Intra-arterial bromodeoxyuridine radiosensitization and radiation in treatment of malignant astrocytomas

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Bromodeoxyuridine (BUdR), a nonhypoxic radiosensitizing drug, is a halogenated pyrimidine analog that is incorporated into the deoxyribonucleic acid of dividing cells in a competitive process with thymidine; BUdR also sensitizes these cells to radiation therapy. Neurons and glial cells have a very low mitotic rate. They will not incorporate BUdR and will not be sensitized. Bromodeoxyuridine is best delivered intra-arterially because of its regional advantage, calculated to be between 6 and 16. An 8-week BUdR infusion is delivered before and during radiation therapy through a permanently implanted pump with a catheter placed retrograde into the external carotid artery. Eighteen patients with malignant glioma (15 grade IV, and three grade III) were entered into a Phase I dose-escalation protocol with BUdR dosages ranging from 400 to 600 mg/sq m/day. The maximum dose that can be tolerated appears to be 400 mg/sq m/day for 8 weeks. The 18 patients entered in this study have a median Kaplan-Meier estimated survival time (+ standard error of the mean) of 22 ± 5 months with 11 patients still alive. Three patients are alive at 30, 29, and 21 months after diagnosis with no evidence of tumor on computerized tomography. There have been no vascular complications. Side effects in all patients have included anorexia, fatigue, ipsilateral forehead dermatitis, blepharitis, iritis, and nail ridging. Myelosuppression requiring dose reduction occurred in one patient. One patient had a Stevens-Johnson syndrome requiring termination of BUdR. It is concluded that intra-arterial BUdR may improve survival times in patients with malignant gliomas.

KEY WORDS - bromodeoxyuridine □9 astrocytoma □9 brain neoplasm □9 intra-arterial infusion □9 radiation therapy

Malignant gliomas of the brain that are treated with “conventional” therapy consisting of maximal surgical resection followed by radiation therapy, with or without intravenous nitrosourea chemotherapy, have a poor prognosis. Surgery followed by radiation therapy has resulted in a median survival time of 36 weeks and a 24-month survival rate of only 10%. The addition of intravenous BCNU (1,3-bis(2-chloroethyl)-1-nitrosourea) or oral procarbazine chemotherapy has only extended the median survival time to 51 weeks and increased the 24-month survival rate to 15%.25

External beam radiation therapy is beneficial in the treatment of malignant gliomas of the brain but the dose is limited by the tolerance of normal brain.20,26 This limitation has led many investigators to explore the interaction of external beam radiation and drugs that selectively increase tumor kill without increasing toxicity to normal tissue. Bromodeoxyuridine (BUdR), a halogenated pyrimidine analog (the bromine in BUdR replaces the methyl group in thymidine),13 is incorporated into the deoxyribonucleic acid (DNA) of dividing cells in place of thymidine. Bromodeoxyuridine has been shown to sensitize both bacterial and mammalian dividing cells to ultraviolet light and radiation.3,6,8,14,23 A relationship between BUdR dose and radiation effect has been demonstrated in experiments both in vitro and in vivo.2,4

The optimal route of delivery of BUdR has been controversial. Initial studies have indicated that BUdR
has its maximum effect when given intra-arterially by prolonged constant infusion. A low tumor mitotic rate requires prolonged continuous BUdR exposure for incorporation into all dividing cells. Metabolism of BUdR was previously thought to be primarily by dehalogenation in the liver; however, plasma clearance of BUdR is approximately three times hepatic plasma flow, indicating that extrahepatic metabolism is also important. This high rate of metabolism may necessitate intra-arterial infusion so as to deliver therapeutic concentrations to tumor. Russo, et al., concluded that "common carotid IA [intra-arterial] infusion could yield a regional BUdR concentration 11 to 16 fold (1 log) higher than with IV [intravenous] infusion, resulting in optimum delivery of BUdR to tumor with minimal systemic toxicity."

Several clinical trials have been undertaken to investigate the efficacy of radiation sensitization with intra-arterial halogenated pyrimidines. In the late 1960's and early 1970's, Hoshino and coworkers reported a clinical trial of intra-arterial radiosensitization in 107 patients with malignant brain tumors. Drug infusion in their cases began 7 to 14 days prior to radiation therapy and was continued throughout the period of radiation therapy. In their study, 48 patients had malignant gliomas and 50% survived more than 18 months. This trial was ultimately discontinued due to difficulties with percutaneous intra-arterial delivery of BUdR. A trial evaluating intra-arterial BUdR radiosensitization in the treatment of head and neck tumors showed no advantage in local tumor control and indicated significant toxicity to normal tissue. Toxicity to oral mucosa was substantial and was probably related to the high mitotic rate of the oral mucosa.

Malignant gliomas have several characteristics which make them ideally suited for intra-arterial radiosensitization with BUdR. Malignant gliomas are heterogeneous tumors and rarely metastasize. Local tumor progression in a confined inelastic space is the cause of death in virtually all cases. Total surgical excision of malignant gliomas is rarely feasible because of the tumor's infiltrative nature. They are surrounded by supporting glia and neurons which have a low mitotic index. This tissue will not incorporate BUdR, resulting in a therapeutic advantage between radiosensitized tumor and nonradiosensitized normal tissue. Approximately 75% of malignant gliomas are unilateral and are supplied by a single internal carotid artery, allowing intra-arterial delivery of BUdR. We have developed a totally implantable pump system to deliver a prolonged continuous high regional concentration of BUdR to brain tumors. This paper reports the results of use of this system in a Phase I clinical trial.

Clinical Material and Methods

Patients with histologically confirmed unilateral malignant gliomas (grade III and IV anaplastic astrocytoma, malignant astrocytoma, and glioblastoma multiforme) with blood supply from one internal carotid artery were eligible for this Phase I trial. The patients were required to have a Karnofsky rating of 30 or above at the time of entry into the study and to be capable of giving informed consent. Other eligibility criteria included a normal peripheral blood count (>4000 white blood cells/μl, >200,000 platelets/μl), normal renal function (serum creatinine <1.5 mg/100 ml, blood urea nitrogen <30 mg%), normal liver function studies (bilirubin <2.0 mg/100 ml, serum glutamic-oxaloacetic transaminase less than two times normal, alkaline phosphatase less than two times normal), and a life expectancy of at least 3 months.

The BUdR was continuously infused intra-arterially into the carotid system using an Infusaid pump system.* This system was surgically implanted in a subcutaneous pocket under the clavicle. The outlet catheter of the pump was passed retrograde down the external carotid artery to the carotid bifurcation. The distal external carotid artery and superior thyroid artery were ligated. This resulted in the infused drug flowing exclusively into the internal carotid artery. The patients received the BUdR infusion for 8 weeks, beginning 2 weeks prior to focal external beam radiation therapy and continuing concurrently with the radiation therapy. They also received BUdR at doses ranging from 400 to 600 mg/sq m/day. The BUdR solution in the pump reservoir was emptied and refilled to a total volume of 50 cc weekly for the 8-week period. After the 8-week BUdR infusion the pump was filled with buffer solution for 1 week, followed by water, then 17%, 22%, and finally 35% glycerol solution. Heparin (10,000 U/50 cc) was added to all solutions placed in the pump.

Radiation therapy was begun 2 weeks after initiation of the BUdR infusion. The patients received focal brain irradiation to the tumor volume. Tumor volume was defined by the rim of pathological contrast enhancement plus a 3- to 4-cm margin around this rim. A custom cerrobend block was utilized in shielding the scalp, nasopharynx, and orbits. Treatment was administered with 6- to 10-MV photons delivered via a linear accelerator. The daily dose was 180 cGy to a total dose of 5940 cGy over 6½ weeks of treatment. The patients presented weekly for refilling of the pump and for neurological and general physical examinations. A complete blood count and platelet count were obtained weekly, and liver function studies were performed prior to and following radiation therapy. Computerized tomography (CT) was performed pre- and postoperatively, 6 weeks following radiation therapy, and every 3 months thereafter. Positron emission tomography (PET) scans using 18F-fluorodeoxyglucose were obtained in selected cases and were correlated with the CT findings and neurological examination.

Criteria for assessing treatment response were as fol-

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### TABLE 1

Summary of clinical data in 18 patients with malignant astrocytoma treated with IA BUdR and RT *

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs)</th>
<th>Tumor Grade</th>
<th>Karnofsky Score at Entry</th>
<th>BUdR Dose (mg/sq m/day)</th>
<th>Initial Response to IA BUdR + RT</th>
<th>Response Duration (mos)</th>
<th>Other Treatment, Status</th>
<th>Survival Time (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>39</td>
<td>IV</td>
<td>70</td>
<td>400</td>
<td>CR</td>
<td>30+</td>
<td>chemo × 4, PR, died</td>
<td>30+</td>
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<tr>
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<td>44</td>
<td>IV</td>
<td>70</td>
<td>400</td>
<td>PR</td>
<td>12</td>
<td></td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>III</td>
<td>90</td>
<td>400</td>
<td>CR</td>
<td>29+</td>
<td>chemo × 7, NR</td>
<td>27+</td>
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<tr>
<td>4</td>
<td>36</td>
<td>IV</td>
<td>90</td>
<td>500</td>
<td>S</td>
<td>8</td>
<td>died</td>
<td>11</td>
</tr>
<tr>
<td>5</td>
<td>71</td>
<td>IV</td>
<td>70</td>
<td>400</td>
<td>S</td>
<td>8</td>
<td>died</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>67</td>
<td>IV</td>
<td>70</td>
<td>450</td>
<td>PR</td>
<td>10</td>
<td>chemo × 1, NR, died</td>
<td>14</td>
</tr>
<tr>
<td>7</td>
<td>59</td>
<td>IV</td>
<td>50</td>
<td>500</td>
<td>NR, progression at 4 mos</td>
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<td>8</td>
<td>29</td>
<td>III</td>
<td>90</td>
<td>500</td>
<td>S</td>
<td>11</td>
<td>chemo × 3, NR</td>
<td>21</td>
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<tr>
<td>9</td>
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<td>IV</td>
<td>60</td>
<td>600</td>
<td>NR, progression at 4 mos</td>
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<td>17+</td>
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<td>III</td>
<td>90</td>
<td>600</td>
<td>PR</td>
<td>3</td>
<td>chemo × 1, NR</td>
<td>16+</td>
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<tr>
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<td>90</td>
<td>600</td>
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<td>42</td>
<td>IV</td>
<td>50</td>
<td>600</td>
<td>NR, progression at 3 mos</td>
<td>3</td>
<td>died</td>
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<tr>
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<td>53</td>
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<td>500</td>
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<td>IV</td>
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<td>500</td>
<td>PR</td>
<td>10</td>
<td>chemo × 1</td>
<td>11+</td>
</tr>
</tbody>
</table>

* IA = intra-arterial; BUdR = bromodeoxyuridine; RT = radiation therapy. Response to treatment: CR = complete response; PR = partial response; S = stable; NR = no response; for further explanation of response see text. + = ongoing. In this study the average age of the patients was 48 years, the average Karnofsky score at entry was 70, the median follow-up time was 21 months, and the Kaplan-Meier estimated median survival time was 22 months.

A DNA assay of BUdR incorporation in the tumor tissue resected from one patient was performed using gas chromatography/mass spectrometry with selected-ion monitoring.

## Results

Eighteen patients were treated in this study through July 1, 1987 (Table 1), and 17 completed the external beam radiation therapy and a full course of BUdR infusion. Fifteen of the patients had grade IV astrocytomas or glioblastoma multiforme and the other three had grade III anaplastic astrocytomas. The average age of the patients was 48 years (range 20 to 71 years), and the average Karnofsky rating was 70 (range 50 to 90). Daily doses of BUdR were as follows: 400 mg/sq m in four patients, 450 mg/sq m in one, 500 mg/sq m in eight, and 600 mg/sq m in five. The maximum tolerated dose was 400 mg/sq m/day for an 8-week continuous intra-arterial infusion.

The Kaplan-Meier estimated median survival time (± standard error of the mean) was 22 ± 5 months. Twelve patients were stable or had a partial or complete response following intra-arterial BUdR radiosensitization and radiation therapy. Four stable patients had a median time to tumor progression of 9 months and one patient is stable at 21 months. In five patients with a partial response the median duration of response was 11 months, and in three with a complete response it was 29 months. Six patients had tumor progression despite therapy, with a median time to progression of 4 months and a median survival time of 7 months.

Patients with progression of their disease had development of CT-enhancing lesions consistent with tumor progression: 1) complete response, complete disappearance of tumor on CT scans and an improved or normal neurological examination without corticosteroid medication; 2) partial response, a decrease in the size of the measurable mass lesion on CT plus a stable or improved neurological examination with unchanged or decreasing doses of corticosteroids; 3) stable disease, no change in the size of the tumor on CT and no significant change in the neurological examination with unchanged or decreasing doses of corticosteroids; or 4) progressive disease, an increase in the size of the tumor on CT and/or progressive worsening of neurological function directly attributable to the growth of the tumor. Determination of response was made by comparing the CT scan obtained 6 weeks following radiation therapy with the scan obtained following surgery prior to irradiation. The duration of response lasted from surgical diagnosis until demonstration of disease progression.

Systemic venous plasma steady-state BUdR levels were measured in all patients using high-performance liquid chromatography with ultraviolet-absorption peak detection. An estimated regional advantage (R_d) was calculated utilizing the definition of the ratio of tumor exposure following intra-arterial and intravenous administration, where exposure is the concentration-time integral. Assuming linear kinetics of drug distribution and metabolism with negligible clearance by the lungs, the following equation is appropriate:

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R_d = 1 + \frac{CL}{F}
\]

In this equation, F is flow in the artery infused (liters/min) and CL is the rate of metabolic clearance of the drug (liters/min).
growth in addition to deterioration of their clinical symptoms. In one patient, PET scans showed increased metabolism of $^{18}$F-fluorodeoxyglucose in the area of the CT abnormality consistent with recurrent tumor.

In three patients (Cases 1, 3, and 8; see Table 1), early posttreatment CT identified new areas of abnormal, increased contrast enhancement within the radiation field (Fig. 1). These abnormalities were initially noted on CT at 4 to 6 weeks following treatment. Two of these patients underwent PET to assess the local metabolic rate for glucose and no hypermetabolic foci suggestive of tumor were revealed. These patients were followed clinically and are doing well without treatment. The enhancing abnormalities persisted on CT until approximately 6 months after treatment and then gradually resolved completely.

One patient (Case 7) developed progressive aphasia and right hemiparesis during the 4th week of BUdR radiosensitization and the 2nd week of radiation therapy. He underwent surgical decompression and resection of the tumor. Tissue specimens were obtained for analysis of BUdR incorporation in DNA. The DNA assay revealed 2.2% to 5.0% BUdR substitution for thymidine in different regions of the tumor. The systemic venous plasma BUdR level in this patient was 0.30 $\mu$M with a BUdR infusion rate of 500 mg/sq m/day.

There have been no vascular complications from the presence of the intra-arterial pump system (Table 2). The most severe side effects noted have been forehead dermatitis, blepharitis, conjunctivitis, and iritis ipsilateral to the BUdR infusion, seen to a varying degree in all patients. Two patients (Cases 10 and 13) required dose reduction because of the severity of the reaction. One patient (Case 7), who was receiving 500 mg/sq m/day of BUdR, had chronic left corneal irritation and a coagulase-positive staphylococcal infection which responded to sodium sulfacetamide 10% (Sulamyd) ophthalmic drops. He was then treated with Pred Forte ophthalmic drops and developed corneal ulceration and a posterior vitreous chamber leak with blindness, necessitating eye enucleation. In all other patients, unilateral blepharitis and iritis cleared within 1 month of discontinuing BUdR, and the forehead dermatitis cleared within 2 to 3 months. One patient (Case 14) developed a Stevens-Johnson syndrome requiring treatment in our burn unit and discontinuation of intraarterial BUdR and radiation therapy.

Expected side effects, including myelosuppression, anorexia, weight loss, and fatigue, have been seen and vary in severity with the dose administered. Nail ridging occurred in all patients. One patient (Case 9) required...
a reduction of the drug dose due to myelotoxicity (white blood cell count nadir of 1500/ml, platelet count of 28,000/ml, and hematocrit of 25%), necessitating transfusion of 2 units of packed red blood cells and 2 units of platelets. This patient was receiving 600 mg/sq m/day of BUdR.

Systemic venous blood levels of BUdR after intra-arterial infusion were measured in all patients and varied from 0.18 to 1.25 μM with total body clearance ranging from 0.99 to 11.3 liters/min at an infused dose of 400 to 600 mg/sq m/day. Increasing the daily BUdR dose produced a variable response in the venous blood level. Assuming minimal regional brain extraction, the systemic venous blood levels obtained with intra-arterial infusion give a total body clearance that results in an estimated R of BUdR of 6 to 16, a finding similar to that calculated by Russo et al. 17 The patient with Stevens-Johnson syndrome (Case 14) had the lowest clearances of BUdR and the highest plasma levels at all determinations.

Discussion

In the past, intra-arterial infusion of BUdR has been limited by the technical limitations and vascular toxicity of percutaneous infusion. 9,18,19 Our primate study of intra-arterial BUdR infusion with an implantable pump system with concurrent external beam radiation showed no asymmetrical hemispheric toxicity ipsilateral to the intra-arterial BUdR infusion when compared to the non-infused hemisphere in the BUdR group or to the hemisphere receiving intra-arterial buffer solution in the control group. 7 Based on these results, our Phase I study was undertaken to assess the feasibility of delivering continuous-infusion intra-arterial BUdR concurrent with radiation therapy for the treatment of malignant gliomas.

A median projected Kaplan-Meier survival time of 22 months is encouraging in these patients. Seven patients have died. Two patients are disease-free at 30 and 29 months. The short follow-up duration in the remaining patients prevents further data analysis.

One patient (Case 7) underwent emergency surgical resection of his glioma during the 8-week period of BUdR infusion after having been diagnosed by biopsy elsewhere. This patient had a 2.2% to 5.0% BUdR substitution for thymidine in DNA of tumor tissue. Thomas et al. 24 found that a comparable level of BUdR incorporation in DNA was necessary for radiosensitization.

The most important toxic effect of this treatment has been inflammation of skin and mucosal surfaces outside the irradiation portal. Ipsilateral blepharitis, iritis, and conjunctivitis do not occur with focal brain external beam irradiation alone and are likely due to BUdR being delivered via the ophthalmic artery to the territory normally supplied by the external carotid artery, which has been ligated. The BUdR exposure of these structures is increased, and with a high mitotic rate the BUdR will be incorporated, resulting in sensitization to scattered radiation and ambient ultraviolet light. An effort will be made to reduce this toxicity by the development of topical thymidine eyedrops and ointment. Topical thymidine should compete with BUdR for incorporation into DNA of these normal tissues.

Studies of intravenously administered BUdR have found that escalation of the dose beyond 700 mg/sq m/12 hours is limited by systemic myelosuppression. 10,11 Systemic toxicity has not been a limiting factor in our study of intra-arterial BUdR: only one of our patients experienced moderately severe myelosuppression at a dose 600 mg/sq m/day administered continuously for 8 weeks. Our study indicates that the maximum dose that can be tolerated is 400 mg/sq m/day for an 8-week continuous intra-arterial infusion, because of local skin and mucosal toxicity. Vascular complications have not occurred.

The occurrence of regions of new contrast-enhanced abnormalities on early follow-up CT scans is of uncertain significance. The areas of CT contrast enhancement in two patients were correlated with PET images which revealed no congruent regions of hypermetabolism. Subsequent follow-up CT revealed gradual complete resolution of these abnormalities. This may represent a delayed effect secondary to endothelial incorporation of BUdR and sensitization with external beam radiation. The evanescent CT abnormalities did not correlate with clinical neurological deterioration in these patients. To our knowledge these findings have not been described following conventional external beam radiation therapy.

In summary, our preliminary Phase I–II clinical study has shown the feasibility of administering continuous intra-arterial doses of BUdR with concomitant external beam radiation treatment over an 8-week period. The maximum tolerated dose has been established.

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