The Uptake of ACNU in the Experimental Brain Tumor and the Effect of Induced Hypertension - Part II -

III. 5 The Uptake of ACNU in the Experimental Brain Tumor and the Effect of Induced Hypertension – Part II –

Tsurumi Y., Kameyama M., Shirane R., Muraishi K., Katakura R. and Suzuki J.
Division of Neurosurgery, Institute of Brain Diseases, Tohoku University School of Medicine

The usefulness of induced hypertension when administrating anititumoral agent — 1-(4-amino-2-methyl-5-pyrimidyl)-methyl-3-(2-chloroethyl)-3-nitrosourea hydrochloride (ACNU) — has already been reported in our previous issue.[1] In this paper, further investigations are presented particulary from the view points of optimal duration of induced hypertension chemotherapy and its effect upon survival time in the experimental rat brain tumor.

Materials and Method

1) Experimental rat brain tumor model

KEG-1 cells (1×10^5) were implanted semistereotaxically into the brains of WKA rats weighing 200 g around. About 10 days later, these rats were used in the experiments. The production of brain tumor was almost 100%, and they were found in subcortex.

2) Effect of induced hypertension

Under sodium pentobarbital anesthesia, canuli were introduced into the femoral artery and vein, and blood pressure was continuously monitored. Rats were immobilized with pancuronium bromide and artificially ventilated. Body temperature, pH, PaO_2 and $PaCO_2$ were maintained within physiological range throughout the experiment. Ten μCi of ethylene-^{14}C-ACNU (specific activity 26.1 μCi/mg) was administered intravenously following the continuous elevation of blood pressure by angiotensin II i.v. Rats were decapitated at 2, 5, 10, 20 and 30 minutes after the injection of ^{14}C-ACNU, and the tumor tissue together with contralateral brain tissue was sampled. These samples were burned with sample oxidizer (Aloka ASC-113) and the radioactivity of ^{14}C was counted with liquid scintillation counter (Aloka LSC-903).

3) Retention of ACNU

To examine the retention of ACNU in the tissue, blood pressure was elevated for 5 minutes and then rats were decapitated at 20 or 30 minutes after the injection of ^{14}C-ACNU. The uptake of ^{14}C in the tumor tissue was compared with that of continuous induced hypertension group.

4) Survival time

Five days after implantation, 5 mg/Kg of ACNU was administered

intravenously under the sodium pentobarbital anesthesia. Induced hypertension was continued for 5 minutes after adminstration of ACNU, and the survival time was compared with those of the non-hypertensive ACNU i.v. group and the non-treated group.

Results

1) Uptake of ^{14}C-ACNU

In 6 rats of non-hypertensive control group decapitated at 5 minutes following the injection of ^{14}C-ACNU, the uptake of ^{14}C-ACNU in the brain tumor tissue was 0.32±0.03 %dose/g tissue (mean ± SE). In 7 rats sacrificed at 10 minutes, it was 0.53±0.10 %dose/g tissue. On the other hand, in 5 rats of induced hypertension group decapitated at 5 minutes and 7 rats at 10 minutes, the uptake of ^{14}C-ACNU were 1.20±0.09 and 1.12±0.07 %dose/g tissue respectively. The values at 5 and 10 minutes in the induced hypertension group were statistically significant comparing with those of non-hypertensive control group ($p<0.01$).

Whereas in the rats of induced hypertension group sacrificed at 2, 20 and 30 minutes, the uptake of ^{14}C-ACNU was almost the same as those of the non-hypertensive control group. Also the uptake of ^{14}C-ACNU in the contralateral brain tissue of the two groups did not show any statistical difference throughout the experiment.

2) Retention of ACNU (Fig. 2)

The uptake of ^{14}C-ACNU in the group of rats decapitated at 20 or 30 minutes, in which induced hypertension was maintained for the first 5 minutes, showed higher accumulation than those in which induced hypertension was continued till decapitation.

3) Survival time

In 13 rats of non-treatment group, survival time was 12.3±0.53 days (mean ± SD). In 14 rats of ACNU treated non-hypertensive control group, it was 14.1±0.59 days. On the other hand, in 7 rats of ACNU treatment group with induced hypertension it was 18.1±0.60 days and showed a statistically significant difference ($p<0.005$) to the non-treatment and ACNU treated non-hypertensive control groups.

Discussion

Alkylating anti-cancer drugs like ACNU has been thought as a cell cycle non-specific drug[2], and the one shot high dose administration has been reported superior in suppressing the recurrence of brain tumor and in the occurrence of side effects rather than divided administration.[3] On the other hand, ACNU is generally administered intravenously with the dose of 1-2 mg/Kg in the routine clinical usage, due to its side effects appearing dose dependently. According to the recent report which examined the concentration

of ACNU in the brain tumor tissue taken during surgery, however, one shot intravenous administration of 3-4 mg/Kg of ACNU is necessary to deliver sufficient ACNU in the tumor when comparing with the results of in vitro investigation.[4] Therefore, it is mandatory to develop a new administration method which can increase the concentration of ACNU in brain tumor 1.5 to 4 times more without causing any additional side effects.

One of the characteristics of tumor vessels has been pointed out as the lack of autoregulation[5], which suggests that the microcirculation in brain tumors may be dependent on perfusion pressure. As a fact, it has already been reported that elevation of blood pressure produced a several fold increase in blood flow in transplanted AH109A tumor selectively.[6] On the basis of these theoretical background, the effect of induced hypertension was investigated using the experimental brain tumor from the view points of pharmacokinetics of ACNU and survival time.

As results, in the induced hypertension group of rats, the uptake of ^{14}C-ACNU in the brain tumor was 2 to 4 times more as that of the non-hypertensive control group. On the other hand, the uptake of ^{14}C-ACNU in the contralateral brain tissue did not show meaningful difference between the two groups. These results clearly demonstrate the possibility that the method of induced hypertension can selectively increase the delivery of ACNU into the brain tumor tissue without causing additional side effects to normal brain tissue and other organs.

Ethylene-^{14}C-ACNU used in this experiment was labeled by ^{14}C of the active site of ACNU. Thus the increased uptake of ^{14}C in the brain tumor tissue was thought to be highly correlates with the anti-tumoral effect, and this was substantiated by the prolongation of the survival time under the induced hypertension treatment for 5 minutes.

The induced hypertension chemotherapy of only 5 minutes is an easily applicable maneuver to the human patients and will be effective in the management of malignant brain tumor patients without producing adjunctive side effects of chemotherapeutic agents.

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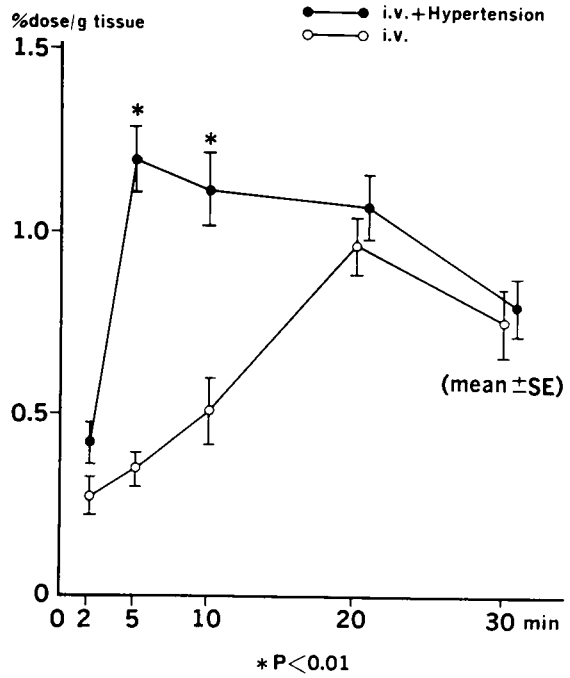

Fig. 1. The uptake of ^{14}C-ACNU in the experimental brain tumor with and without induced hypertension.

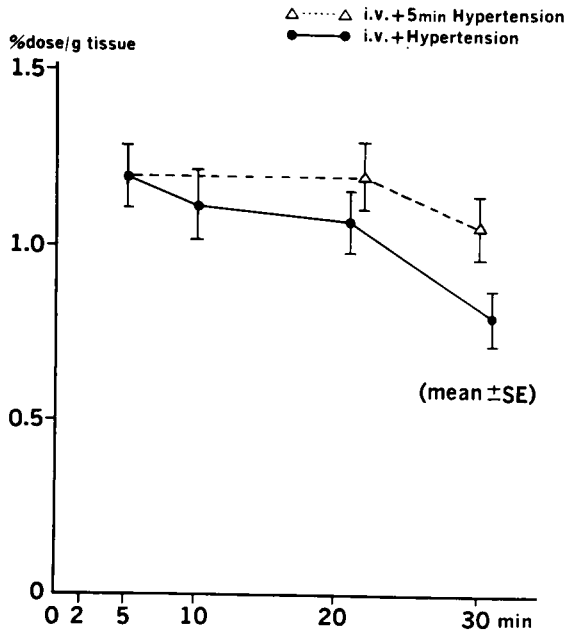

Fig. 2. The uptake of ^{14}C-ACNU in the experimental brain tumor and the duration of induced hypertension.

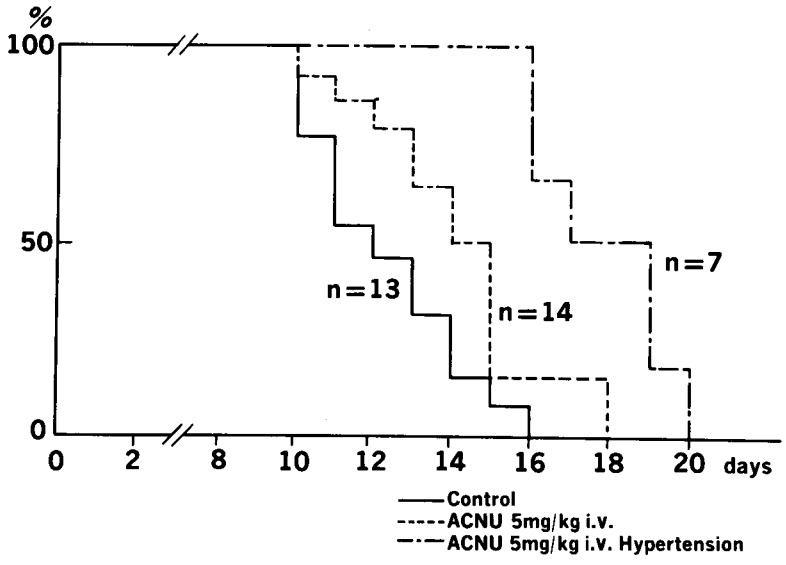

Fig. 3. Survival time in the non-treatment control, ACNU i.v. group and ACNU i.v. with induced hypertension group.