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Treatment of Brain Tumors with 1-(2-Chloroethyl)-3-Cyclohexyl-1-Nitrosourea (CCNU)

by

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CCNU is one of the group of nitrosourea derivatives with antitumor activity simulating alkylating agents. It has been shown that metabolism of DNA[1] and protein[8] was affected with CCNU. In animal experiment, it was observed that CCNU was effective in daily treatment but more effective as a single treatment or when given repeatedly after a long interval.

CCNU has an advantage of solubility in lipid, which enables it to enter brain cells through blood-brain-barrier[5,7]. Following the clear life-prolonging effect against murine intracerebral ependymoblastoma[5], Hansen et al[4] reported the effectiveness of CCNU against human brain tumors. We are reporting our own experience with CCNU against various human brain tumors.

Clinical Material

Between September 1971 and June 1972, CCNU was given once to several times to 15 patients with brain tumors including primary or recurrent gliomas, metastatic tumors, craniopharyngiomas, fibrosarcoma, and others. All of the patients had undergone a partial removal or biopsy one to several weeks before treatment of CCNU. Histological diagnosis was established in all cases except one case who had a large tumor in the right temporal region extending to the basal ganglia. Histological examination of the biopsy specimen revealed only gliosis and we included this case in the miscellaneous group.

Patient Evaluation

The initial evaluation of a patient included a general physical and neurologic examination, blood examination (erythrocyte, leucocyte, thrombocyte, Ht, Hb, bleeding time, coagulation time, prothrombin time), serum biochemical survey (total protein, albumin, BUN, glucose, total cholesterol, Ca^{++}, phosphorus, alkaline phosphatase, GOT, GPT, total bilirubin, lactic dehydrogenase, Na^{+}, K^{+}, Cl^{-}), liver function test(Co, Cd, TTT, ZTT, direct bilirubin), PSP test. Each patient had a ^{99m}Technetium

pertechnetate brain scan and two or more contrast radiographic studies pertinent to the type and location of the tumor. Blood examination and, if necessary, biochemical survey were repeated at least once a week. In all cases except one, CCNU was not administered before operation, The interval between surgery and drug administration was one week or more.

Cerebrospinal fluid was obtained routinely for protein and sugar determination and, in some cases, for cultivation of tumor cells in vitro.

After each treatment, each patient was discharged home or to another hospital. Ambulatory patients were followed in our outpatient clinic for assessment of physical and neurologic conditions.

Treatment

CCNU was yellow powder and was kept in a desiccator at −20°C. The drug was given orally about 3 hours after meal. The usual dose ranged from 2.0 to 4.0mg/kg. The treatment was repeated in some cases at an interval of 2. 4 or 6 weeks.

Termination of Treatment

A patient was considered to have failed to respond to CCNU if he showed no neurological improvement or if he showed clinical deterioration one week after the administration. At first, treatment was not repeated when a patient failed to respond. But later at least 2 treatments were considered to be necessary for the evaluation of antitumor activity of the drug.

CCNU was usually administered during hospitalization except in 2 patients who were given the drug after discharge.

We considered that CCNU was effective when a patient showed clear clinical neurological or psychic improvement, or when remarkable reduction of skin tension overlying a skull defect was noted in the cases whose bone flap were removed at operation.

Results

The 15 patients received a total of 33 doses of CCNU. Among them 14 patients could be followed for assessment of the effects of CCNU. Table 1 shows the diagnosis of these 15 patients the rate of effectiveness, and follow-up periods after treatment. Neurological improvement, when noticed, was observed about 1 week or more after administration and perisisted for several weeks. In highly malignant gliomas, neurological improvement was not obvious, but rapidly progressing symptoms were sometimes arrested for several weeks. Any way in all patients except those with craniopharyngioma and one included in miscellaneous group, exacerbation was noticed again after several weeks of improvement. One miscellaneous patient (probably astrocytoma) has been showing steady and gradual improvement over 5 months. Two patients with craniopharyngiomas are unable to be evaluated for response in a short time period because of their benign nature of the disease. More long interval of observation will be necessary.

Correlation between the rate of effectiveness and the number of doses are shown in Table 2. The data does not show that a single dose of CCNU was not effective

Table 1 Chemotherapy data on fifteem patients receiving CCNU

Diagnosis	Total number of patients	Effective	Follow-up periods in months*
Glioblastoma	7	4/7	$6\frac{1}{3}$, 9, $9\frac{1}{3}$, 8, $3\frac{1}{3}$, $3\frac{2}{3}$, 3
Astrocytoma	1	1/1	$7\frac{1}{3}$
Ependymoblastoma	1	1/1	$6\frac{1}{3}$
Craniopharyngioma	2	0/2	$4\frac{3}{1}$, $3\frac{1}{3}$
Metastasis (Squamous cell carcinoma)	1	0/1	$1\frac{2}{3}$
Fibrosarcoma	1	?/1	?
Miscellaneous	2	1/2	$7\frac{1}{3}$, $8\frac{1}{3}$
Total response		7/14	

* Patients underlined died.

Table 2 Correlation between the rate of effectiveness and the number of doses

Number of doses	Total number of patients	Rate of effectiveness
1	4	0/4
2	9	5/9
3	0	
4	0	
5	1	1/1
6	1	1/1

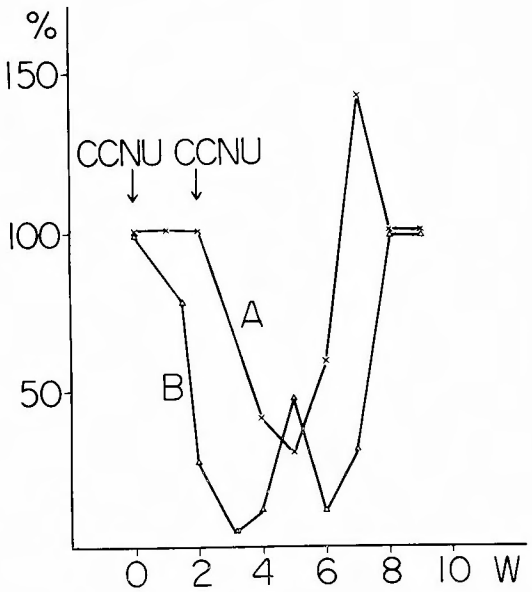

Fig. 1. Two typical courses of thrombocyte count after 2 treatment of CCNU. Patient (A) received CCNU 2.7 mg/kg (first) and 3.5 mg/kg (second) respectively, and patient (B) received CCNU 3.5mg/kg both times.

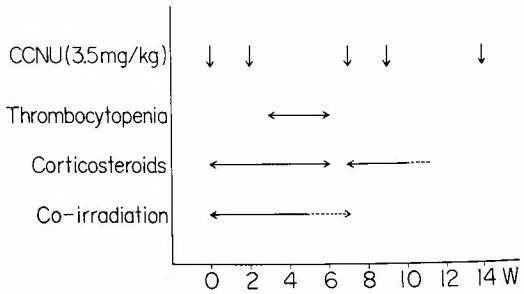

Fig. 2. The treatment schedule we are performing recently. The indincation of cobalt irradiation depends on the histological type of the tumor.

and multiple doses were effective. At first in our studies, second treatment was not adopted when first treatment failed to evoke response. But later at least two treatments were given for each case.

The main adverse effects observed were grave thrombocytopenia, mild leucopenia (usually>3,000 cells/mm^3), and mild elevation of GOT 50-80mU/ml. These adverse effects were usually observed 2 to 4 weeks after the first treatment or one to 3 weeks after the second treatment of our dose schedule and persisted for a few days

to 2 weeks (Fig. 1). Only one exception was a patient who showed permanent thrombocytopenia (about 10,000) after 2 treatments of CCNU and cobalt irradiation. Bone marrow toxicity of CCNU seemed to be cumultive. Patients who received CCNU over 5 times showed a tendency to be more severely affected in thrombocyte count in association with their number of treatments. In one patient with craniopharyngioma (Fig. 1), thrombocytopenia was so grave (about 10,000) that whole blood was transfused, although he showed as hemorrhagic diathesis. Another patient with craniopharyngioma showed the same tendency as well. Therefore, we consider that the dose of CCNU should be reduced in patients with craniopharyngioma.

Leucocytopenia was observed only in a few cases in mild degree ($>$3,000 cells/mm^3). No clinically evident infections were observed in all patients. Mild elevation of GOT titer was observed in about half of the patients. The elevation usually continued for one or more weeks. But other liver function tests including GPT, or serum biochemical analysis remained within normal limits.

No disturbances of kidney function was noted.

Recently 3.5mg/kg of CCNU is administered at 2 weeks interval. This schedule is repeated at 4 to 6 weeks interval. Corticosteroids and, if necessary, cobalt irradiation are combined (Fig. 2). Corticosteroids may be useful to prevent severe bone marrow depression, and to eliminate brain edema occurring in and around tumors, in association with its suspected antitumor activity[3,6].

Discussion

CCNU has an advantage of being administered orally in a single dose. Moreover, as already mentioned, CCNU can be given to the patients after discharge. In fact, one of our series was controlled by CCNU after hospitalization. Recently CCNU is administered as shown in Fig. 2. This dose regimen seems to be more effective than the usual regimen (at a dose of 130mg/M^2 every six weeks)[2], but precise comparison is not yet made. This dose regimen has a tendency to evoke severe cumulative thrombocytopenia, which, however, will improve in a week or so. In craniopharyngioma, cumulative cytotoxicity of CCNU seemed to be more severe and it might be appropriate to reduce the dose of CCNU from 3.5 to 3.0mg/kg. With 3.5mg/kg of CCNU, all of the patients developed nausea or vomiting on the day of administration, and anorexia for 2 to 3 days thereafter. But otherwise every patient was doing well. Even severe thrombocytopenia evoked no hemorrhagic diathesis.

One patient in this series and the another patient not included in this series, treated with cobalt irradiation previously, responded to CCNU. One patient in this series and the another patient not included in this series, treated with vincristine previously, also responded to CCNU. These indicate no cross reactivity between CCNU and cobalt irradiation or vincristine.

Neurological improvement in glioblastoma group differed from patient to patient. As a rule, a patient with highly malignant tumor responded to CCNU for a short period and weakly, whereas one with low malignancy responded for a long period and strongly.

As for termination of this treatment, any rule was not concluded. Permanent

bone marrow depression, as was observed in one of our series must be, of course, one of the indication for termination. Whether a patient who responds to CCNU and shows steady neurological improvement, should be treated repeatedly, will be decided in future.

Our results suggest that CCNU have mild antitumor activity against brain tumors and is more effective if other antitumor drugs or cobalt irradiation are combined.

Abstract

Fifteen patients with various brain tumors have been treated with CCNU between September 1971 and June 1972. Neurological improvement was observed in 7 of 14 patients (50%), and 6 of 9 glioma patients (66%). Neurological improvement persisted usually for two to several weeks, indicating mild anti-tumor activity of CCNU against human brain tumors. Dose-limiting factors were severe delayed thrombocytopenia and mild leucocytopenia, which, however, all of the patients tolerated well. Other severe adverse effects were not observed. The drug was also tolerated by the patients who had been treated by vincristine or cobalt irradiation. Our results suggest that CCNU might be a useful adjunct to other antitumor drugs or cobalt irradiation.

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和文抄録

1-(2-Chloroethyl)-3-Cyclohexyl-1-Nihosourea (CCNU) による脳腫瘍に対する治療

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1971年9月から1972年6月までの間に15例の脳腫瘍患者に CCNU を投与した．神経学的症状の軽快は14例中7例 (50%)， glioma は9例あり，この中6例 (66%) にみられた．神経学的軽快は2週間から数週間に亘って持続した． 副作用としては thrombocytopenia と軽度の leucocytopenia であるが，重篤なものではない．CCNU は vincristine を投与した患者や cobalt 照射後の患者にも投与できる利点があるので，併用療法が望ましい．