Supraophthalmic Placement of Microleak Balloon Catheters for Intracranial Chemotherapy Infusion: Complications and Results of Therapy

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In previous reports, the limiting factor in intracranial perfusion of chemotherapeutic agents has been their toxicity to ocular structures [1–6]. We report our experience with six patients using a transfemoral approach in the supraophthalmic placement of a microleak balloon catheter for chemotherapy infusion.

Technique

Our technique is similar to that described by Debrun et al. [7] and consists of the introduction of a microleak balloon catheter by way of a transfemoral approach, placing the balloon above the takeoff of the ophthalmic artery so that chemotherapy can be delivered to an intracranial malignant neoplasm without causing chemosis and/or ophthalmoplegia to the ipsilateral eye.

An 8 French introducing catheter is placed into the internal carotid artery and is continuously flushed with heparinized saline (1000 units in 1000 ml of D50 · 0.9NS) by way of a coaxial system. The 2 French jet-controlled microleak balloon catheter (Ingenor, Paris), inside a prototype Plexiglas coiling chamber (Dresco Machine Tool Co., Bay City, MI), is subsequently attached to the introducing catheter, and the balloon catheter is propelled through the introducer. The position of the radioopaque microleak balloon catheter is then substantiated fluoroscopically with test injections of contrast material. Digital subtraction filming is subsequently performed to document the position of the balloon. Repositioning may be necessary if the balloon tip is not seen to be above the takeoff of the ophthalmic artery as shown on a prechemotherapy angiogram. Once the balloon is in place, the appropriate chemotherapeutic agent is delivered through the catheter. The dosage of 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) is 100 mg/m² and that of cis-platinum is 60 mg/m². The chemicals are infused at a rate of 5 ml/min. The patient is carefully monitored for signs of chemosis and developing neurologic deficits during the infusion process. Mannitol and steroids are used to help prevent brain edema, which may be a toxic side effect of the chemotherapeutic agents. Prechemotherapy and postchemotherapy CT scans enhanced with 150 ml of Hypaque 60 via drip infusion were used to establish success of this treatment. Severe arterial tortuosity may be a limiting factor preventing the supraophthalmic placement of the balloon portion of the catheter.

BCNU was the protocol chemotherapeutic agent chosen by the oncology department. Second and third doses of BCNU were administered at 4–6 week intervals depending on the patient’s clinical course, tolerance to the catheterization procedure, and/or partial or complete remission. Cis-platinum was substituted for BCNU only if the patients were refractory to the latter drug as evidenced by tumor progression.

The balloon remained in the supraclinoid carotid artery about 40 min. During slow infusion rates of chemotherapy into the balloon catheter, there was very little if any distension of the balloon.

Results

Table 1 summarizes our clinical experience with supraophthalmic chemotherapeutic infusion. Only one metastatic tumor was treated (case 1), and, although CT showed less enhancement after the initial infusion of BCNU, no significant change in the CT scan was seen after the second infusion. It was then decided to alter the chemotherapeutic agent, and cis-platinum was infused. The balloon catheter was not supraophthalmic in location for the cis-platinum infusion because of vascular tortuosity hindering catheter advancement, and some of the chemotherapeutic agent entered the ipsilateral ophthalmic artery resulting in blindness.

Cases 2–6 were all malignant astrocytomas (biopsy-proven). Case 2 had CT evidence of less enhancement after an initial infusion, but further chemotherapy was refused.

Case 3 was treated with three BCNU infusions and one cis-platinum infusion. Figure 1A is a CT scan obtained before
chemotherapy and indicates a left-temporal-lobe glioma. Figure 1B, a CT scan 1 month after initial infusion, shows decreased enhancement of the neoplasm. Figure 1C was obtained 1 month after the second BCNU infusion. A CT scan 1 day after the third BCNU infusion indicated less tumor enhancement compared with the initial preinfusion scan; however, the patient deteriorated clinically, and an enhanced scan 1 month after the third BCNU infusion (fig. 1D) demonstrated tumor progression. Because this scan appearance was disappointing, cis-platinum was substituted for BCNU, and this agent was infused instead. Figure 1E is a scan obtained 1 day after the cis-platinum infusion. Although this scan shows decreased enhancement, clinically the patient deteriorated, suffering a dense right hemiparesis and dysphasia. He died 1 month later.

Cases 4–6 showed essentially no significant CT improvement and even showed progression of tumor after BCNU infusion. A left frontotemporal glioma was surgically proven in case 4. Figure 2A is a CT scan obtained 2 months after the initial BCNU infusion with little change noted. One day after the second BCNU treatment (fig. 2B), CT shows less enhancement of tumor but no change in mass effect; however, 2 months after the second infusion, the tumor had significantly progressed.

Case 5 is a biopsy-proven grade IV left temporal astrocytoma. After two BCNU infusions, follow-up CT scans demonstrated no decrease in mass effect or cerebral edema. There was some decrease in contrast enhancement of the neoplasm. The patient did not improve clinically, and further intraarterial chemotherapy was discontinued.

Case 6 is a pathologically proven glioblastoma of the right temporal lobe. A preinfusion CT scan showed a diffuse right-temporal-lobe infiltration. However a CT scan 1 month after BCNU infusion indicated definite neoplastic progression. The patient refused further therapy.

In our series of patients, a transient complication was internal carotid artery vasospasm due to manipulation of the main introducing catheter. This occurred during three of the infusion episodes but did not contribute to the permanent neurologic deficits in four of the patients. No evidence of vasospasm occurred with jet-propulsion manipulation of the microleak balloon catheter.

During three separate infusion episodes transient neurologic deficits such as hemiparesis and dysphasia/aphasia occurred. These deficits were believed to be secondary to cerebral edema and/or cerebral ischemia possibly related to known toxic arteritis side effects of the chemotherapeutic agents. At the time of these infusions, steroids and mannitol limited the intensity and duration of the above deficits; however, three separate patients eventually developed permanent neurologic deficits. In all of our patients, steroids were used to help prevent brain edema during the infusion process, often in conjunction with mannitol. We cannot exclude the possibility that the steroids may have affected contrast enhancement on follow-up CT scans. A dramatic decrease in the contrast enhancement of several of these neoplasms scanned 1 day after chemotherapy infusion may be a direct result of steroid administration.

Distal migration of the balloon catheter occurred during three infusion episodes; but this was corrected by repositioning the balloon and withdrawal of all catheter slack before infusion. Significantly increased brain edema as a result of chemotherapeutic infusion was not evident on our postinfusion CT scans when compared with our preinfusion scans. We noted that the patients developed fewer neurologic complications during the initial chemotherapeutic infusions when mannitol and steroids were administered; however, multiple chemotherapeutic infusions per patient increased the chances of permanent neurologic complications. There were no deaths in the immediate postinfusion period.

Discussion

Intraarterial chemotherapy for intracranial neoplasms has been the subject of extensive research by several investiga-
tors. The chemotherapeutic agents thought to be most effective are in a group called nitrosoureas, which are antineoplastic agents. They exhibit pharmacologic properties that readily allow penetration of the blood-brain barrier. Dewys and Fowler [1] injected BCNU into the internal carotid arteries of eight dogs. Corneal opacity and blindness from corneal and retinal edema were observed in three of four dogs injected intraarterially and in none of the four dogs treated intravenously. Arteriolitis and brain infarction were among the other significant complications noted by these authors. Crafts et al. [8] studied the effects of BCNU administered into the carotid arteries of six rhesus monkeys. Vascular and ophthalmic toxic effects were minor, and at autopsy no ophthalmic lesions were found. Fenstermacher and Cowles [9] performed extensive theoretic research with intracarotid chemotherapy infusion techniques. They concluded that, at low rates of tissue perfusion, the intracarotid infusion produced both a large peak concentration and a large exposure of drug to the tissue. Omojola et al. [2] described a selective nonocclusive technique for administration of BCNU into the internal carotid artery of the dog. The tip of the catheter was manipulated into the carotid bulb without occluding the vessel lumen. An ipsilateral necrotizing cerebral arteriolitis was a significant complication. Ocular toxicity was not shown, but the authors
believed that this finding may be related to the protection offered the dog by having both the internal and external carotid arteries supplying the eye.

Yamada et al. [3] and, more recently, Madajewicz et al. [4] infused intraarterial BCNU into human patients for therapy of metastatic brain tumors. Yamada et al. treated nine patients with intracerebral metastasis from lung carcinoma. Most of their patients manifested ipsilateral periorbital discomfort with episcleral vasodilatation during the infusion period.

Kapp et al. recently published two significant articles pertaining to intraarterial chemotherapeutic infusion [10, 11]. They stressed the importance of supraophthalmic carotid artery catheter positioning before infusion of BCNU to prevent severe ocular complications. Kapp et al. used the technique of arteriography in the bulb of the carotid artery to place their catheter into the lumen of the vessel.

Greenberg et al. [5] and, more recently, Gebarski et al. [6] stressed the orbital problems encountered with intracarotid BCNU chemotherapy infusion. The most severe toxic effect associated with the infusion was ipsilateral retinal vasculitis resulting in transient or permanent loss of vision. Despite decreasing the ethanol concentration in the BCNU mixture, the authors still noted orbital pain to be a problem in their patients. Gebarski et al. showed arteriographic evidence of increased orbital vascularity and vasodilation during the perfusion procedure.

Layton and her University of Michigan coauthors [12] recently attempted to reduce ocular toxicity by decreasing the amount of BCNU diluent, ethanol, and substituting a D$_2$W base in its place. These authors concluded that D$_2$W was a satisfactory substitute for the ethanol and may decrease the possibility of ocular and brain damage during chemotherapeutic infusion.

This same group of workers [13] treated 36 glioma patients with BCNU every 6–8 weeks, either by transfemoral catheterization of the internal carotid or vertebral artery or through an implantable intracarotid drug delivery system. Twelve patients with grade III or IV astrocytomas were treated after partial resection of the tumor without prior radiation therapy. The median duration of survival in the 12 patients was 54 weeks (range, 21–156 weeks or longer), with an 18 month survival rate of 42%. Twenty-four patients with recurrent grades I–IV astrocytomas received two to eight courses of intraarterial BCNU therapy. Seventeen of these patients had a response or were stable for a median of 20 weeks (range, 6–66 weeks or more). These authors experienced delayed ocular complications in nine of these patients.

Although the overall results of our six patients are disappointing with regard to long-term survival, initial infusions with BCNU produced significant clinical improvement in three cases. The supraophthalmic delivery technique eliminated ocular problems in all but one patient and, if the balloon catheter is properly placed, all future ocular toxicity should be eliminated. The encouraging work of Greenberg et al. [13] with regard to increased survival rates in 30 patients is indeed important. Combining BCNU therapy with radiotherapy or other types of intraarterial chemotherapeutic agents may be effective in increasing the longevity of these glioma patients.

Dewys and Fowler [1] and Omojola et al. [2] noted that BCNU produced brain infarction in experimental animals, and, thus, cerebral infarction may have been responsible for the right hemiparesis and aphasia/dysphasia in our cases 3–5. In clinical practice, absolute alcohol is used to precipitate thrombosis and infarction in renal neoplasms. Therefore, it is possible that the ethanol diluent, rather than the BCNU, causes the infarctions that were seen on some of our postinfusion CT scans. The low-density abnormalities in the white matter, noted on the postinfusion CT scan in case 4, may be a chemotherapy-produced leukoencephalopathy [13].

Supraophthalmic infusion of chemotherapy has almost completely eliminated the chemosis and ophthalmoplegia associated with infraophthalmic placement of arterial infusion...
catheters. The results of supraophthalmic infusion of BCNU and cis-platinum have not proven them to be curative agents in primary malignant supratentorial tumors. Development of newer water-soluble chemotherapeutic agents could make this technique a valuable method of treatment.

REFERENCES