ACTINOMYCIN D (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate*)

A comparison was made in the USA between survivors of childhood cancer who developed second malignant neoplasms and controls, also survivors, matched on hospital,

primary diagnosis, length of follow-up, site and dose of radiotherapy, and chronological period. Subjects who had received no radiotherapy, or who were believed to have some 'predisposing genetic syndrome', and whose second tumour had been diagnosed within six months of the first diagnosis, or with tumours that lay outside the field previously treated with radiation were excluded. Unexpectedly, cases had been treated much less often with actinomycin D than controls (relative risk, 0.13; upper 95% confidence limit, 0.47), and those who had been treated had received fewer courses of treatment (median, 2, compared to 6.5). For each type of primary childhood malignancy, except for bone tumours, the majority of cases had not been treated with actinomycin D. Second malignancies included soft-tissue sarcomas, haematological malignancies and various solid tumours. A relationship is plausible in view of the radiomimetic properties of actinomycin D, the simultaneous exposure of the treated patients to radiation, and the modal shape of radiation dose-effect curves in some laboratory systems[1].

A single attempt to confirm this finding covered only eight second malignancies (meeting criteria comparable to those in the first study) occurring among 412 patients who had been treated with radiation for Wilms' tumour of whom 222 had also received actinomycin D. No similar reduction in risk was observed. This study differed from the original in the small sample size, the uniformity with respect to primary diagnosis and that the comparison was made with historical controls[2].

B. Evidence for carcinogenicity to animals (*limited*)

Actinomycin D was tested for carcinogenicity in rats by intraperitoneal injection and by intragastric administration and in mice by repeated subcutaneous injections. It produced peritoneal sarcomas in rats following intraperitoneal injections[3,4], and a low incidence of subcutaneous sarcomas occurred in mice following repeated subcutaneous injections[3]. No tumour was observed in rats after intragastric administration of actinomycin D, but the duration of the experiment was short[5].

C. Other relevant data

Actinomycin D did not induce sister chromatid exchanges in peripheral blood lymphocytes of treated patients in one study[6].

Actinomycin D induced chromosomal aberrations and DNA strand breaks in human cells *in vitro*. It transformed mouse C3H 10T1/2 cells and induced chromosomal aberrations, sister chromatid exchanges, mutation, DNA strand breaks and unscheduled DNA synthesis, but not aneuploidy, in rodent cells *in vitro*. It induced sex-linked recessive lethal mutations in *Drosophila*. Actinomycin D did not cause chromosomal aberrations in plants. It was mutagenic to *Neurospora crassa* but not to *Saccharomyces cerevisiae*, and conflicting results were obtained for gene conversion and mitotic recombination. It did not induce DNA damage in *Schizosaccharomyces pombe*. It was not mutagenic to bacteria and did not induce prophage[6].

References

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