Pergamon

European Journal of Cancer, Vol. 34, Suppl. 4, p. S63, 1998

Printed in Great Britain
0959-8049/98$—see front matter

PII: S0959-8049(98)00119-1

VI.1 Tamoxifen-induced DNA Adducts

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IT IS now generally accepted that tamoxifen is a genotoxic, mutagenic liver carcinogen in the rat. However, the drug does not cause liver cancer when administered to mice and although it initially causes DNA damage, it appears that on prolonged administration there is no cumulative DNA adduct formation compared with control mice.

In humans, the available data from chemical trials and epidemiological survey provide reassurance that there is no excess in liver cancer in patients treated with tamoxifen. However, the majority of investigators reviewing the incidence of endometrial cancer in tamoxifen-treated women have concluded that there is evidence of a 3- to 7-fold increase in this cancer in women on tamoxifen therapy. The importance of this association is strengthened by the scientifically plausible explanations which can be advanced to explain this association. In brief, it can be argued that tamoxifen (1) promotes the development of tumours through its oestrogen agonist effect on the uterus; or (2) it is genotoxic to uterine cells and this is related to the subsequent development of tumours; or (3) a combination of (1) and (2) leads to uterine tumours.

Irrespective of the mechanism of tumour formation associated with tamoxifen therapy, it must be stressed that there is an overwhelming case for the prolonged use of this drug in the treatment of breast cancer. However, if tamoxifen 'causes' uterine cancer through a genotoxic mechanism, it might be possible to avoid this problem by the therapeutic use of alternative anti-oestrogenic drugs which are not genotoxic. Also, with the development of chemoprevention strategies involving the long-term administration of tamoxifen to healthy women to reduce the incidence of breast cancer, the issue of the genotoxicity of tamoxifen becomes more relevant to the risk–benefit analysis that would govern its use.

At present, the issue of whether tamoxifen is genotoxic to the human uterus is controversial, with debate on whether the methods used to produce positive evidence of DNA adducts in uterine tissue taken from women on tamoxifen is producing genuinely positive results.

European Journal of Cancer, Vol. 34, Suppl. 4, p. S63, 1998

Printed in Great Britain
0959-8049/98$—see front matter

PII: S0959-8049(98)00120-8

VI.2 Cytogenetic Changes in Endometrial Polyps from Tamoxifen Users

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THE INCREASED incidence of endometrial changes including endometrial polyps in tamoxifen users called for a study of the chromosome changes that may be occurring in these tumours in comparison with similar changes in endometrial polyps arising in a non-tamoxifen context. In both groups characteristic chromosome changes would identify genomic segments prone to re-arrangement and allow for preliminary conclusions on whether genetic pathways of tumorigenesis in both groups could be expected to be different or similar.

In a series of endometrial polyps from 36 postmenopausal breast cancer patients treated with tamoxifen the most prevalent chromosome changes found were affecting 6p21 and 12q15, as in non-tamoxifen patients. In addition, *in situ* hybridisation studies showed that in both groups the same genes, *HMGIY* and *HMGIC* were affected.