Radiosensitization of Brain Tumor Cells with a Thymidine Analogue (Bromouridine)*

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TREATMENT of malignant brain tumors has been one of the biggest problems in neurosurgery. If surgical removal is not feasible, two other ways of treatment are available at present, namely, radiation therapy and chemotherapy. Chemotherapy has not yet produced satisfactory results. Radiation therapy is variably effective in some kinds of brain tumor, such as medulloblastoma, ependymoma, pinealoma, and pituitary adenoma. If a way could be found to enhance the radiosensitivity of these and other brain tumors, it would make radiotherapy much more valuable. Many such agents have been examined. Bagshaw classified these agents into four groups according to the mode of action: 1) sensitization, 2) augmentation, 3) potentiation, and 4) additivity.

We have been greatly interested in one of thymidine analogues that strongly enhances the radiosensitivity of the cells, 5-bromo-2-deoxyuridine (bromouridine or BUdR), which belongs to Bagshaw's group 1 (sensitization). In this agent, only the methyl radical of the 5th position of the pyrimidine ring of thymidine is replaced by bromine, as shown below.

\[
\begin{align*}
N & \equiv S\text{CH} \\
N & \equiv S\text{CH} \\
N & \equiv S\text{CH} \\
\text{Pyrimidine}
\end{align*}
\]

\[
\begin{align*}
O & \equiv C \\
O & \equiv C \\
N & \equiv C \\
\text{Riboze}
\end{align*}
\]

\[
\begin{align*}
O & \equiv C \\
O & \equiv C \\
N & \equiv C \\
\text{Deoxyribose}
\end{align*}
\]

\[
\begin{align*}
O & \equiv C \\
O & \equiv C \\
N & \equiv C \\
\text{Thymidine}
\end{align*}
\]

\[
\begin{align*}
O & \equiv C \\
O & \equiv C \\
N & \equiv C \\
\text{BUdR}
\end{align*}
\]

The BUdR is picked up by the deoxyribo-
nucleic acid (DNA) of the dividing cells instead of the thymidine; the sensitivity to irradiation of the cells that have incorporated the BUdR into DNA increases about two to three times, as measured by a single exposure to irradiation in vitro in such experimental tumors as D93S, D98Az, H. Ep. 1 (human epidermoid carcinoma of the cervix), ascitic P-388 (lymphocytic leukemia), L cell, Hepatoma 129, and E. coli. The BUdR, however, has almost no cytocidal or anti-metabolic effects on unirradiated cells. This fact aroused a keen interest from a view point of radiotherapy. Malignant tumors have higher mitotic rates and, accordingly, are thought to be much more vigorous in synthesizing DNA than normal tissues. Therefore, the rate of uptake of the BUdR into DNA should be much higher in tumors than in surrounding normal tissues, and the destructive effect of radiation could be enhanced selectively in the tumor cells.

Experimental Studies

Uptake of BUdR into the Human Brain Tumor Cell in Vitro. There have been no reports concerning incorporation of BUdR into brain tumor cells. We therefore wanted to confirm that this was possible with human brain tumor cells cultured by trypsinization monolayer method, using BUdR-3H (0.156 µg/ml or 1.56 µg/ml in the medium). It was confirmed that BUdR-3H was in fact taken up into the nuclei of cultured brain tumor cells such as those from glialblastoma, ependymoma, astrocytoma, oligodendrogliaoma, meningioma, and meningoarcoma. This was observed in five or six experiments with each tumor by radioautography. Figure 1 shows cultured cells of a case of astrocytoma; here radioautography was done after 2 days of incubation. As is seen, the black grains were concentrated in the cell nuclei.

The labelling index of BUdR-3H was found to be about the same as that of thymidine-3H; this fact seemed to indicate that BUdR was taken up by dividing cells at about the same rate as that for thymidine.

Received for publication September 6, 1967.

530
Brain Tumor Radiosensitization by Bromouridine

**Radiosensitizing Ability of BUdR in Vitro.** We had no established strains of brain tumor cell lines in the laboratory and were doubtful that we could do a quantitative study using primary cultures of brain tumors. However, since good constant growth had been obtained by the trypsinization monolayer technique in primary culture of brain tumors, we applied this simple and reliable method to investigating the effect of BUdR *in vitro*. The method used was as follows:

After obtaining a good proliferation of brain tumor cells in culture, we added 10 to 40 μg/ml of BUdR to the medium and incubated the bottles at 37°C for a period corresponding to the specific generation time of the tumor cells already obtained from the studies with labelling index of thymidine-3H. Then we irradiated the bottles with various amounts of x-ray (500 to 8000 r) in serial divided bands. Control bottles without BUdR were also irradiated at the same time. After the irradiation, the bottles were incubated at 37°C for 7 to 20 days. The materials were then fixed and stained. We determined the effect of the irradiation on the cells by observing the population of the cells and their morphological changes.19

Figure 2 shows the effect on cells grown from an oligodendroglioma. As seen in Fig. 2 (center), the effect of simple irradiation was usually slight. In the BUdR plus irradiation group (Fig. 2 right), however, pyknosis of the nuclei, decrease of stainability, and fibrous change of the cells were noted. The cell population was markedly reduced in this group.

These experiments show that cells that have incorporated BUdR *in vitro* are much more sensitive to irradiation. We would like to emphasize that BUdR alone had no in-

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**Fig. 1.** Radioautography of astrocytoma cells incubated for 2 days in the medium (60% Eagle L + 20% NCTC 109 + 20% calf serum) with 1.56 μg/ml of BUdR-3H (specific activity 10 μc/ml). Giemsa, ×400.

**Fig. 2.** Effect of BUdR on radiosensitization of tumor cells. Left: Oligodendrogioma incubated for 48 days in the medium (80% Eagle L + 20% calf serum) with 20 μg/ml of BUdR. The characteristics of the cells were almost the same as the cells cultured without BUdR. Giemsa, ×100. Center: The same oligodendrogioma cultured for 48 days without BUdR, then given 8000 r of x-ray. Giemsa, ×100. Right: The same oligodendrogioma cultured for 48 days with 20 μg/ml of BUdR, then given 8000 r of x-ray. Giemsa, ×100.
hibitory effect on the cells in vitro even in a long-term culture lasting 100 days.

Enhancement of BUdR Incorporation into Tumor Cells. The amount of BUdR incorporated into DNA was in proportion to the amount of BUdR in the medium, and this amount in turn determined the susceptibility of the cells to irradiation. The administration of a large amount of BUdR to accomplish this was impractical. We then found that a very small amount of an antimetabolite, such as Methotrexate, 5-fluoro-uracil (5-FU), or 5-fluoro-2'-deoxyuridine (FUdR), increased the uptake of BUdR into the cell nuclei in vitro. This fact was proved by the analysis of the number of grains of BUdR-3H in the nuclei of FL cells and oligodendroglio-

<table>
<thead>
<tr>
<th>Concentration in Medium</th>
<th>Grain Index with*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Methotrexate</td>
</tr>
<tr>
<td>0.1 mg/ml</td>
<td>3-5</td>
</tr>
<tr>
<td>0.001 mg/ml</td>
<td>3-5</td>
</tr>
</tbody>
</table>

* Grain index: The number of grains in the nuclei with antimetabolites in the medium divided by the number of grains in the nuclei without antimetabolites in the medium.

Fig. 3. Diagram of the role of antimetabolites in enhancing BUdR pick-up by DNA (thy = thymidine).

TABLE 1

Effect of antimetabolites on the incorporation of BUdR-3H in DNA

BAR Therapy

Based on these experimental results, we have set up a clinical trial of BUdR-antimetabolite-continuous intra-arterial infusion-radiation therapy. For brevity we call it BAR therapy.

The advantages of the therapy for malignant brain tumors are based on the following factors: 1) most brain tumors are solitary and rarely metastasize; 2) the surrounding nerve cells have no mitotic ability, and consequently they incorporate little BUdR into their DNA; 3) normal brain tissue should be protected by the blood-brain barrier from the administered BUdR whereas the tumor cells can be expected to be exposed to this drug because of breakdown of that barrier; 4) administration by intra-arterial infusion is easy. Intra-arterial infusion of the drug is necessary not only to obtain a high concen-
tation of BUdR in the tumor tissue but also to avoid dehalogenation of BUdR by the liver. More than 90% of BUdR is dehalogenated by the liver within 1 hour if it is administered intravenously. The fact that the effects of this drug can thus be minimized after it reaches the general circulation creates still another advantage for the method.

Method. The principle of BAR therapy involves administration of BUdR, which makes tumor cells radiosensitive, and an anti-metabolite (Methotrexate or 5-FU), which enhances BUdR incorporation into tumor cells by means of continuous intra-arterial infusion for a period longer than the estimated generation time of the tumor cells, and combined irradiation.

Usually, decompressive craniotomy was performed and a part of the malignant tumor excised. Then, after the pathological diagnosis had been confirmed, the carotid artery was exposed in the neck, and a siliconized polyethylene tube (1.4 mm in outer diameter and 1.0 mm in inner diameter) was usually inserted into the internal carotid artery via the common carotid artery as far as 3 to 4 cm distal to the bifurcation; 2 to 3 ml of 10% Patent Blue were then injected through the catheter to confirm the location of the tip of the catheter. If the tip was in the internal carotid artery, the ipsilateral forehead supplied by the ophthalmic artery was stained green. In two cases of scalp-skull cancer, the catheter was inserted into the external carotid artery. In one case of infratentorial tumor, the catheter was inserted into the vertebral artery. Continuous infusion was performed by means of a small infusion pump connected to the catheter.

Usually, 600 to 1000 mg of BUdR (in adults) and 1 to 5 mg (2 mg on average) of Methotrexate or 3 to 5 mg of 5-FU were infused per day, dissolved in 200 to 700 ml of saline without heparin. The amount of saline to be infused per day depends on the infusing ability of the pump. More than 700 ml of saline a day may cause brain edema, and less than 200 ml may cause occlusion of the catheter. A pump that infused 250 ml of saline a day was used in most of the cases. The duration of infusion was 4 to 7 weeks (an average of 5 weeks), the reason of which will be discussed later. The total amount of BUdR administered to each patient averaged 25,000 mg, the maximum so far being 34,000 mg.

Radiation therapy was started 7 to 14 days after commencement of the infusion and was repeated every day. During the radiotherapy, which lasted a little less than 1 hour, the infusion was temporarily interrupted and the catheter filled with heparin solution. The daily tumor dose of irradiation was about 150 to 200 r, for a total dose of 5,000 to 6,000 r.

Clinical Material. We selected 30 cases for BAR therapy as follows: 14 highly malignant gliomas (11 glioblastomas, 2 oligodendroblastomas, and 1 ependymoblastoma); 6 moderately malignant gliomas (3 oligodendrogliomas, 2 ependymomas, and 1 astrocytoma); 4 meningosarcomas; 4 other malignant tumors (one each of anaplastic papilloma of the choroid plexus, melanoma, scalp-skull cancer, and unverified thalamic tumor); and 2 metastatic tumors.

Results. Four patients died during BAR therapy. The first death was in a patient with glioblastoma of the left basal ganglia. A catheter was inserted into the left internal carotid artery and one course of the therapy (4 weeks of infusion and 6405 r of radiation) was completed. At the end of the therapy, left carotid angiography revealed a negative shift of the anterior cerebral artery, and right carotid angiography showed another vascularized tumor shadow in the right basal ganglia. Treatment through the right internal carotid artery was started, but the patient died during this second course of therapy. A second patient with glioblastoma in the temporal lobe died of uncal herniation due to involvement of the uncus itself by glioblastoma. A third patient with metastatic cancer died of incidental cerebral hemorrhage on the non-infused side, probably irrelevant to this therapy. The last patient had three episodes of acute gastric dilatation and died in hepatic coma; necropsy revealed a hepatoma in addition to the original brain tumor (glioblastoma).

In three cases the therapy had to be discontinued, two because of severe infection of the catheterized region and one (metastatic cancer) because of the appearance of metastasis on the opposite side.

The other 23 cases were discharged improved (Table 2). One of these, a 60-year-old man with a glioblastoma, died 5 months after
discharge because of bronchopneumonia. The remaining 22 cases have been checked monthly in the outpatient clinic; none, so far, has shown signs of recurrence.

**Evaluation of BAR Therapy.** It is often difficult to evaluate the effects of this therapy merely by the improvement in neurological signs and symptoms, since improvement is defined by the location or size of the tumor and the status of the neurological deficits present before therapy. Radiological improvements, namely, in carotid angiography, pneumoencephalography, and pneumoventriculography, were recognized in all cases. One patient with an oligodendroblastoma was submitted to reoperation 1 week after finishing the BAR therapy; biopsies were done in 10 different areas involved by the tumor at the time of the first operation. Marked necrosis was noted in these areas, but no tumor was detected microscopically or macroscopically.

The effect of this therapy on the cerebrospinal fluid pressure in representative cases is shown in Fig. 4. The pressure gradually decreased, although it may have been temporarily elevated with the installation of radiation therapy. Most of the cases showed normal pressure 2 months after completion of the therapy.

Laboratory examinations during BAR therapy showed no remarkable change in the number of red blood cells and amount of hemoglobin in blood examinations. The number of white blood cells, however, went down rather quickly when BUdR and Methotrexate were infused at the same time, although the count recovered after Methotrexate was stopped, as shown in Fig. 5. Although the daily dose of Methotrexate was very small, the decrease of the number of white blood cells seemed to be accelerated by simultaneous administration of BUdR. The BUdR itself showed little depressive action on the hematopoietic system.

Other laboratory findings, such as serum protein, serum urea, serum electrolytes, and the results of liver function tests were within normal limits during and after the BAR therapy except for transient rise in serum GOT (glutamic-oxaloacetic transaminase) and GPT (glutamic-pyruvic transaminase).

The serum bromine level must be checked because BUdR is debrominated by the liver and the released bromine could be stored up

<table>
<thead>
<tr>
<th>Tumor</th>
<th>No. of Cases</th>
<th>Died During BAR Therapy</th>
<th>Therapy Discontinued</th>
<th>Alive after Therapy (mos)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>0-6</td>
<td>7-12</td>
</tr>
<tr>
<td>Highly malignant glioma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>alive</td>
<td>10</td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>dead</td>
<td>4</td>
<td>3</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Moderately malignant glioma</td>
<td></td>
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<tr>
<td>alive</td>
<td>6</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>dead</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Meningosarcoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>alive</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>dead</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Metastatic tumor</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>alive</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>dead</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other malignant tumor</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>alive</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>dead</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total: alive</td>
<td>25</td>
<td>3</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>dead</td>
<td>5</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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Keiji Sano, Takao Hoshino and Masakatsu Nagai

**TABLE 2**

Follow-up of 30 cases receiving “BAR” therapy
Brain Tumor Radiosensitization by Bromouridine

Fig. 4. Effect of BAR therapy on cerebrospinal fluid pressure (op = operation, w = weeks).

to the level of intoxication. We checked this level by measuring the serum chloride level, since the bromine replaces chloride. The serum chloride level showed almost no change in any case.

Two side effects of BUdR are worth mentioning. Onychomadesis of the finger nails, sometimes of the toe nails, appeared after 2 to 3 months, although new nails replaced them soon. Another complication was seen when radiation was given in such a way as to cover the forehead of the patient. Epilation and radiodermatitis appeared more severely than in other parts of the irradiated scalp. It may be explained as follows: the forehead is fed by the internal carotid artery, conse-

Fig. 5. Blood studies during BAR therapy (Mtx = Methotrexate, op = operation, RBC = red blood cell counts, Sahli = percentage of hemoglobin content as compared with the normal control (100% = 16 g/dl), WBC = white blood cell counts, and w = weeks).
quently the skin of the forehead was radiosensitized by BUdR. These skin changes, however, did not reach the point of ulceration, probably because the multiple portal irradiation had been used.

Discussion

In BAR therapy, continuous infusion of BUdR is necessary, because mitosis of the tumor cells apparently occurs at random, rather than at predictable periods. The problem is to determine the duration of the continuous infusion. The right answer to this question is to infuse for a period longer than one generation time of the tumor cells so that all of the tumor cells can incorporate BUdR into their DNA. But it is difficult to determine the accurate generation time of brain tumors in vivo. We have been studying the generation time of various brain tumors in vitro by three methods; 19,20 Table 3 shows the calculated generation time from the labelling index of thymidine-3H by Johnson’s formula12 in these three methods. Even in glioblastoma, the generation time differed from 2 to 3 days in the Roller tube culture method of 20–30 days by the bloc immersion method, although a recent report of Kury and Carter16 showed much shorter generation time by the same bloc immersion method. Besides, there are evidences that not all the tumor cells have the ability to divide or have the same generation time. So, these data cannot be accepted without question. Therefore, for the sake of safety, the duration of infusion should be more than 4 weeks. We have been continuing the infusion for 4 to 7 weeks, adjusting the duration in relation to the malignancy of the tumor (glioblastoma, 4 weeks; oligodendroglioma, 6 weeks).

Theoretically, irradiation should be done after the infusion therapy is finished, because mitosis of the cells could be depressed by irradiation. But, practically speaking, this is rather difficult because of the long period of hospitalization. We have therefore started the radiation therapy 7 to 14 days after the commencement of the infusion.

In our BAR therapy, antimetabolites are used only to facilitate incorporation of BUdR into tumor cells and not to potentiate irradiation effects as Bagshaw reported.2 The doses of Methotrexate and 5-FU in this therapy are less than one-tenth of the ordinary doses administered as anticancer drugs.21 As shown in Table 1, the incorporation-enhancing effects of these antimetabolites in vitro were apparent even in the concentration of 1 μg/ml of the medium. In vivo doses of the antimetabolites were calculated at 2 to 3 mg, with the blood plasma as the medium, which was estimated at 2 to 3 liter. Methotrexate, 5-FU, and FUdR are known to inhibit the synthesis of thymidylic acid.2,6,9 Since thymidylic acid is found only in DNA and not in RNA (ribonucleic acid), the biosynthetic mechanisms for this compound may be on a smaller scale, as compared with those of other nucleotides. This might be the reason why thymidylic acid synthesis is inhibited (not necessarily destroyed) by such a small amount of antimetabolite. BUdR is a competitor of thymidine, and the tumor cells may easily take up the competitor provided in the blood stream in order to duplicate their DNA whenever the thymidine synthesis is depressed.

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Roller Tube</th>
<th>Trypsinization Monolayer</th>
<th>Bloc Immersion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LI (%)</td>
<td>GT (days)</td>
<td>LI (%)</td>
</tr>
<tr>
<td>Glioblastomas</td>
<td>3–12</td>
<td>2–7</td>
<td>4</td>
</tr>
<tr>
<td>Astrocytomas</td>
<td>3–12</td>
<td>2–7</td>
<td>1</td>
</tr>
<tr>
<td>Oligodendrogliomas</td>
<td>3–12</td>
<td>2–7</td>
<td>1</td>
</tr>
<tr>
<td>Meningiomas</td>
<td></td>
<td></td>
<td>8</td>
</tr>
</tbody>
</table>

TABLE 3

Labelling index (LI) and generation time (GT) in three methods of tissue culture of brain tumors
Other halogenated pyrimidines, namely, 5-iodo-2'-deoxyuridine (I UdR) and 5-fluoro-2'-deoxyuridine (FUdR), are also known as radiosensitizers. According to Kaplan, et al., radiosensitizing activity of BUdR is stronger than that of IUdR. There are reports that FUdR is not incorporated into DNA, but into RNA. The results of our experiments showing that FUdR facilitated BUdR incorporation into the cell nuclei may suggest that FUdR is not a competitor of thymidine, hence not a thymidine analogue. FUdR should be regarded as a potentiating agent of radiation effects, and not as a sensitizer. All of these facts favor the use of BUdR to radiosensitize brain tumors.

The effect of BUdR incorporated into normal dividing cells should be checked. Although BUdR is reported to be destroyed very quickly by the liver and only a small amount of administered BUdR may flow into the general circulation, accumulation of side effects of the small amount of BUdR can not be neglected, since this therapy usually continues for more than 4 weeks. One obvious evidence of it is the onychomadesis of finger nails. There are some reports of mutagenicity of BUdR in prenatal animals. The amount of BUdR we have been administering was too small to cause acute BUdR intoxication. The LD 50 of BUdR administered intravenously to ICR-JCL male mice, 4 weeks postnata1, was 2700 mg/kg. Table 4 shows the results of the experiments done in our laboratory. The most effective yet harmless daily dosage, however, should be determined in the future.

BAR therapy requires a long-term continuous intra-arterial infusion, which may cause various complications. Fortunately, the method we have established has been successful, and most of the cases were able to complete the proposed course of continuous infusion. The only complication was local skin infection around the catheter. We were confronted with local infection in 4 of 30 cases. In two of them, local abscess advanced to sepsis which was controlled by antibiotic therapy. After the infection subsided, a mycotic aneurysm was found on the common carotid artery and was resected successfully. Other possible complications such as cerebral thrombosis or occlusion of the carotid artery have not been experienced. In one case in which the catheter was inserted into the vertebral artery, occlusion of the vertebral artery was recognized 2 weeks after the insertion. This occlusion may be ascribed to the size of the catheter, which was too big for the vertebral artery.

Lastly, we recommend decompressive craniectomy for those patients in whom sufficient tumor could not be removed to reduce intracranial pressure. In some cases, marked intracranial hypertension developed after the start of radiotherapy. Even at the end of this therapy, some of the patients had severe bulging at the cranietomized area, but this bulging usually disappeared 2 to 3 months later.

Summary

1. The agent 5-bromo-2'-deoxyuridine (bromouridine or BUdR), which is known to sensitize bacterial or tumor cells to irradiation, can be incorporated into the nuclei of human brain tumor cells cultured by the trypsinization monolayer method.

2. The BUdR had neither antimetabolic nor cytotoxic effect but did increase the radiosensitivity of the cells that took it up.

3. The uptake of BUdR into the tumor cell nuclei in tissue culture was enhanced by addition of a small amount of antimetabolites such as Methotrexate, 5-FU, or FUdR. This fact may be explained by the hypothesis that the antimetabolites inhibited the biosynthesis of thymidine and thus forced dividing cells to incorporate the newly arrived thymidine analogue (BUdR) to duplicate their DNA.

<table>
<thead>
<tr>
<th>BUdR Dose (mg/kg)</th>
<th>Fatal Ratio</th>
<th>Fatal Day†</th>
</tr>
</thead>
<tbody>
<tr>
<td>3472</td>
<td>6/6</td>
<td>1</td>
</tr>
<tr>
<td>2893</td>
<td>4/6</td>
<td>1</td>
</tr>
<tr>
<td>2411</td>
<td>2/6</td>
<td>1</td>
</tr>
<tr>
<td>2009</td>
<td>0/6</td>
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</table>

* LD50 = 2700 mg/kg
† Main toxic symptoms: animals lay prone immediately after injection of BUdR, and tachypnea and dyspnea soon appeared. At the high dosage, some animals died instantly.
4. Based on these facts, the authors have performed BUdR-antimetabolite-continuous intra-arterial infusion-radiation therapy (BAR therapy) for malignant brain tumors. The principle of the therapy included administration of BUdR, 600–1000 mg/day with a small amount of antimetabolite (1 to 5 mg of Methotrexate or 3 to 5 mg of 5-FU) by means of continuous intra-arterial infusion for a period longer than the estimated generation time of the brain tumor cells (4 to 7 weeks), and combined irradiation.

5. We believe this therapy is promising in the treatment of malignant brain tumors, although final evaluation will need long-term follow-up.

References


