The rationale and methodology for intra-arterial chemotherapy with BCNU as treatment for glioblastoma

Fred H. Hochberg, M.D., Amy A. Pruitt, M.D., Deborah O. Beck, M.D., Gerard DeBrun, M.D., and Kenneth Davis, M.D.

Services of Neurology and Radiology, Massachusetts General Hospital, Boston, Massachusetts

Intra-arterial administration represents a safe and easily performed means of achieving greater brain tumor levels of 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) compared to parenteral administration. Despite 22 years of use, clinical administration of BCNU has been shown to be no more than marginally effective in the treatment of glioblastoma. Intravenous delivery of BCNU at doses of 240 mg/sq m provides only 20% improvement in survival time for glioblastoma patients after operative resection and irradiation. No clear evidence of improvement in quality of life has been noted. In theory, however, BCNU is an ideal drug for the treatment of intracraniat tumors by virtue of its characteristics: 1) high lipid solubility; 2) short half-life; 3) steep dose-response relationship against glial tumor targets in tissue culture and in experimental animals in vivo; and 4) effectiveness against intracranial tumors in animal studies.

The risk of systemic toxicity, most often myelosuppression, has required limitation of single parenteral doses to less than 600 mg/sq m. Cumulative and single doses in excess of 1500 mg/sq m damage the kidneys in 50% of patients, the lungs in 20%, the liver in 10%, and the central nervous system (CNS) in 2%. Attempts to circumvent this myelosuppression have included the infusion of frozen or refrigerated autologous bone marrow harvested prior to the infusion of BCNU doses to a maximum of 1400 mg/sq m. These approaches are cumbersome and are associated with toxicity to other systems.

The rationale for arterial infusion of BCNU in the treatment of glioblastoma is based on six hypotheses or findings. 1) Regional therapy is a logical approach to treatment of a "regional disease." Although 4% are multicentric tumors, glioblastoma is usually a "localized" malignancy, often well defined by computerized tomographic techniques. 2) The major dose limitations to BCNU administration result from non-CNS toxicities. Arterial administration of BCNU allows for higher regional drug levels without increasing the dose and thus the risk of systemic toxicity. 3) BCNU represents an excellent choice of drug for arterial infusion by virtue of its short half-life, high lipid solubility, and steep dose-response relationship found in vivo in animal stud-
Intra-arterial BCNU treatment for glioblastoma

ies. 4) Tumor vessels most often lie within the distribution of the internal carotid artery, as seen angiographically. Exceptions are malignant pinealine tumors or the rare subarachnoid or systemic glioblastoma metastasis found in children. 5) In most centers, the use of angiographic techniques permits rapid placement of catheters into the infraophthalmic or balloon-guided catheterization of the supraophthalmic carotid artery, with low morbidity. 6) Levin, et al., using carbon-14 \(^{(14C)}\)-labeled BCNU, demonstrated brain concentrations of BCNU four times greater following carotid artery infusion than with intravenous administration. This work supported the hypothesis of Fenstermacher and Cowles that brain drug levels might be as much as 10 times greater with this technique, without increased bone marrow exposure. Direct measurements of BCNU have confirmed these studies. Phase 1 and 2 clinical trials performed by West, et al., and Greenberg, et al., have demonstrated the safety of the technique.

Since 1979, we have treated 79 glioblastoma patients with 258 BCNU infusions. These patients received chemotherapy after irradiation, either as part of an adjuvant program or at the time of tumor recurrence. Drug administration was by infusion into the infra- or supraophthalmic carotid artery. We report the results of this treatment, and discuss their implications.

Clinical Material and Methods

Patient Population

Patients with tumor recurrence had received radiation therapy (4000 to 4500 rads to the whole brain plus a 1500-rad tumor boost in 30 to 40 fractions) following histological confirmation of tumor diagnosis. These patients had undergone irradiation of Kernohan grade IV astrocytoma at least 5 months before, and had shown recurrence of a CT contrast-enhancing mass and evidence of cerebral edema despite a reduction in the corticosteroid dose. No attempt was made to verify the histology of the recurrent tumor. Patients receiving intra-arterial BCNU in an adjuvant setting were treated within 2 weeks of the cessation of irradiation. No attempt was made to stratify patients by age, extent of operation, or Karnofsky scale score.

This treatment modality was withheld if: 1) there was evidence of intratumoral hemorrhage or subarachnoid dissemination of tumor on the CT scan; 2) there were arterial features that contraindicated infusion, such as carotid artery stenosis or carotid dissection; 3) there was hematological toxicity (white blood cell count < 2500/cu mm, platelet count < 125,000/cu mm); 4) the patient’s Karnofsky score was less than 60% at the outset; or 5) cerebral edema was not controlled by steroid therapy or osmotic diuresis. Prior chemotherapy was not a contraindication to treatment of patients with recurrent glioblastoma, nor was the presence of tumor within the territory of two intracranial arteries, including the basilar artery.

| Table 1 |
| Complications of arterial infusion of BCNU* |
| **Factor** | **Infra-ophthalmic** | **Supra-ophthalmic** |
| no. of cases | 59 | 20 |
| no. of infusions | 192 | 66 |
| eye pain | 154 | 6 |
| seizures | 3 | 3 |
| blindness | 1 | 0 |
| retinal change | 3 | 0 |
| tumor hemorrhage | 2 | 0 |
| decreased CT attenuation (edema/leukoencephalopathy) | 4 | 7 |
| “stroke” (MCA) | 3 | 2 |
| hematological toxicity | 0 | 0 |

* Miscellaneous complications included carotid dissection in one patient, asthmatic reaction in one, and bradycardia in one. CT = computerized tomography; MCA = middle cerebral artery.

BCNU Delivery Method

On the morning of chemotherapy, an intravenous line is inserted and the patient is not fed. Patients are premedicated with 5 mg morphine sulfate, but pretreatment corticosteroids are not administered. A Foley catheter is inserted prior to supraophthalmic carotid artery, multivessel, or cisplatin infusions, and osmotic diuresis is established with mannitol (20%) under these conditions.

The internal carotid artery is catheterized by the Seldinger technique to the level of the C-2 vertebral body or the supraophthalmic carotid artery. Catheterization for supraophthalmic carotid artery infusion involves use of the DeBrun calibrated-leak balloon. A Silastic catheter (0.4-mm internal and 0.8-mm external diameters, and ending in the fenestrated balloon) is introduced within a No. 7 French polyethylene sheath.* The balloon does not become inflated during infusion of BCNU and never occludes the vessel during the procedure, which is performed under systemic heparinization. The neurologist, who is present during the procedure, mixes the BCNU (100 mg BCNU/1 cc alcohol) and dilutes it with 125 cc of normal saline. The mixture is continuously agitated in a darkened room and is administered by pump-infusion at 2 to 3 cc/min. After infusion, the patient receives intramuscular Compazine (prochlorperazine maleate, 10 mg) and Solu-Medrol (methylprednisolone sodium succinate, 80 mg).

Infraophthalmic carotid artery infusions often cause ocular pain, conjunctival injection, erythema, and unilateral rhinorrhea (Table 1). The retro-orbital pain may be diminished by reduction of the alcohol to 1 cc/100 mg BCNU (which may reduce the amount of drug in solution), by the addition of intravenous sulfate (to 15 mg), or by the use of retro-orbital block using equal parts of 0.5% bupivacaine and 2% xylocaine with epinephrine. In all instances, ocular pain resolved within

* French polyethylene sheath, No. 7, manufactured by Ingenor, 70 rue Orfila, Paris, France.
10 minutes of the end of infusion, but one patient experienced diminished visual acuity to 20/40 in that eye, and retinal infarction was seen. A second patient with pre-existing bilateral papilledema experienced bilateral loss of vision with a similar funduscopic picture.

Supraophthalmic carotid artery infusions were associated with hemispheric head pain in 10% of patients and a higher frequency of seizure activity (Table 1). Surprisingly, the incidence of BCNU-associated leukopenia, pulmonary toxicity, and hepatic toxicity has not been significant. Cumulative doses of BCNU have been kept below 1250 mg.

Protocols for Drug Delivery

We have evaluated the use of intra-arterial BCNU at various dose levels (Protocol IA) and at a commonly used fixed dose (Protocol IB) in the treatment of recurrent glioblastoma. Our experience with these patients encouraged us to treat newly diagnosed and irradiated glioblastoma patients with BCNU (240 mg/sq m) administered into the infraophthalmic carotid artery (Protocol IIA) or supraophthalmic carotid artery (Protocol IIB). Preirradiation intra-ophthalmic carotid BCNU administration (Protocol III) is offered as a means of avoiding radiation-drug leukoencephalopathy. The protocols are described below.

Protocol I. Thirty patients were given BCNU according to Protocol I. These patients had recurrent glioblastoma and had undergone surgery and radiation therapy for their initial tumor more than 5 months before. Administration of BCNU was by infraophthalmic or supraophthalmic carotid artery infusion every 5 to 6 weeks. These patients received one of two dose regimens: of 12 patients in Protocol IA, three received a BCNU dose of 250 mg/sq m, three 350 mg/sq m, and three 600 mg/sq m. Eighteen patients received Protocol IB: a BCNU dose of 240 mg/sq m.

Protocol II. Forty-three patients received BCNU as adjuvant therapy for newly diagnosed glioblastoma after treatment by surgery and radiation therapy. The drug was administered in a dose of 240 mg/sq m every 5 to 6 weeks. Of these patients, 25 received the drug by infraophthalmic carotid artery infusion (Protocol IIA) and 18 by selective DeBrun balloon-guided supraophthalmic carotid artery infusion (Protocol IIB).

Protocol III. Six patients were in the BCNU Protocol III group. All had newly diagnosed glioblastomas and had undergone surgery more than 10 days before, but had not received radiation therapy. Drug delivery was by infraophthalmic carotid artery infusion, with one 240-mg/sq m infusion every 4 weeks, for a total of four infusions. Irradiation was then given 16 weeks after surgery, or earlier if clinical or CT evidence of deterioration was observed.

Results

A total of 258 infusions (192 infraophthalmic and 66 supraophthalmic) were performed on 79 patients. The supraophthalmic carotid artery infusions included nine infusions for recurrent tumor (Protocol IA) and 57 infusions as adjuvant chemotherapy for patients after radiation therapy (Protocol IIB). Patients receiving BCNU at the time of tumor recurrence (Protocol I) or prior to irradiation (Protocol III) fared the best (Table 2).

Protocol I

Twelve patients received 37 infusions of BCNU for a recurrent glioblastoma through an infra- or supraophthalmic route as part of this protocol (Protocol IA). There was no significant difference in immediate toxicity between dose levels. Doses to 600 mg/sq m could successfully be infused without systemic or hematological toxicity. This patient population has been followed for 200 weeks (as of September, 1984). The median survival time for this group was 54 weeks following recurrence (92 weeks from diagnosis). Eleven of the 12 patients were alive 1 year from the date of recurrence and three survived almost 3 years after tumor recurrence. These three continue to show contrast-enhancing abnormalities of smaller size than noted previously. Similar survival times were experienced by the additional 13 patients with recurrent glioblastoma who received BCNU (240 mg/sq m) (Protocol IB). These patients lived 44 weeks following the start of chemotherapy for tumor recurrence. Five patients with glial malignancies in the vertebrobasilar circulation received vertebral artery infusion, and none responded.

Protocol IIA

We have treated 25 patients with adjuvant BCNU, performing 90 infusions into infraophthalmic carotid artery sites for newly diagnosed and irradiated glioblas-
Intra-arterial BCNU treatment for glioblastoma

toma. These patients have been followed for 160 weeks (through October, 1984), at which time the median survival time was 64+ weeks. Thirteen patients showed either complete or partial response on follow-up CT scans. The longest postoperative survival times are now 159+, 150+, 150+, 119+, and 116+ weeks. No patient removed himself from the protocol. Two patients were excluded because of treatment-related complications, one with infusion-related asthma and one with a small hemorrhage into his tumor. One patient died from a pulmonary embolus and one due to infection (neither related to BCNU treatment). Nine of these patients have developed recurrent tumor within the original vascular distribution.

Protocol II B

Eighteen patients were given postirradiation adjuvant BCNU via a DeBrun balloon catheter. Median survival time for this group was 49.5 weeks. Only seven survived for 1 year. Those receiving three or more infusions survived 56+ weeks, with the longest survivors living 156+, 150+, 138+, 136+, 94+, and 76+ weeks. Although visual difficulties were avoided, the abrupt development of neurological deficits and cerebral edema was noted in three patients without tumor progression. These changes were indistinguishable from an acute cerebrovascular accident. Similar edema was seen within weeks of the second or third infusion in nine other patients. Although responsive to mannitol diuresis and/or corticosteroid therapy, areas of persisting decreased attenuation were seen on CT scan.

Discussion

Intra-arterial chemotherapy of glioblastoma is a logical and easily performed extension of available chemotherapy. Our experience demonstrates that BCNU (to a total of 600 mg/sq m) can be administered into the infraophthalmic carotid artery with retinal (but negligible systemic) toxicity. Ocular pain and retinal vasculopathy can be avoided by the infusion of 240 mg/sq m of BCNU (dissolved in alcohol at a concentration of 1 cc/100 mg BCNU) into the supraophthalmic carotid artery. In patients with newly diagnosed glioblastoma, these infra- and supraophthalmic carotid artery infusions after irradiation produced survival times of 64 and 49.5 weeks, respectively, with approximately one-quarter of both groups living 2 years from diagnosis. These survival times added little to those recorded after conventional therapy regimens. This negative experience with postirradiation patients is in contrast to results of intra-arterial BCNU infusion in patients with recurrent glioblastoma. For these patients, this treatment provided an additional year of life and extended the average postoperative survival period to 88 weeks.

Why is adjuvant intra-arterial BCNU therapy less impressive than similar therapy provided at the time of tumor recurrence? Two factors were at play. The first factor was dose-related BCNU and/or alcohol toxicity to irradiated tissue. Twenty percent of the patients treated immediately after irradiation showed a profound and persistent decreased attenuation on their CT scans. These toxic changes, which were more notable following supraophthalmic infusions, appeared as infarcts in the distribution of the middle cerebral artery within 1 day of infusion (7%) or as slowly evolving neurological impairment after the third or subsequent infusions (13%). The morbidity accompanying these changes reduced survival times. The toxicities of most chemotherapeutic agents have not been evaluated in animals bearing irradiated tumors. New and unexpected drug toxicity may emerge as a consequence of prior irradiation and escalated drug concentrations.

The second factor, the pharmacokinetics of arterial BCNU administration into irradiated tissue, has not been explored. Early studies did not measure the distribution and half-life of combinations of drug and solvent entering irradiated tissues. The effects of pre-existent radiation-induced changes (arterial/arteriolar hyalinization, tumor necrosis, and vasogenic edema) have not been ascertained. The extended survival period experienced by patients treated for tumor recurrence may reflect better drug penetration.

Our experience suggests that intra-arterial BCNU infusion prior to radiation therapy is a logical approach for future therapy of glioblastoma. This approach (Protocol III) has been used to treat six patients through 23 infraophthalmic carotid artery infusions. In only one patient did the tumor size increase prior to irradiation. During the 16 weeks prior to irradiation, white-matter toxicity has not been seen in these patients.

Several factors support the preirradiation intra-arterial infusion of BCNU. They are as follows: 1) This treatment modality improves the survival time of patients with recurrent glioblastoma. 2) It avoids or reduces the vascular and white-matter damage that follows infusion of BCNU into irradiated tissue. 3) Good results have been obtained with preirradiation chemotherapy in other "regional" radiation resistant malignancies, such as those of hepatic, gastrointestinal, and hematological origin. 4) Extended experience with arterial infusion has shown minimal risk of systemic toxicity and infusion-related retinal damage with preirradiation infraophthalmic carotid artery infusion. 5) The use of preirradiation chemotherapy has built-in safeguards. The use of preinfusion CT scans permits irradiation in the event of tumor progression, so that the delay in providing irradiation is limited to the interval since the last CT scan (no longer than 4 weeks). 6) Socioeconomic concerns argue for preirradiation chemotherapy. The regimen of intra-arterial BCNU infusion every 4 weeks for four infusions delivers most chemotherapy at a time of maximum postoperative patient function. The total of 4 days' hospitalization (1 day per infusion) replaces the current daily irradiation schedules (30 to 40 radiation fractions over 35 to 45 elapsed days).
References


Manuscript received November 26, 1984. Accepted in final form March 28, 1985. This work was supported by the Narragansett Foundation and the Farber and Sanford Funds. Address reprint requests to: Fred H. Hochberg, M.D., Neurology Service, Massachusetts General Hospital, Boston, Massachusetts 02114.