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CHEMOPREVENTION OF BREAST CANCER WITH TAMOXIFEN

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A pilot randomized placebo-controlled trial was started at the Royal Marsden Hospital in 1986 using tamoxifen in healthy women at increased risk of developing breast cancer. Nearly 2400 women with a strong family history of breast cancer have since been accrued into this pilot programme. Participants have been randomly allocated to receive either tamoxifen 20 mgs/day or placebo for up to 8 years. Compliance at 5 years is maintained at approximately 80% for women on placebo, compared to 70% for those on tamoxifen. Acute symptomatic toxicity is low and primarily relates to hot flushes, vaginal discharge and menstrual irregularities. Monitoring of cholesterol and clotting factors showed no adverse effects. The results of bone mineral density as measured by dual energy x-ray absorption are currently being evaluated. Gynaecological assessment using transvaginal ultrasonography has been carried out in this programme. We have identified a significant increase in the incidence of ovarian cysts, uterine fibroids enlarged uterus, endometrial thickening (ET), endometrial polyps and histological evidence of atypical hyperplasia (AH) in patients on tamoxifen. Histological evidence of AH occurred only in women with ET > 8 mms on transvaginal ultrasound, thereby identifying a subgroup for further assessment including hysteroscopy, endometrial biopsy and removal of endometrial polyps.

Success of this pilot programme has encouraged the commencement of National trials in the U.S.A., U.K. and Italy aimed at evaluating tamoxifen as a breast cancer chemopreventative agent.

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BREAST CANCER CHEMOPREVENTION WITH RETINOIDS AND TAMOXIFEN

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In March 1987, a breast cancer chemoprevention study with Fenretinide (4-HPR) started at the Milan Cancer Institute with the aim of evaluating the effectiveness of this retinoid in reducing the incidence of contralateral breast primaries in breast cancer patients. Subjects take 4-HPR at the daily dose of 200 mg for 5 years vs no treatment. Accrual is closed with 2,972 randomized patients. No difference is shown at present between the two groups but some preliminary data seem to suggest that the agent might be effective in inhibiting the growth of hormone independent tumours. Other aims are to contribute to a better understanding of the pharmacokinetics and mechanisms of action of this drug, as well as to determine its effectiveness in prevention or protection of women against ovarian cancer.

Another breast cancer chemoprevention trial using Tamoxifen (TAM) began in September 1992 from an original idea of U. Veronesi and C. Maltoni. Presently, more than 3,500 hysterectomized women aged 35–70 are participating in the study. According to a double blind design, the subjects take either 20 mg/day of TAM or placebo for 5 years. The decision to include only hysterectomized women was made to avoid the unjustified risk of endometrial cancer in those taking TAM. The study involves 43 Italian centres and 3 associated centres in South America. The Data Centre and the National Coordinating Centre are in Milan, at the European Institute of Oncology.

Most randomized patients (89%) are between 45 and 65 years of age (median age: 51); 56% have had minor side effects (mainly menopausal symptoms).

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CHEMOPREVENTION OF (PRE)MALIGNANCY OF THE UPPER AERODIGESTIVE TRACT WITH RETINOIDS

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Of the various possible level of risk at which chemoprevention can be applied 1) premalignant conditions (in the oral cavity: leukoplakia) and 2) patient who have been treated for cancer, but who are at risk to develop a new cancer, are for the upper aerodigestive tract the most important. Studies in oral leukoplakia as well as in the second primary tumors group will be discussed, with emphasis on EUROSCAN.

EUROSCAN is an European Organization of Research and Treatment of Cancer (EORTC) chemoprevention study in curatively treated patients with oral cancer, laryngeal cancer and lung cancer which started in 1988; the end of the accrual phase was in 1994.

The end of the intervention period is in 1996.

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LUNG CANCER CHEMOPREVENTION

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A number of prospective clinical trials on human cancer chemoprevention have been conducted during the last decade, testing potentially active agents (retinoids, antioxidants, micronutrients), alone and in combination, in various populations of high risk individuals. A recent large trial conducted on heavy smokers failed to demonstrate any benefit beta-carotene and/or alpha-tocoferol administration. However, more encouraging results have been achieved in the chemoprevention of second primary cancer, particularly in the upper aerodigestive tract cancers. In fact, patients curatively treated for a early stage tumours have become an ideal target population for chemoprevention of second primary malignancies. The "field cancerization" theory implies that repeated exposure of the entire bronchial epithelial surface to known carcinogens may result in the occurrence of multiple, independent premalignant or malignant foci, and represents the conceptual basis for secondary chemoprevention in these patients. The first successful trial conducted in these diseases have shown that high dose retinol palmytate significantly reduced the probability of tobacco-related new primary tumors and improved the total disease-free interval in 307 patients resected for T1-2 NO non small cell lung cancer. In particular, 50% of new primary lung cancers were prevented by retinol administration. A second European trial (EUROSCAN) has accrued 2595 patients with a prior cancer of the oral cavity, larynx or lung to receive retinol and/or n-acetyl-cysteine for 2 years. Other major clinical trials are ongoing in the United States and Europe to investigate the preventive potential of 13-cis-RA in resected stage I lung cancer. Within these prospective studies a number of cytogenetic and molecular biology markers are being investigated to identify optimal candidates for chemoprevention programs, and monitor the results of intervention in the short and intermediate term.

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NO ABSTRACT

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PROLIFERATIVE T-CELL RESPONSES TO HPV16.L1 IN PATIENTS WITH CIN: CORRELATION WITH HPV TYPE AND CERVICAL BIOPSY HISTOLOGY

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We have previously demonstrated that 73% of patients with CIN (n = 17) can mount a proliferative T-cell response to an immunodominant region of HPV16.L1 between aa305–345 using short term cell lines expanded with an L1 fusion protein and mapped with overlapping synthetic peptides(15 mers) to this region. The T-cell responses to HPV16.L1 region 199–409 have now been mapped in a larger group of patients (n = 41) and in 11 healthy controls and the patient data correlated with cervical biopsy histology and the presence of HPV DNA as detected by PCR. 26 patients (63%) and 5 controls (45%) responded to one or more peptides representing HPV16.L1 aa199–409. 19 patients(46%) responded to aa region 311–345 as compared to 2 controls (18%,). The patient responses to this region were significantly associated with peptides 311–325($P = 0.04$) and 321–335($P = 0.004$) and to the presence of HPV16 ($P = 0.006$) in their cervical biopsies. Overall, 30% (n = 12) of patients cervical biopsies were HPV16 positive and 92% (n = 11) of these were CIN III lesions, demonstrating the strong association between the presence of HPV16 and high grade lesions ($P = 0.0001$). All of the HPV16 positive patients (n = 12) demonstrated proliferative T-cell responses to one or more peptides and this association between T-cell responses and the presence of HPV16 DNA was found to be highly significant ($P = 0.0004$). Individuals whose biopsies were HPV negative or contained other HPV types also responded to some of the peptides (HPV X, n = 5/12; HPV 33, n = 1/1; and HPV-ve, n = 8/13) but with a lower number of responding cell lines.