CHLOROETHYL NITROSOUREAS: BISCHLOROETHYL NITROSOUREA (BCNU) (Group 2A) 1-(2-CHLOROETHYL)-3-CYCLOHEXYL-1-NITROSOUREA (CCNU) (Group 2A) 1-(2-CHLOROETHYL)-3-(4-METHYLCYCLOHEXYL)-1-NITROSOUREA (METHYL-CCNU) (Group 1)

A. Evidence for carcinogenicity to humans (*limited* for BCNU; *inadequate* for CCNU; *sufficient* for methyl-CCNU)

In seven randomized trials of treatment for brain tumours, two cases of acute nonlymphocytic leukaemia (ANLL) occurred among 1628 patients treated with BCNU (0.08 expected) within the first two years of treatment, whereas no such case occurred among 1028 patients not treated with BCNU[1].

No epidemiological study of CCNU as a single agent was available to the Working Group[2].

Adjuvant treatment with methyl-CCNU has been evaluated in 3633 patients with gastrointestinal cancer treated in nine randomized trials. Among 2067 patients treated with methyl-CCNU, 14 cases of ANLL occurred (relative risk, 12.4; 95% confidence interval, 1.7-250), whereas one occurred among 1566 patients treated with other therapies. Cumulative (actuarial) risk was 4% at six years and was not affected by concomitant radiotherapy or immunotherapy[3]. A subsequent report described a strong dose-response relationship, adjusted for survival time, giving a relative risk of almost 40 fold among patients who had received the highest dose[4].

B. Evidence for carcinogenicity to animals (*sufficient* for BCNU and CCNU; *limited* for methyl-CCNU)

BCNU produced malignant tumours of the lung and an increased risk for neurogenic tumours in rats after its repeated intraperitoneal or intravenous administration, and

tumours in the peritoneal cavity after its intraperitoneal administration[2,5,6]. Tests in mice by intraperitoneal administration and in rats by oral administration could not be evaluated[2]. When tested in mice by skin application together with ultraviolet B irradiation, BCNU caused an earlier appearance of skin tumours[2]. Two studies by skin painting in mice were inadequate[2,7].

CCNU produced lung tumours in rats following its intraperitoneal or intravenous injection[2,5]. When tested in mice by intraperitoneal injection, it induced a slight increase in the incidence of lymphomas. Tests in rats by oral administration could not be evaluated[2]. In one study by skin application to mice, no skin tumour was observed, but the duration of the experiment was inadequate[7].

Data on methyl-CCNU were included in a report in which a large number of cancer chemotherapeutic agents were tested for carcinogenicity by intraperitoneal injection in Sprague-Dawley rats and Swiss mice. In male rats injected with methyl-CCNU thrice weekly for six months, total tumour incidence was reported to be increased 1.5-2 fold over that in controls at 18 months. A slight increase in tumour incidence was reported in mice[8]. Intravenous administration of methyl CCNU to rats induced lung tumours[5].

C. Other relevant data

BCNU, CCNU and Me-CCNU are directly-acting, bifunctional alkylating agents[9].

No data were available on the genetic and related effects of BCNU in humans. An increased frequency of sister chromatid exchanges was observed in a single study of peripheral blood lymphocytes of patients treated with CCNU.

BCNU induced chromosomal aberrations, micronuclei and sister chromatid exchanges in cells of mice treated *in vivo*, DNA damage in human cells *in vitro*, and aneuploidy, chromosomal aberrations, sister chromatid exchanges, mutation and DNA damage in rodent cells *in vitro*. It induced sex-linked recessive lethal mutations in *Drosophila* and gene conversion in yeast. It was mutagenic and caused DNA damage in bacteria[9].

CCNU induced dominant lethal mutations in rats and DNA damage in cells of mice and rats treated *in vivo*. It induced DNA damage in human and rodent cells *in vitro* and sister chromatid exchanges and mutation in cultured Chinese hamster cells. It induced mutation and DNA damage in bacteria[9].

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