Intra-arterial ACNU Chemotherapy Employing 20% Mannitol Osmotic Blood-brain Barrier Disruption for Malignant Brain Tumors

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Abstract

The clinical effects and problems of intra-arterial water-soluble antitumor nitrosourea (ACNU) therapy following osmotic blood-brain barrier modification are discussed. Twenty-one patients with malignant brain tumors were divided into two groups. Group 1 consisted of 16 patients treated by operation, irradiation, and two or more courses of intracarotid infusion of ACNU 100 mg/body (1.7-2.2 mg/kg) following 20% mannitol 200 ml (1.3-1.6 ml/sec) (7 grade 4 astrocytomas, 5 grade 3 astrocytomas, and 4 others). Group 2 consisted of five patients treated by operation, irradiation, and repeated intracarotid infusion of ACNU 100 mg/body alone (grade 4 astrocytoma). The 2-year survival rate in Group 1 was 79% (11 of 14 cases followed up for longer than 2 years) and the 3-year survival rate was 67%. Five of seven grade 4 astrocytoma patients (71%) in Group 1 survived for more than 1 year 6 months, whereas four of five grade 4 astrocytoma in Group 2 died within 1 year 6 months. The measurement of the ACNU concentration in tumor tissues and blood in 11 brain tumors, after intracarotid infusion of ACNU with blood-brain barrier disruption, showed peak values in the tumor tissues of 3.02-32.53 μg/gm (mean, 9.67 μg/gm), about three to five times as high as that in blood in most cases. This method used in Group 1 appears to be relatively safe without permanent neurological deficits and offers a potential therapeutic effect when used in combination with appropriate premedication in suitable patients.

Key words: chemotherapy, osmotic blood-brain barrier disruption, ACNU, malignant glioma, intra-arterial chemotherapy

Introduction

Although various therapeutic methods have been tried to treat malignant brain tumors, no established method can predictably enhance the survival prognosis at present. According to Shapiro and Ausman and Edwards et al., the mean survival time for glioblastoma patients treated by surgical removal and radiation therapy is 7.5-9.5 months. The Brain Tumor Registry in Japan documents the 2-year survival rate of glioblastoma patients at 21% and the 5-year survival rate at 10%, thus further substantiating this poor prognosis.

One important factor affecting the therapeutic effects of chemotherapy on malignant brain tumors is the diffusion of medication across the blood-brain barrier (BBB). Recently, it has been shown that the nature of the BBB differs with location even within a tumor itself, independent of histology, size, and anatomical localization. Electron microscopy has shown the endothelial cell clefts in microvessels of brain tumors vary widely, from normal to abnormal, for different parts of a single tumor. Rapoport et al., Bullard and Bigner, and Kagawa have reported that the BBB was temporarily and reversibly disrupted by intra-arterial infusion of high osmotic pressure solutions. Furthermore, Neuwelt et al. and Bonstelle et al. have applied this phenomenon clinically. Working with 9L gliosarcoma-transplanted rats, we previously reported the efficacy of a combination therapy including intra-arterial infusion of a high osmotic pressure solution and ACNU [3-(14-amino-2-methyl-5-pyrimidinyl)
methyl)-1-(2-chloroethyl)-1-nitrosourea hydrochloride]. In the present study, intra-arterial infusion of ACNU and 20% mannitol, as a high osmotic pressure solution, was performed on patients with malignant brain tumors. The therapeutic results, drug delivery into the tumor and adjacent normal brain, and neurotoxicity complications are reported.

Materials and Methods

I. Therapeutic methods and materials

Twenty-one patients with malignant brain tumors were divided into two groups.

Group 1 consisted of 16 patients, who received two or more courses of intracarotid infusion of 20% mannitol 200 ml and ACNU 100 mg/body in addition to surgical tumor removal and irradiation (Table 1). All patients except one were adults from 19 to 72 years in age. Histologically, seven cases were grade 4 astrocytoma, five grade 3 astrocytoma, and one each of anaplastic oligodendroglialoma, malignant ependymoma, malignant lymphoma, and germinoma in the basal ganglia. The tumor site was the frontal lobe in eight cases, the temporal lobe in two, the parietal lobe in two, and the basal ganglia and thalamus in four.

Surgery involved total removal of the tumor in seven cases, subtotal removal in three, and partial removal in six. Irradiation was performed in 12 patients at doses ranging from 4000 to 6000 rads, except one irradiated at 7000 rads. Following premedication with atropine sulfate, diazepam, pentazocine, etc., selective intra-arterial infusion via the internal carotid artery was performed using either the Seldinger method or catheterization with a 4-Fr. introducer through the common carotid artery via

### Table 1 Clinical summary of Group 1 patients

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age/Sex</th>
<th>Location of tumor</th>
<th>Histological diagnosis</th>
<th>Extent of tumor removal</th>
<th>Times of intra-arterial infusion of 20% mannitol and ACNU</th>
<th>Radiation (rads)</th>
<th>Outcome (survival time after operation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>42/M</td>
<td>basal ganglia</td>
<td>astrocytoma, grade 4</td>
<td>partial</td>
<td>8</td>
<td>5050</td>
<td>died (2 yrs 11 mos)</td>
</tr>
<tr>
<td>2</td>
<td>55/F</td>
<td>rt frontal</td>
<td>astrocytoma, grade 4</td>
<td>total</td>
<td>6</td>
<td>5400</td>
<td>alive (4 yrs)</td>
</tr>
<tr>
<td>3</td>
<td>41/M</td>
<td>rt frontal</td>
<td>astrocytoma, grade 4</td>
<td>subtotal</td>
<td>3</td>
<td>—</td>
<td>died (1 yr)</td>
</tr>
<tr>
<td>4</td>
<td>72/F</td>
<td>lt thalamus</td>
<td>astrocytoma, grade 4</td>
<td>total</td>
<td>2</td>
<td>5940</td>
<td>died (1 yr)</td>
</tr>
<tr>
<td>5</td>
<td>47/M</td>
<td>temporo-occipital</td>
<td>astrocytoma, grade 4</td>
<td>total</td>
<td>2</td>
<td>6000</td>
<td>alive (1 yr 8 mos)</td>
</tr>
<tr>
<td>6</td>
<td>60/M</td>
<td>lt parietal</td>
<td>astrocytoma, grade 4</td>
<td>total</td>
<td>2</td>
<td>4840</td>
<td>alive (1 yr 8 mos)</td>
</tr>
<tr>
<td>7</td>
<td>31/M</td>
<td>rt temporal</td>
<td>astrocytoma, grade 4</td>
<td>subtotal</td>
<td>2</td>
<td>4780</td>
<td>died (1 yr 6 mos)</td>
</tr>
<tr>
<td>8</td>
<td>54/F</td>
<td>rt frontal, corpus callosum</td>
<td>astrocytoma, grade 3</td>
<td>total</td>
<td>4</td>
<td>—</td>
<td>alive (3 yrs 8 mos)</td>
</tr>
<tr>
<td>9</td>
<td>46/F</td>
<td>lt occipito-parietal</td>
<td>astrocytoma, grade 3</td>
<td>total</td>
<td>3</td>
<td>4000</td>
<td>alive (3 yrs 6 mos)</td>
</tr>
<tr>
<td>10</td>
<td>36/F</td>
<td>rt frontal</td>
<td>astrocytoma, grade 4</td>
<td>partial</td>
<td>3</td>
<td>—</td>
<td>alive (2 yrs 11 mos)</td>
</tr>
<tr>
<td>11</td>
<td>24/F</td>
<td>rt frontal, corpus callosum</td>
<td>astrocytoma, grade 3</td>
<td>partial</td>
<td>6</td>
<td>5150</td>
<td>alive (3 yrs 6 mos)</td>
</tr>
<tr>
<td>12</td>
<td>42/M</td>
<td>rt frontal, basal ganglia, temporal</td>
<td>astrocytoma, grade 3</td>
<td>total</td>
<td>2</td>
<td>—</td>
<td>alive (2 yrs)</td>
</tr>
<tr>
<td>13</td>
<td>37/F</td>
<td>rt frontal</td>
<td>anaplastic oligodendrogloma</td>
<td>partial</td>
<td>2</td>
<td>5000</td>
<td>alive (3 yrs 9 mos)</td>
</tr>
<tr>
<td>14</td>
<td>19/M</td>
<td>lt basal ganglia</td>
<td>germinoma</td>
<td>partial</td>
<td>6</td>
<td>7000</td>
<td>died (3 yrs 4 mos)</td>
</tr>
<tr>
<td>15</td>
<td>58/M</td>
<td>lt basal ganglia</td>
<td>malignant lymphoma</td>
<td>partial</td>
<td>2</td>
<td>5000</td>
<td>alive (3 yrs 8 mos)</td>
</tr>
<tr>
<td>16</td>
<td>1/M</td>
<td>rt frontal, paraventricle</td>
<td>malignant ependymoma</td>
<td>subtotal</td>
<td>3</td>
<td>4980</td>
<td>alive (3 yrs 11 mos)</td>
</tr>
</tbody>
</table>

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direct puncture. Infusion of 20% mannitol 200 ml (1.3–1.6 ml/sec) was followed by infusion of ACNU 100 mg/body/5 min (1.7–2.2 mg/kg), except one child who was infused with 20% mannitol 50 ml (0.7 ml/sec) following by ACNU 30 mg/body/3 min. The frequency of intra-arterial infusion of ACNU and 20% mannitol was twice in six cases, three times in five, four in one, six in three, and eight in one.

The follow-up period as of now ranges from 1.5 to 4 years. Evaluation of the results using computed tomography (CT) was based on the criteria presented by the Brain Tumor Study Group, the Ministry of Health and Welfare, Japan. Group 2 consisted of five grade 4 astrocytoma patients, who received repeated intra-arterial infusion of 100 mg/body of ACNU in addition to surgical tumor removal and irradiation (Table 2). Their ages ranged from 12 to 58 years, and the tumor site was the frontal lobe in two cases, the parietal lobe in one, the occipital lobe in one, and the thalamus in one.

Surgery included subtotal removal in three cases and partial removal in two. Irradiation was performed at doses of 5040 to 6300 rads. After surgery, intra-arterial infusion of ACNU was repeated from two to four times.

### II. ACNU tissue concentration

ACNU delivery into the tumor tissue and blood was examined in 11 brain tumor cases (7 grade 4 astrocytomas, 1 grade 3 astrocytoma, 2 grade 2 astrocytomas, and 1 germinoma). After catheterization of the internal carotid artery using the Seldinger method, 200 ml of 20% mannitol and 100 mg/body of ACNU were intra-arterially infused during surgery. At 5, 10, 15, 20, 25, 30, 40, and 60 minutes after the infusion, a 2 ml blood sample and tumor specimens were taken and immediately frozen. Tumor sampling was performed in marginal solid sections and in relatively deep necrotic sections for comparison. In the three of seven grade 4 astrocytoma cases, the ACNU concentration in the normal brain tissue adjacent to the tumor was also determined to compare with that in the tumor tissue.

The determinations of ACNU concentration in the tumor, surrounding normal brain, and blood were performed according to the method described by Nakamura et al. as follows. The frozen specimen was extracted with 1,2-dichloroethane at 0°C in the dark. ACNU was separated by high-performance liquid ion exchange chromatography using a reverse phase column and analyzed using the UV absorption at 254 nm.

### III. Complications

The incidence of complications was assessed in 32 patients who received intra-arterial infusion of 20% mannitol plus ACNU or 20% mannitol plus 60% Conray (19 grade 3 and 4 astrocytomas, 5 grade 2 astrocytomas, 1 anaplastic oligodendroglioma, 1 malignant ependymoma, 1 pontine glioma, and 5 other non-gliomas). In 27 of the 32 cases, intra-arterial infusion of 20% mannitol 200 ml and ACNU was performed a total of 45 times. The infusion of 20% mannitol and 60% Conray 100 ml into the internal carotid artery was performed once for each of 30 cases.

Possible complications were assessed with reference to: 1) clinical symptoms, changes in neurological findings, and various investigations including hematology and liver functional tests; 2) changes in blood pressure, pulse rate, and electrocardiogram (EKG) before and after the infusion; and 3) continuous electroencephalographic (EEG) recording before and after the infusion.

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**Table 2** Clinical summary of Group 2 patients

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age/ Sex</th>
<th>Location of tumor</th>
<th>Histological diagnosis</th>
<th>Extent of tumor removal</th>
<th>Times of intra-arterial infusion of ACNU</th>
<th>Radiation (rads)</th>
<th>Outcome (survival time after operation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>12/M</td>
<td>Lt frontoparietal</td>
<td>astrocytoma, grade 4</td>
<td>partial</td>
<td>3</td>
<td>5040</td>
<td>died (1 yr 3 mos)</td>
</tr>
<tr>
<td>18</td>
<td>37/M</td>
<td>Lt frontal</td>
<td>astrocytoma, grade 4</td>
<td>subtotal</td>
<td>4</td>
<td>6000</td>
<td>died (3 yrs 7 mos)</td>
</tr>
<tr>
<td>19</td>
<td>17/F</td>
<td>Lt occipital</td>
<td>astrocytoma, grade 4</td>
<td>subtotal</td>
<td>3</td>
<td>6150</td>
<td>died (1 yr)</td>
</tr>
<tr>
<td>20</td>
<td>58/M</td>
<td>Lt occipitoparietal</td>
<td>astrocytoma, grade 4</td>
<td>subtotal</td>
<td>4</td>
<td>6060</td>
<td>died (7 mos)</td>
</tr>
<tr>
<td>21</td>
<td>55/M</td>
<td>Lt thalamus</td>
<td>astrocytoma, grade 4</td>
<td>partial</td>
<td>2</td>
<td>6300</td>
<td>died (1 yr 2 mos)</td>
</tr>
</tbody>
</table>
Results

I. Therapeutic effects

Group 1: Eleven of the 16 patients are alive at present. Death occurred about 1 year after operation in two cases and at 1 year 6 months, 2 years 11 months, and 3 years 4 months in one each. Two-year survival has been achieved by 11 of the 14 patients (79%) who could be followed over that period and 3-year survival by eight of 12 (67%). Among seven patients with grade 4 astrocytoma, two died about 1 year after surgery and one each died after 1 year 6 months and 2 years 11 months. The three cases surviving comprise one for whom 4 years have elapsed since surgery and two for whom 1 year 8 months have elapsed (Fig. 1, Table 1).

Therapeutic evaluation using CT was performed by dividing the subjects into two subgroups: the seven cases with a residual tumor image on a postoperative CT scan and nine showing no residual tumor image. In the seven cases with a residual tumor, therapeutic effect was observed in four (57%), consisting of two complete remission (CR) cases where the tumor image had disappeared and two partial remission (PR) cases with a 50% or more reduction in tumor size. The remaining three cases showed no change. Five of the nine cases with no residual tumor showed no recurrence during follow-up periods. The remaining four cases showed tumor progression at 11 months, 1 year 3 months, 1 year 6 months, and 3 years 6 months after surgery.

Group 2: Except for one patient who died 3 years 7 months after surgery, all died within 1 year 6 months (Fig. 1, Table 2). Regarding CT findings, two cases at first showed PR but died due to the re-enlargement of the tumor soon after.

II. Case reports

Case 1: A 42-year-old male underwent partial removal of the grade 4 astrocytoma (about 30% removed) in parallel with intra-arterial infusion of 200 ml of 20% mannitol and 100 mg of ACNU. Reduction in the tumor size was found following postoperative irradiation at a dose of 5050 rads, becoming more evident after an additional intra-arterial infusion of the 20% mannitol and ACNU. A CT scan showed only slight enhancement in the tumor margin, and the therapeutic effect was assessed as PR (Fig. 2). His condition was fairly good

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Fig. 1 Percent survival rate of malignant glioma patients: five grade 3 astrocytoma in Group 1 (○), seven grade 4 astrocytoma in Group 1 (●: alive, □: died), and five grade 4 astrocytoma in Group 2 (○).

Fig. 2 Postcontrast CT scans in Case 1, grade 4 astrocytoma in the left temporal lobe and basal ganglia. left: Before treatment (1984), center: after irradiation and two courses of intra-arterial infusion of 20% mannitol and ACNU (Apr., 1984), right: after additional intra-arterial infusion (Sept., 1985).

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after five courses of intra-arterial infusion of 20% mannitol and ACNU. However, tumor progression appeared 2 years 5 months after the operation and he died due to spinal and ventricular wall metastases 6 months later.

Case 15: A 58-year-old male suffered from primary malignant lymphoma in the left basal ganglia. Although only biopsy could be performed during surgery, the tumor was reduced in size following intra-arterial infusion of 20% mannitol and ACNU in addition to postoperative irradiation at a dose of 5000 rads. An additional intra-arterial infusion of 20% mannitol and ACNU succeeded in diminishing the tumor image (Fig. 3), and he still survived without any disturbances in daily life 3 years 8 months after surgery.

Case 22 (a recent case not listed in Tables 1 and 2): A 65-year-old female received macroscopic total removal of a grade 4 astrocytoma in the left temporal lobe at another hospital on April 27, 1987. Two intra-arterial infusions of ACNU 100 mg, intravenous infusion of a total of 93 x 10^6 units of interferon β, and subcutaneous injection of OK 432 were given after surgery, however, 5 months later, the tumor gradually increased in size. On October 28, 1987, macroscopic total removal was again performed and a total of 25 x 10^6 units of interferon β were locally infused through an Ommaya reservoir. She was admitted to our department due to distinct tumor recurrence detected on a CT scan taken on December 18, about 1.5 months after surgery. On December 24, 200 ml of 20% mannitol and 80 mg/body of ACNU were intra-arterially infused and radiation therapy was performed at a dose of about 3000 rads. A CT scan taken on January 27, 1988, showed CR (Fig. 4).

III. ACNU delivery into tissue

The ACNU concentration in the blood in 11 cases showed a peak of 2.05-4.45 μg/ml 5 minutes after the intra-arterial infusion of 100 mg/body of ACNU and 200 ml of 20% mannitol, as reported in a previous paper. The half-life was 20 minutes at a drug concentration of 0.86-2.70 μg/ml decreasing to 0.29-0.85 μg/ml after 1 hour. These values were generally lower than those in the tumor.

The ACNU concentration in the (solid) tumor in 11 cases reached a peak of 3.02-32.53 μg/gm (mean, 9.67 μg/gm) 5-10 minutes after the intra-arterial infusion, and many cases showed a high ACNU concentration in the tumor of approximately three to five times that in the blood. The ACNU concentration in the marginal solid tumor was two to three times that in the relatively deep necrotic tumor. The ACNU concentration in the surrounding normal brain tissue examined in three cases of grade 4 astrocytoma showed a peak of 2.49-3.22 μg/gm (mean, 2.88 μg/gm) 5-15 minutes after the intra-

Fig. 3 Postcontrast CT scans in Case 15, malignant lymphoma in the left basal ganglia. left: Before treatment (Apr., 1984), right: after irradiation and two courses of intra-arterial infusion of 20% mannitol and ACNU (Sept., 1984).

Fig. 4 Postcontrast CT scans in Case 22, grade 4 astrocytoma in the left temporal lobe. upper: Before treatment (Dec., 1987), lower: after irradiation (1000 rads) and intra-arterial infusion of 20% mannitol and ACNU (Jan., 1988).
arterial infusion, similar to that within the tumor. These values were, however, generally lower than those in the tumor, as seen in Fig. 5. The ratio of ACNU concentration in the surrounding normal brain tissue to that in the tumor of the same patient was 3.22/3.02 (1.07), 2.49/3.25 (0.77), and 2.92/3.34 (0.87) in these three cases. Therefore, the ACNU concentration in the surrounding normal brain was slightly lower or almost equal to that in the tumor.

Fig. 5  ACNU concentration in the solid (●) and necrotic (■) tumor tissues and surrounding normal brain tissues (○) after the intra-arterial infusion of ACNU following 20% mannitol. Each bar represents SD.

IV. Complications

Complications in 27 patients treated with the intra-arterial infusion of 20% mannitol and ACNU were: vomiting or headache in eight of 45 infusions (18%), transient neurological deficits which improved within 2–3 days in three (7%) (one each of motor aphasia, hemiparesis, and disorientation), decreased leukocyte level of less than 3000/mm³ in five, decreased platelet level of less than 10⁵/mm³ in two, and liver dysfunction in three (Table 3). Therefore, the ACNU concentration in the surrounding normal brain was slightly lower or almost equal to that in the tumor.

Continuous EEG monitoring for up to 4 hours after the intra-arterial infusion of 20% mannitol and ACNU was performed in five cases. No change was detected before or after the infusion, except for abnormal findings due to the tumor itself. Furthermore, no appearance of bradycardia or sharp spike was observed in any cases examined (Fig. 6).

Complications observed following intra-arterial infusion of 20% mannitol and 60% Conray included vomiting or headache in six of 30 cases (20%), convulsion in two (7%), transient neurological deficits in two (7%), and brain swelling in one (Table 3). The case of brain swelling was a glioblastoma with predominantly increased intracranial pressure. However, the brain swelling seemed to be attributable to the substantial transmigration of the contrast medium (60% Conray) into the brain tissue. The catheterization procedure during examination was also criticized and the cause and effect are now under histological investigation utilizing the brain obtained by autopsy.

Discussion

Although the treatment of malignant brain tumors has improved with the progress in image diagnosis and the various newly developed therapeutic approaches in recent years, therapeutic results are not yet particularly favorable. Factors influencing the prognosis of malignant glioma include the histological and clinical malignancy of the tumor, the patient’s age, the tumor site, the extent of the tumor removal, and combination with radiation therapy and/or chemotherapy.
It is natural that drug sensitivity against a given malignant brain tumor is important in the chemotherapy, however, the extent of drug transfer into the tumor is also important, that is, the vascular permeability is critical. Blood vessels in tumors do not always have an evenly disrupted BBB, especially in the marginal region. The vascular permeability may be influenced by 1) the degree of BBB disruption and 2) the regional blood flow in the tumor, as well as 3) fat or water solubility and 4) the molecular weight of the drug used. In addition, a transient BBB opening caused by intra-arterial infusion of a high osmotic pressure solution such as mannitol has been reported as a method to artificially enhance the vascular permeability of drugs.

Fat-soluble nitrosourea preparations with molecular weights of 214, 234, and 309 (BCNU, CCNU, ACNU) are now widely used to treat malignant glioma, because of their high permeability across the BBB. In the present study, ACNU delivery into the tumor tissue following intra-arterial administration of 200 ml of mannitol and 100 mg/body of ACNU reached a peak of 3.02–32.53 μg/gm after 5–10 minutes. The ACNU concentration in the tumor was about three to five times as high as that in the blood. This suggests that the ACNU concentration in the tumor varies according to the route of administration even though the drug has a high permeability across the BBB. The ACNU concentration in the marginal solid tumor, with an abundant supply of regional blood flow, was about two to three times as high as that in the relatively deep necrotic tumor. In the cases showing a markedly enhanced tumor image on postcontrast CT scans using 20% mannitol, a high ACNU concentration in the tumor, correlating with the degree of enhancement on CT, was found.

In our previous study using an experimentally induced brain tumor (9L gliosarcoma), the mean survival time was 1.51 days after implantation in the untreated group, 21.8 days in the ACNU intraperitoneally treated group, and 27.9 days in the 20% mannitol plus ACNU intra-arterially treated group. A significantly prolonged survival time was shown in the last group. With regard to tumor size, histological findings, and tumor proliferation according to the labeling index of bromodeoxyuridine, the therapeutic effect appeared to be better in the mannitol and ACNU intra-arterially treated group. Neuwelt et al. used an intra-arterial infusion of methotrexate, cytoxan, and procarbazine with BBB modification combined with surgical removal and radiation therapy in 38 gliosarcoma-transplanted animals. They reported a mean survival time of 17.5 months, which was significantly longer than that in the systemically treated group with surgical removal, radiation therapy, and chemotherapy. Bonstelle et al. employed a combination therapy of intra-arterial infusion of 120 ml of 25% mannitol, 5 FU, and adriamycin and intravenous infusion of BCNU, and observed that six of seven patients with comatose glioblastoma regained consciousness and 11 of 13 tumors reduced in size on CT scans.

In the present study, the ACNU concentration in normal brain tissue adjacent to the tumor ranged from 2.49 to 3.22 μg/gm. The ratio of ACNU concentration in the surrounding normal brain to that in the tumor of the same subjects was 1.07, 0.87, and 0.77 in the three cases, showing the former level to be slightly lower or almost equal to the latter. ACNU...
concentration in distal normal brain tissues could not be assessed, because the subjects in this study were pathological cases. In addition, ACNU delivery by intra-arterial infusion of ACNU alone (Group 2) will be studied in the future.

In our previous study with an experimental 9L gliosarcoma-implanted brain tumor, the cisplatin concentration in the tumor after intra-arterial infusion of a high osmotic pressure solution and cisplatin via the internal carotid artery was found to be about 10 times as high as that after intravenous infusion of these drugs and about two times as high as that after intra-arterial infusion of cisplatin alone. Although almost no difference was found in the drug concentration within the tumor between 25% and 20% mannitol, that in the surrounding normal brain was relatively less when 20% mannitol was used. On the other hand, some investigators, using experimentally induced brain tumors, observed marked drug transfer into the surrounding normal brain but no increase in drug delivery into the tumor when a high osmotic pressure solution was intra-arterially administered. The discrepancy in these results might be due to various factors including the experimental animals used, the tumor model employed, the vascular construction of the tumor, the drugs used, and the method of administration.

The possible complications in the cases of intra-arterial infusion with BBB disruption using a high osmotic pressure solution differ according to the concentration of the high osmotic pressure solution used, its infusion rate, and the kind of drug used. Neuwelt et al. reported that combination therapy of 25% mannitol infusion at a rate of 240–300 ml/30 sec and intra-arterial infusion of methotrexate resulted in no deaths but permanent neurological deficits, transient neurological deficits, and convulsion in three, 22, and 21 of 38 cases examined. They also observed, in four autopsied glioblastoma cases after treatment, no leukoencephalopathy due to the drug in the normal hemisphere on the tumor side. Bonstelle et al. treated 18 patients of glioblastoma with intra-arterial infusion of 25% mannitol at a rate of 120 ml/2 min followed by adriamycin and 5 FU, and found brain swelling in two cases and seizure in two.

In the present study, only three of 27 cases (3/45 infusions) showed transient neurological deficits after intra-arterial infusion of 200 ml 20% mannitol and 100 mg/body ACNU, while intra-arterial infusion of 20% mannitol and 100 ml 60% Conray induced convulsion in two cases, transient neurological deficits in two, and brain swelling in one. 60% Conray is no longer used in our clinic, because of its high incidence of complications compared to ACNU.

Chemotherapy using osmotic BBB disruption is only a supplementary treatment to stimulate the delivery of a given chemotherapeutic agent to tumor tissues. The drug sensitivity of the tumor is thus an important factor influencing the therapeutic effect, and more effective drugs are expected to be developed in the future. Furthermore, chemotherapy using the present method seems to be fairly effective in patients who have a high regional blood flow, that is, those who exhibit a markedly enhanced tumor image on CT scans. We intend to continue our follow-up survey of clinical cases and to examine an approach to prevent complications as much as possible.

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**References**


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