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Superselective Arterial BCNU Infusion in the Treatment of Patients with Malignant Gliomas

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Retinal and CNS toxicity have been reported with infraophthalmic infusion of BCNU in the treatment of patients with malignant gliomas. It is known, however, that the CNS toxicity can be reduced if the BCNU is dissolved in dextrose in water. This article describes the results from 15 patients who received 42 courses of BCNU administered by supraophthalmic internal carotid, middle cerebral, or posterior cerebral artery infusions. None of the patients developed leuкоencephalopathy as demonstrated by CT scanning. The average reduction in tumor volume was 36%, and the median survival time from the date of diagnosis was 73 weeks. These values are comparable to those of a previous group of 20 patients treated with infraophthalmic infusions, with the exception that none of the patients in the present group developed retinal damage.

Treatment regimens of 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) dissolved in ethanol, saline, or 5% dextrose in water (D5W) have been used in the intravascular treatment of patients with malignant gliomas [1-4]. With infraophthalmic infusion of the drug, complications such as retinal and CNS toxicity have been reported [1]. Retinal toxicity is eliminated if the BCNU is delivered above the level of the ophthalmic artery [5, 6]; and, theoretically, CNS toxicity should be reduced if the drug is delivered close to the tumor with little of it delivered to normal surrounding brain, although reports have appeared of leuкоencephalopathy with supraophthalmic infusion of BCNU dissolved in ethanol [4, 7].

To test the effectiveness of supraophthalmic arterial and selective posterior cerebral arterial infusion of BCNU dissolved in D5W, we used this regimen to treat 15 patients with malignant gliomas. We analyzed the toxic effects, complications, changes in tumor size as assessed by contrast-enhanced CT scans, and survival rates of the patients. All the patients had had radiation therapy at least 6 weeks before infusion therapy. Quantitative assessment of tumor response to therapy in the 15 patients was through a detailed analysis of the CT scans as described previously [3]. Survival data were assessed through analysis of standard survival curves. We also compared the toxic effects, complications, changes in tumor size, and survival curves of the present group of 15 patients with a previous group of 20 patients from this medical center who had been treated with subophthalmic BCNU infusions [3].

Materials and Methods

Patient Population

Between December 1986 and May 1988, 15 patients, all with malignant gliomas, received a total of 42 courses of BCNU administered by supraophthalmic internal carotid, middle cerebral, or posterior cerebral artery infusions. We treated nine men and six women, ranging in age from 23 to 65 years old. Only patients with biopsy or surgically proved grade III or IV astrocytomas, whether de novo (n = 12), recurrent (n = 2), or progressive from a lower-grade tumor (n = 1), were entered into the study. All the patients initially had stereotactic
biopsy and/or surgical debulking. Six patients received 6000 cGy of external-beam radiation and interstitial iridium-192 implantation (6000–10,000 cGy) prior to intraarterial chemotherapy. One of these patients received a single additional course of intraarterial cis-platinum. Two patients were treated initially with iridium-192 implants followed by intraarterial chemotherapy, and then received external-beam radiotherapy at the time of progression. Seven patients received only external-beam therapy prior to intraarterial infusions; the one patient whose tumor progressed from a lower-grade (grade II) astrocytoma had previously been treated with phosphorus-32 injected into a tumor cyst, and another patient in this group had previously received systemic BCNU therapy.

Not all the patients had suprachiasmatic or selective posterior cerebral artery perfusions exclusively. Prior to December 1986, five of the 15 patients received nine courses of BCNU via a subophthalmic internal carotid artery injection. Two of these patients received three subophthalmic injections each and the remaining three patients received only one injection each by this route.

**Drug Administration**

Following a transfemoral arterial approach, we placed a 5-French catheter into the internal carotid artery ipsilateral to the tumor, at the level of C2 or C3, or into the vertebral artery contralateral to the tumor. Angiography was routinely performed to confirm patency of the major vessel that supplied the tumor and that was subsequently selectively catheterized. The patients were placed on heparin and a 3-French Tracker-18 catheter was passed in a coaxial fashion through the 5-French catheter with a 0.018 in. (0.046 cm) guidewire leading the Tracker by about 1 mm into the selected intracranial artery as previously described [6]. BCNU was reconstituted in D5W (100 mg of BCNU per 30 ml of D5W) administered at a dose of 150 mg/m² at a rate of 2–5 ml per min. Intravenous Droperidol and Nalbuphine were used as premedication and were given 10 to 30 min before BCNU infusion. Morphine sulfate was given if needed during the infusion.

The patients received BCNU at 6-week intervals for a maximum of five courses. Forty-two superselective infusions were carried out; 12 into a posterior cerebral artery (Fig. 1), one into a left vertebral artery, nine into the suprachiasmatic segment of an internal carotid artery, and 20 into a middle cerebral artery.

**Tumor Assessment**

Responses to previous therapy were monitored at approximately 6-week intervals by contrast-enhanced CT scanning within 24 hr of the subsequent BCNU infusion. Three hundred milliliters of Renografin-30* were given by IV drip infusion over 15 min. All the CT scans were completed within 30 min of the end of the drip infusion, with 8-mm sections, on a Somatom 2 or DR3 scanner.† Volume reconstructions of the area of contrast enhancement (blood-brain barrier breakdown and tumor vascularity), including the area of central low density when present, were obtained with the standard Siemens software program (area of defined region of interest multiplied by the slice thickness) (Fig. 2). The total volumes were obtained by summation of contiguous abnormal slice volumes. The tumor volume was plotted as a function of time. Tumor doubling times were obtained from these data by using the formula

\[
Td = \frac{\log 2}{\log V_b - \log V_a} t
\]

where \(V_a\) is the initial tumor volume and \(V_b\) is the tumor volume after an interval of \(t\) days [8].

**Results**

**Tumor Location**

Seven patients had tumors in the frontal, frontoparietal, or high parietal lobes. One patient had a tumor in the perinsular brain involving frontal, parietal, and temporal lobes as well as the basal ganglia. Another patient had involvement of the temporal lobe and basal ganglia. Three patients had tumors in the temporal and temporoparietal lobes supplied predominantly by the anterior circulation while another three patients had temporoparietal lesions supplied by the posterior circulation. Two of the patients with lesions crossing vascular territories received treatment in both anterior and posterior circulations.

* Meglumine diatrizoate; Squibb, Princeton, NJ.
† Siemens, Iselin, NJ.
Toxicity

Two patients receiving one and three courses of subophthalmic internal carotid artery BCNU infusions, respectively, had their therapy stopped because of retinal toxicity. Therapy was reinstated once the technique for superselective infusion became available. Initially, ophthalmic examinations were carried out on all patients receiving supraophthalmic infusions but in none was there any evidence of retinal damage nor did any patient complain of visual loss. Therefore, the ophthalmic examinations were subsequently discontinued.

Complications

An evaluation of serial CT scans failed to demonstrate evidence acceptable as BCNU leukoencephalopathy, which has been characterized as increasing brain edema evidenced by increasing low attenuation in the cerebral white matter together with clinical worsening necessitating increasing steroids [4].

In carrying out the 42 superselective infusions, two complications occurred. In one patient, the 0.018-in. (0.046-cm) guidewire leading the Tracker-18 catheter fractured and could not be retrieved from the vertebrobasilar artery. In a second patient, spasm developed in the catheterized peduncular segment of the posterior cerebral artery with resultant infarction of the ipsilateral thalamus.

Tumor Volumes

Initial tumor volumes ranged from 7.7-96 cm^3, with an average of 40 cm^3. In no patient did the tumor completely disappear after intraarterial BCNU therapy. Six patients (40%) had reductions in tumor volumes ranging from 5-84% (Fig. 3), with an average of 36% after three to five courses of BCNU (Table 1). Only one of these patients had a greater than 50% reduction in tumor volume. Four of these patients died 21–60 weeks after initiation of intraarterial therapy, with tumor doubling times of 53–101 days. The two remaining patients are alive at 23 and 30 weeks, respectively, beyond the initiation of BCNU therapy. The first patient had a continued decline in tumor enhancement and the other had documented tumor regrowth (doubling time = 53 days).

Survival

The median survival time of all patients both deceased and alive from the date of diagnosis of high-grade glioma to the conclusion of the study was 73 weeks, with a range of 27–130 weeks (Tables 1 and 2). The median time interval from diagnosis to BCNU treatment was 20 weeks, with a range of 1–53 weeks. At the time of completion of the study, eight patients had died and seven were still alive. The time between initiation of therapy and death or completion of study varied from 21 to 107 weeks, with a median survival time of 32 weeks (Table 2). Forty-six weeks prior to receiving superselective chemotherapy, one patient received a single subophthalmic infusion of BCNU; this single course was excluded from calculations of survival rates following chemotherapy.

Discussion

The development of leukoencephalopathy following intraarterial infusion has been a major limiting complication of this approach and occurs in 10–20% of patients. This toxicity is thought to result from the dose of BCNU and alcohol diluent used. Most patients receiving chemotherapy have also received radiation therapy, and this may increase the likelihood of leukoencephalopathy developing. However, leukoenceph-
our patients may believe severe enough to necessitate steroid treatment, we do not beam radiation and/or interstitial iridium implantation prior to ophthalmic infusion of BCNU dissolved in ethanol [3]. The latter chemotherapy concomitantly with radiation therapy [7]. Leukoencephalopathy also has been reported in patients receiving preirradiation subophthalmic BCNU infusion, tumor, the use of dextrose in water rather than ethanol as the diluent, and the administration of BCNU weeks after completion of the radiation therapy rather than concurrently with the therapy. BCNU toxicity has been shown to be dose-related [9]. Bashir et al. [4] used a subophthalmic technique to infuse BCNU at 400 mg/m^2 into the internal carotid artery of patients prior to radiation therapy. These researchers concluded that only a small group of patients benefit from preirradiation BCNU and that the associated severe leukoencephalopathy makes a phase III trial unacceptable.

We acknowledge that radiation necrosis may have occurred after the intraarterial infusion of the BCNU and not been recognized on the contrast-enhanced CT scans. Positron emission tomography with 18F-deoxyglucose, which increases the ability to differentiate between tumor and cerebral necrosis [10], was not available to us.

None of our patients receiving supraophthalmic infusions developed retinal damage. However, retroorbital pain and headache were exquisitely severe in some patients despite premedication with Droperidol and Nalbuphine. Our cases are not without complications. A fractured guidewire occurred in one patient and posterior cerebral arterial spasm with subsequent thalamic infarction occurred in another. These were the only complications in a series of 42 infusions.

Volumetric analysis of enhancing brain tumors by CT scan has been reported previously [3]. In the earlier experience at this institution with subophthalmic BCNU infusion, tumor location was a critical issue because only internal carotid infusions were performed and therefore tumors within watershed locations with supply from the carotid and vertebral systems could only be treated partially. In the present study, the ability to superselect the supraclinoid ICA and the middle and posterior cerebral arteries allowed treatment of tumors crossing vascular territories in two patients.

TABLE 1: Summary of Patients Treated with Supraophthalmic Arterial BCNU Infusions

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age</th>
<th>Gender</th>
<th>No. of Infusions</th>
<th>Subophthalmic Infusion</th>
<th>Superselective Infusion</th>
<th>Percent Reduction</th>
<th>Outcome</th>
<th>Weeks* from Treatment</th>
<th>Weeks* from Oper.</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>37</td>
<td>F</td>
<td>1</td>
<td>5^a</td>
<td>0</td>
<td>A</td>
<td>107</td>
<td>130</td>
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<tr>
<td>9</td>
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<td>0</td>
<td>A</td>
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<td>A</td>
<td>21</td>
<td>39</td>
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<td></td>
</tr>
</tbody>
</table>

^a Number of weeks from treatment or operation to death or termination of study.
^b Posterior cerebral artery.
\(\text{Vertebral artery (one infusion).}\)

Note.—A = alive, D = deceased.

TABLE 2: Comparison of Survival Time (in Weeks) of 20 Patients Treated with Subophthalmic and 15 Patients Treated with Supraophthalmic Arterial BCNU Infusions

<table>
<thead>
<tr>
<th>Survival Category</th>
<th>Group</th>
<th>No. of Patients</th>
<th>Mean Survival Time (Weeks)*</th>
<th>SD</th>
<th>Median</th>
<th>Range</th>
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</thead>
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<tr>
<td>Operation to death</td>
<td>Old</td>
<td>20</td>
<td>94.6</td>
<td>111.62</td>
<td>51</td>
<td>20-487</td>
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<td></td>
<td>New</td>
<td>15</td>
<td>66.9</td>
<td>25.52</td>
<td>73</td>
<td>27-130</td>
</tr>
<tr>
<td>Operation to treatment</td>
<td>Old</td>
<td>20</td>
<td>59.4</td>
<td>98.15</td>
<td>21.5</td>
<td>6-400</td>
</tr>
<tr>
<td></td>
<td>New</td>
<td>15</td>
<td>18</td>
<td>13.16</td>
<td>20</td>
<td>1-53</td>
</tr>
<tr>
<td>Treatment to death</td>
<td>Old</td>
<td>20</td>
<td>35.2</td>
<td>30.49</td>
<td>25.5</td>
<td>8-113</td>
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<tr>
<td></td>
<td>New</td>
<td>15</td>
<td>42.3</td>
<td>12.42</td>
<td>32</td>
<td>21-107</td>
</tr>
</tbody>
</table>

^* Student's two-sample t test and Wilcoxon's two-sample test were used to compare means on each of the three variables. All were nonsignificant (p > .10).
\(\text{Note.—Old = subophthalmic study, new = superselective study.}\)
We understand that tumor can occur in the edema surrounding a contrast-enhancing lesion, but we nevertheless believe that assessment of tumor size is still the best method for estimating the presence of viable tumor by CT scan. Only one of the 15 patients in this series had a partial response (defined as a 50% reduction in the maximal tumor diameter, an eightfold reduction in tumor volume) [11]. Four other patients had measurable decreases in tumor volume and one had a 5% decrease. These results are similar to our earlier subophthalmic study in which two of 20 patients had partial responses and six had measurable reductions in tumor volume [3]. Unfortunately, the two groups are not strictly comparable. First, the subophthalmic group consisted of 20 patients and the present group consists of 15 patients. Second, five of the present group had received infraophthalmic infusions prior to the availability of superselective infusions. Third, the protocol for initiation of BCNU therapy differed slightly between the two groups. The subophthalmic group started chemotherapy upon CT evidence of tumor recurrence while the superselective group had chemotherapy initiated approximately 8 weeks after completion of radiotherapy. However, in comparing the median time from diagnosis and operation to chemotherapy initiation between the two groups, there was only a difference of 1.5 weeks (subophthalmic group, median = 21.5 weeks; superselective group, median = 20 weeks). Finally, the study time for the subophthalmic group lasted much longer than that for the present group and therefore included more deaths [17] and much longer times to either death or the end of the study. (In the statistical analysis these differences were taken into account by using the Kaplan-Meier survival estimates.)

The overall median survival time from operation to death or study conclusion for the subophthalmic group was 51 weeks, and the overall median survival time for the present group was 73 weeks. A comparison of the time from chemotherapy initiation to death or study conclusion revealed a median of 25.5 weeks for the subophthalmic group and a median of 32 weeks for our present group. Statistically, there was no difference between the two groups in the times between operation and death, operation and treatment, and treatment and death (Table 2).

Selection of a posterior cerebral artery for infusion has not to our knowledge been used before. One of the patients treated with a posterior cerebral artery infusion experienced a measurable reduction in tumor volume.

In conclusion, patients with brain tumors treated first with radiation and then with a superselective infusion of BCNU dissolved in D5W at a dose of 150 mg/m² had the benefits of no or minimal toxicity, no leukoencephalopathy, and survival times comparable to patients treated with radiation therapy followed by subophthalmic internal carotid BCNU infusions. A lower BCNU dose delivered more selectively into the tumor bed than was done in this study may deliver even more of the chemotherapeutic agent directly to the tumor while sparing normal brain and be still more efficacious. As other drugs become available for the treatment of malignant brain tumors, it will be useful to be able to deliver highly regional therapy. We are currently exploring the value of delivering cis-platinum by superselective intracranial infusion.

REFERENCES