COMBINED EFFECT OF NITROGEN MUSTARD AND DNA REPAIR INHIBITOR ON THE RESISTANT TUMOR

It has been known that the damage of DNA caused by the effect of alkylating agents is restored by its own repairing mechanisms. Consequently it is probable that sensitivity of the tumor cells to alkylating agents should depend at least partially on the potency of DNA repairing activity of the cells.

We reported earlier that the acquired resistance of Yoshida sarcoma to nitrogen mustard (HN₂) is due to decreased transport of the agents through the cell membrane, but there is no difference in the transport between two lines of rat ascites hepatomas, AH-13 and AH-44, which are naturally sensitive and resistant to nitrogen mustard, respectively. Recently, Kann et al. reported that 2-chloroethyl isocyanate, a metabolic product of 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU), inhibits repair of DNA damage of L-1210 cells produced by X-irradiation.

This communication deals with the effect of nitrogen mustard with concomitant use of 2-chloroethyl isocyanate on a HN₂-resistant line of hepatoma, AH-44. The enhancement of cytotoxic effect of HN₂ by this DNA-repair inhibitor was proved by the following experiment.

Intraperitoneal injection of either 0.05 mg/kg of HN₂ or 5 mg/kg of BCNU to Donryu rats bearing AH-44 does not produce life prolongation but, as shown in Fig. 1, the combined use of both agents in the same doses showed a remarkable effect. By the combined treatment of the same tumor with 0.05 mg/kg of HN₂ and 50 mg/kg of 2-chloroethyl isocyanate, the tumor-bearing rats survived nearly twice longer than the control, as shown in Fig. 2. The treatment by the same dose of 2-chloroethyl isocyanate alone was almost ineffective. The smear preparation of the tumor cells treated by 0.05 mg/kg of HN₂ alone showed...
no cytomorphological change at all, but a re-
markable change occurred by the above com-
bination treatment with HN$_2$ and the isocyanate; ap-
pearance of huge cells, and chromosomal aberra-
tion of mitotic cells, which are characteristic in the treatment with alkylating agents,
were observed under a microscope by Giemsa
staining.

Further investigation on the enhancing effect
of DNA repair inhibitors on the cytostatic action
of monofunctional and bifunctional alkylating
agents is under progress.

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References

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