AJNR

Intracarotid chemotherapy of glioblastoma after induced blood-brain barrier disruption.

C T Bonstelle, S H Kori and H Rekate

AJNR Am J Neuroradiol 1983, 4 (3) 810-812
http://www.ajnr.org/content/4/3/810

Intracarotid Chemotherapy of Glioblastoma after Induced Blood-Brain Barrier Disruption

Charles T. Bonstelle,[1] Shashidhar H. Kori,[2] and Harold Rekate[3]

Intracarotid chemotherapy has been suggested as an additional mode of therapy in patients with brain tumors. Seven comatose patients received intracarotid 5-fluorouracil and adriamycin after intracarotid infusion of 25% mannitol to open the blood-brain barrier at the tumor site. Five of seven patients became fully functional for 3–12 months. Another 11 patients entered the study, of which nine are currently receiving therapy and are functional, and two have died, one from brain herniation. The results are encouraging and support the need for further research of this therapeutic method.

The end results of malignant brain tumors are uniformly poor. The present therapies involving radiation therapy and/or chemotherapy have been uniformly disappointing. These tumors have an early devastating effect because, not only do they grow within limited space, but their infiltrative nature disturbs function, causing related symptoms and (ultimately) death. The blood-brain barrier prevents the passage of certain chemotherapies into the brain parenchyma surrounding the tumor. The blood-brain barrier is, of course, absent in the central part of the tumor. However, this part of the tumor is usually necrotic and not responsive to chemotherapy. The work by Rapoport et al. [1–4] has shown that the blood-brain barrier can be temporarily opened to allow the passage of substances usually not allowed past the blood-brain barrier, including certain chemotherapeutic drugs. The work by Neuwelt et al. [5–9] has demonstrated that this opening of the blood-brain barrier in patients for subsequent chemotherapy can be performed safely.

Subjects and Methods

The seven initial patients in our study were all comatose and were believed to be terminal. All had received surgery and radiation therapy. Two had received high-dose BCNU chemotherapy with bone marrow transplant. One patient had received intrathecal T-lymphocyte therapy. All patients had tissue confirmation of the diagnosis. All had an arteriogram to delineate the blood supply to the tumor.

The next 11 patients entered the study at an earlier phase of their tumors. All had received radiation therapy and surgery. Five had received chemotherapy. All were believed to have exhausted the normal therapeutic regimens. CT scans of these patients all demonstrated tumors with associated mass effects.

The therapy protocol was constant for all patients (table 1). Immediately before intracarotid chemotherapy, 25% mannitol was rapidly infused into the internal carotid artery to cause osmotic disruption of the blood-brain barrier at the tumor site for 20–30 min [10]. Infusion of 5-fluorouracil and adriamycin into the internal carotid artery occurred within 30 min of the mannitol infusion. The therapy sessions were repeated every 6 weeks until the patient had received the maximum dose of adriamycin. In some cases the dose of chemotherapy was reduced because of leukopenia after previous therapy.

Results

Table 2 lists the results. Six of the first seven patients awoke and had 3–12 months of additional functional life, being ambulatory and self-caring. One of these six patients was limited by contractures that developed before therapy. One patient was withdrawn from the study by the family. One patient was still alive and functioning well after more than 1 year with no evidence of tumor on CT. He developed herpes encephalitis and was confined to a nursing home. Only one patient died with known brain death. CT scans during the period of treatment showed diminution in tumor mass size in 10 of 13 patients (fig. 1). In those patients who were autopsied, residual tumor was present to a small degree in all cases. However, most of the mass present was necrotic tissue.

The next 11 patients were more recent additions to the study (table 2, cases 8–18). Two died, one of pulmonary causes and one of brain herniation. Nine patients have been ambulatory and self-caring. These patients have not been followed long enough to yield data about the use of this therapy in patients whose disease process has not progressed to the point of unconsciousness.

The complications in our group are listed in table 3. All seizures were controlled. The two patients who developed brain swelling after their first chemotherapy were treated with steroids and had further therapy postponed until the brain swelling regressed. The development of fourth cranial nerve palsy appeared to be related to the mannitol infusion because this development could be seen during mannitol infusion.

Discussion

The work of Rapoport, Neuwelt, et al. [1–10] has suggested that opening of the blood-brain barrier offers great potential in the treatment of patients with brain tumors. We undertook to verify their

[1] Department of Radiology, University Hospitals of Cleveland, 2074 Abington Rd., Cleveland, OH 44160. Address reprint requests to C. T. Bonstelle.
[2] Department of Neurology, University Hospitals of Cleveland, Cleveland, OH 44106.
[3] Department of Surgery, University Hospitals of Cleveland, Cleveland, OH 44106.

AJNR 4:810–812, May/June 1983 0195-6108/83/0403-0810 $00.00

optimism on a group of patients who have otherwise exhausted all therapeutic regimens. Our results are encouraging.

We have encountered two definite problems. In one case a large necrotic brain tumor mass resulted in herniation and death of that patient. At autopsy very little tumor was identified within the large necrotic mass. Autopsies on other patients in our protocol have shown relatively decreased numbers of tumor cells in the tumor mass with large areas of necrosis. We believe that if one can define what is tumor and what is necrosis, one could certainly recommend surgery for a large mass that is mostly necrotic tissue. CT has not

TABLE 1: **Protocol for Each Therapy Session**

Day No.	Therapy
1	BCNU, 100 mg/m^2 intravenously (150–200 mg)
2	BCNU, 100 mg/m^2 intravenously (150–200 mg)
5	Intracarotid infusion:
	120 ml of 25% mannitol at 60 ml/min
	5-fluorouracil, 15 mg/kg (900 mg) at 150 mg/min
	Adriamycin, 50–60 mg/m^2 (90 mg) at 2 mg/min × 3 min, then 6 mg/min × 14 min

TABLE 3: **Complications during and after Therapy for Glioblastoma**

Complication	No. Patients (n = 18)
Chemical conjunctivitis	18
Seizures after therapy	2
Hypotensive after therapy	2
Herpes zoster	2
Herpes zoster encephalitis	1
Cranial nerve IV palsy	2
Brain swelling	2
Transient ischemic attacks	1

TABLE 2: **Results of Therapy for Glioblastoma**

Illness Phase: Case No.	Functional Time after Therapy (months)	Time in Study (months)	CT Findings	Results
Comatose:				
1	10	12	Decreased mass	Died (pneumothorax)
2	(Contractures)	7	Decreased mass	Died (bronchopneumonia)
3	12	12	Decreased mass	Died (bleeding esophageal ulcer)
4	4	7	Decreased mass	Died (no autopsy)
5	3	5	Massive swelling	Died (brain herniation)
6	9	9	No residual tumor	Self-care, confusion
7	0	2	No change	Withdrawn from study
Early:				
8	4	4	Decreased mass	Self-care, alert, walking
9	3	3	Decreased mass	Self-care, residual aphasia, walking
10	3	3	Decreased mass	Blind, alert, walking
11	3	3	Decreased mass	Self-care, walking
12	3	3	Decreased mass	Died (pulmonary causes)
13	3	3	Marked swelling	Died (brain herniation)
14	2	2	No change	Self-care, walking, working
15	1	1	No change	Self-care, walking, memory loss
16	1	1	No change	Self-care, walking
17	1	1	No change	Self-care, walking
18	1	1	No change	Partial care, confusion

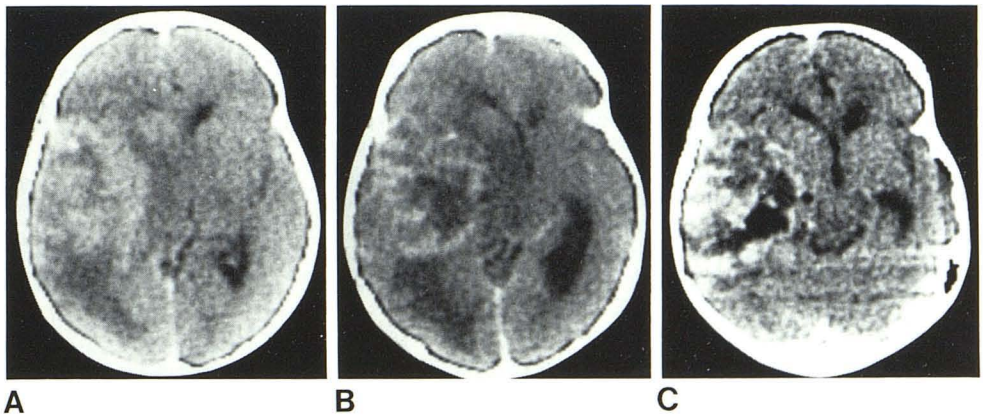

Fig. 1.—**A**, Before intraarterial chemotherapy. Large left hemisphere tumor with midline shift. **B**, After initial intracarotid chemotherapy. Definite increase in left hemisphere mass effect. **C**, After second intracarotid chemotherapy. Marked decrease in left hemisphere mass effect with return of ventricles toward midline.

been helpful in this regard. We are investigating the use of nuclear magnetic resonance scanning in making this differentiation.

A second problem was the marked brain swelling after chemotherapy in two patients. Both of these patients had a repeat craniotomy within the 1–2 months before the start of the chemotherapy protocol. These patients could have responded in the manner they did because of the more aggressive nature of their brain tumors. Or it may be possible that the recent surgery made the brain tissues more susceptible to developing edema. Further investigation of this phenomenon will be undertaken.

Considering that of the seven original comatose patients, six awoke, became functional, and had the opportunity for further meaningful life is encouraging to us. We see the need for further investigations to provide for better treatments of brain tumors via the intracarotid route.

REFERENCES

1. Rapoport SI, Fredericks WR, Ohno K, Pettigrew KD. Quantitative aspects of reversible osmotic opening of the blood-brain barrier. *Am J Physiol* **1980**;283:421–431
2. Rapoport SI, Hori M, Klatzo I. Testing of a hypothesis for osmotic opening of the blood-brain barrier. *Am J Physiol* **1972**;223:323–331
3. Rapoport SI, Mathews K, Thompson HK. Absence of brain edema after reversible osmotic opening of the blood-brain barrier. In Pappius HM, Feindel W, eds. *Dynamic aspects of brain edema.* Berlin: Springer-Verlag, **1976**:1–22
4. Rapoport SI, Thompson HK. Osmotic opening of the blood-brain barrier in the monkey without associated neurological deficits. *Science* **1973**;180:971
5. Neuwelt EA. Therapeutic aspects of neuro-oncology. In: Rosenberg RN, ed. *Current treatment of neurological diseases.* New York: Spectrum, **1979**:205–228
6. Neuwelt EA, Frenkel EP. Is there a therapeutic role for blood-brain barrier disruption? *Ann Intern Med* **1980**;93:137–139
7. Neuwelt EA, Frenkel EP, Diehl J, Vu LH, Rapoport SI, Hill S. Reversible osmotic blood-brain barrier disruption in humans: implications for the chemotherapy of malignant brain tumors. *Neurosurgery* **1980**;7:44–52
8. Neuwelt EA, Frenkel EP, Rapoport SI, Barnett P. Effect of osmotic blood-brain barrier disruption on methotrexate pharmacokinetics in the dog. *Neurosurgery* **1980**;7:36–43
9. Neuwelt EA, Maravilla KR, Frenkel EP, Rapoport SI, Hill S, Barnett P. Osmotic blood-brain barrier disruption: computerized tomographic monitoring of chemotherapeutic agent delivery. *J Clin Invest* **1979**;64:684–688
10. Neuwelt EA, Maravilla KR, Frenkel EP, Barnett P, Hill S, Moore RJ. Use of enhanced computerized tomography to evaluate osmotic blood-brain barrier disruption. *Neurosurgery* **1980**;6:49–56