is consequently at risk for the development of invasive cancer. The initial evidence taken to support this idea was the occurence of histological changes in resected head and neck cancer specimens [5]. Synchronous multiple primary tumours as well as dysplastic epithelium distinct from the tumour were frequently observed. Similar findings have been described in resected lung cancer specimens [6, 7]. Research is now being directed towards identifying the biological characteristics of the carcinogen-exposed epithelium and the resulting field defect. Biomarkers such as chromosomal polysomy and activation of p53 expression have been identified in histologically normal and premalignant upper aerodigestive tract tissue taken from high-risk patients [8–10]. The concept of multi-step carcinogenesis has been well established in animal models. For human studies, this suggests that high-risk patients could potentially be identified by evidence of some of the earlier changes, and then enrolled in intensive early detection or intervention trials.

The tremendous risk of developing a second primary cancer following a head and neck or lung cancer has been used as a model to develop chemoprevention approaches. In this issue of the journal, Bolla and colleagues present the results of a randomised chemoprevention trial performed among patients with a history of head and neck cancer. Patients identified by an initial cancer have demonstrated evidence of both carcinogen exposure and susceptibility. Presumably, other sites in the epithelium have also been genetically damaged, but have not yet progressed into an invasive cancer. Patients who have already received cancer treatment require further close follow-up and

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their participation in a chemoprevention clinical trial may be incorporated into these visits. In addition, these patients, identified by their initial cancer, have a high perceived risk of having recurrent cancer, and are often quite motivated to participate in clinical studies. Because of the tremendously increased risk for developing a second primary tumour following head and neck or lung cancer, it is possible to perform chemoprevention trials using second primary tumour incidence as the end point. These trials typically require a sample size of less than 1500 participants, compared with over 20 000 participants needed for a primary prevention trial.

Chemoprevention trials to reverse premalignant lesions have been used to study regimens which might then be used in trials designed to demonstrate a reduction in cancer incidence [11]. Several agents, including β-carotene, selenium and α-tocopherol have been shown to reverse oral premalignancy. Among the retinoids, randomised trials have demonstrated the ability of isotretinoin, 13-*cis*-retinoic acid, to reverse oral premalignancy [12, 13]. A series of studies have been used to define a dose of isotretinoin which shows both evidence of chemopreventive efficacy and acceptable toxicity. Another retinoid, etretinate, has also been shown to have activity in reversing oral premalignancy [14, 15]. However, this information apparently was not used in the design of the Bolla study. Etretinate was chosen on the therapeutic index in a murine model and results of an uncontrolled study which suggested that the retinoid led to a reduction in squamous metaplasia of the bronchial epithelium in a study of heavy smokers [16, 17]. Recent findings of a randomised trial strongly suggest that the improvement observed in that uncontrolled trial was not due to the retinoid, but rather to variability in carcinogen exposure and the natural history of squamous metaplasia [18]. Therefore, the scientific basis for the choice of drug, dose and schedule in this study is not well substantiated.

Bolla and colleagues report the findings of a multi-institution chemoprevention trial. Using a randomised adjuvant treatment design, the investigators studied the effects of etretinate following surgery and/or radiation for a squamous cell cancer of the oral cavity or oropharynx. It took over 6 years to accrue the 324 patients studied. The results are reported with a median follow-up of 41 months. Given the findings of earlier trials and the large chemoprevention trials which are now ongoing, the findings of this study are quite interesting. In this prospective trial, Bolla and colleagues confirm the very high risk of developing second primary tumours for patients treated with head and neck cancer. For the placebo group, the actuarial rate of developing a second primary tumour during the study was 24%. Not only was the high rate of second primary tumours confirmed but, consistent with the field cancerisation hypothesis, 79% of these second primary tumours occurred within the head and neck, lungs or oesophagus.

Bolla and colleagues did not observe a difference in recurrence, either local-regional or distant, between the two treatment groups. This finding is consistent with that reported by Hong and colleagues [19]. Retinoids by themselves probably will not be effective in reversing already present invasive cancer, based on the results of treatment trials performed in patients with head and neck or lung cancer. The French group also did not observe a difference in either overall or disease-free survival. Hong's study which did demonstrate a reduction in second cancers, did not observe a survival difference. The majority of second cancers following oral cavity or oropharynx cancer will occur within the head and neck, and if found early enough may still be successfully treated.

The striking difference between the reports of Hong and Bolla is the effect of the retinoid on second primary tumours. Hong observed a significant reduction in second primary tumours for patients treated with isotretinoin, 2 patients (4%), compared with placebo-treated patients, 12 patients (24%) ($P = 0.005$) [19]. With a longer median follow-up of 54.5 months, the prevention of second primary tumours within the head and neck, lung and oesophagus in the isotretinoin-treated patients has persisted [20]. In Bolla's trial, the number of second primary tumours was the same for both treatment groups, 28 in etretinate-treated patients and 29 in the placebo-treated patients. The investigators should have described the procedure for reviewing the study end points. In the ongoing large studies, a centralised review of the data is performed in order to rigorously evaluate the occurrence of new primary tumours and recurrent disease.

Bolla and colleagues failed to obtain histories of alcohol and tobacco consumption. These exposures have significant effects on the risk of developing an upper aerodigestive tract tumour, and may also influence the risk of subsequent primary tumours. Consequently, these exposures should have been carefully detailed in this report. In a recent study, individuals who continued smoking after their initial head and neck cancer had the greatest risk of developing a second cancer, whereas a long period of smoking cessation was associated with some reduction of this risk [21].

In their study, Bolla and colleagues describe the frequency of side-effects, but unfortunately not the severity. It is clear from clinical experience that retinoid treatment is associated with side-effects, especially dry skin and cheilitis. However, in order to determine if the toxicities observed are acceptable for a particular patient, it is necessary to know the severity. Reports of side-effects which do not grade toxicity are of limited assistance in balancing the potential toxicity and efficacy of a chemopreventive regimen. For chemoprevention trials which administer the drug for long periods of time, it is also necessary to know when in the treatment period the toxicities occur. Using the same dose of etretinate in a group of smokers, Arnold and colleagues found the drug to be quite well tolerated during a 6-month course [22]. It would be helpful to know if the difference in the observed toxicities between these two studies is the result of the length of administration, or some other reason.

Another area of concern with this report is the limited data presented on patient compliance with treatment. Multi-institution chemoprevention trials are logistically complex and must be rigorously conducted. Adherence with the treatment and follow-up dictated by the protocol is critical to the success of the trial. Poor compliance with the prescribed regimen will greatly compromise the integrity of the study and limit the ability of the investigators to detect an effect from the intervention. The authors state that 33% of the etretinate-treated patients and 23% of the placebo-treated patients discontinued the medication before completing the planned 24 months of treatment. What is not clear, is how much of the study drug was taken by individuals who continued in the trial. Although apparently collected, the results of pill counts are not reported here. The authors also do not report on adherence with the follow-up and evaluation dictated by the protocol. It is not apparent from the report whether the patients took the study medication and were followed as had been intended. Absence of serum drug levels also weakens the ability to draw conclusions from the study.

There are ongoing large scale randomised studies which also address the chemoprevention of second primary tumours. Pastorino and colleagues performed a randomised trial comparing treatment with retinyl palmitate to observation following resection of a non-small cell lung cancer [23]. They found evidence of a chemopreventive effect for the retinoid, with a significant increase in time to the development of a second tumour within the chemoprevention field. The therapy was also well tolerated. Based on these findings, the researchers initiated the ongoing Euroscan study [24]. The study uses a 2×2 factorial design in which patients receive treatment with retinyl palmitate alone, *N*-acetyl cysteine alone, both drugs or placebo. Parallel clinical trials will determine if the treatment reduces the incidence of second primary tumours following resection of a non-small cell lung cancer, or treatment of a head and neck cancer. Over 2000 patients have currently been enrolled in the study.

In the U.S.A., chemoprevention trials are underway based on the findings reported by Hong. These trials use isotretinoin to prevent second primary tumours following head and neck cancer or resection of an early stage non-small cell lung cancer [25]. Based on evidence from oral premalignancy studies of both efficacy and decreased toxicity using lower doses of isotretinoin, these trials use a dose of 30 mg/day. The trials use a randomised, placebo-controlled design with reduction of second primary tumour incidence as the end point. The trial using head and neck cancer patients, which opened in February 1992, has enrolled 503 patients and the trial for non-small cell lung cancer patients, which opened in September 1993, has enrolled 456.

Another second primary tumour prevention trial is being performed by researchers from Yale University. This study uses the Connecticut state tumour registry to identify patients with head and neck cancer, and is studying the effects of β-carotene. The Southwest Oncology Group has also recently begun a β-carotene second primary tumour prevention trial. An adjuvant study using a very low dose of isotretinoin following treatment of a head and neck cancer is being performed in the U.S.A, through the Eastern Cooperative Oncology Group.

The prevention of second primary tumours is an area of active research. Large randomised trials are underway in Europe and the U.S.A. The goal of these studies is to demonstrate a reduction in the incidence of second cancers, and hopefully to establish the clinical usefulness of chemoprevention. These studies will require several more years to complete. The results of these clinical trials and their associated studies to investigate the biology of field carcinogenesis and the mechanism of chemoprevention, may also provide a basis for developing primary cancer prevention strategies. However, it is also possible that results of primary prevention trials, such as the study of α-tocopherol and β-carotene in Finnish smokers or the CARET trial, may influence the development of second primary tumour prevention efforts [26, 27]. Results of the ongoing studies will be available before the year 2000. Chemoprevention of second tumours after head and neck or lung cancer remains an exciting prospect, but not yet a proven clinical practice.

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