CHLORAMBUCIL (Group 1)

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

Many case reports and a few small epidemiological studies of malignancy after therapy with chlorambucil have been reported among patients treated for breast cancer, juvenile arthritis, glomerulonephritis and ovarian cancer. Although in each study an excess of subsequent malignancy, especially acute nonlymphocytic leukaemia (ANLL), is inferred, these reports are difficult to interpret because the cases are few or because they had also received radiation or other putative carcinogens[1,2]. A randomized trial of therapy in 431 polycythemia vera patients[3] showed a significant, 13-fold increase in the incidence of ANLL in those receiving chlorambucil — 2.3 times higher than in patients receiving radioactive phosphorus. The excess was strongly related to dose and persisted throughout the first decade after treatment.

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

Chlorambucil has been tested for carcinogenicity in mice and rats by intraperitoneal injection and in female rats by oral gavage. It produced tumours of the lung and probably tumours of the haematopoietic system and ovaries in mice[1], and produced haematopoietic tumours in male rats and haematopoietic and lymphatic tumours in female rats[1,4]. It had an initiating effect in a two-stage skin carcinogenesis experiment in mice[1].

C. Other relevant data

Chlorambucil is a bifunctional alkylating agent. It induced sister chromatid exchanges in the lymphocytes of treated patients; studies of induction of chromosomal aberrations were inconclusive[5].

Chlorambucil induced chromosomal aberrations in embryo cells of rats treated *in vivo*. Sister chromatid exchanges and chromosomal aberrations were induced in human lymphocytes and sister chromatid exchanges and mutation in Chinese hamster cells *in vitro*. Chlorambucil induced sex-linked recessive lethal mutations in *Drosophila* and mutation and gene conversion in yeast. It was mutagenic to bacteria[5].

References

[1]*IARC Monographs, 26*, 115-136, 1981

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[3]Berk, P.D., Goldberg, J.D., Silverstein, M.N., Weinfeld, A., Donovan, P.B., Ellis, J.T., Landaw, S.A., Laszlo, J., Najean, Y., Pisciotta, A.V. & Wasserman, L.R. (1981) Increased incidence of acute leukemia in polycythemia vera associated with chlorambucil therapy. *New Engl. J. Med., 304*, 441-447

[4]Berger, M.R., Habs, M. & Schmähl, D. (1985) Comparative carcinogenic activity of prednimustine, chlorambucil, prenisolone and chlorambucil plus prednisolone in Sprague-Dawley rats. *Arch. Geschwulstforsch., 55*, 429-442

[5]*IARC Monographs, Suppl. 6*, 139-141, 1987