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AJNR Am J Neuroradiol 1984, 5 (1) 55-58
http://www.ajnr.org/content/5/1/55

This information is current as of April 16, 2024.

Orbital Angiographic Changes after Intracarotid BCNU Chemotherapy

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Seven patients treated with intraarterial internal carotid 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) chemotherapy for malignant gliomas of the brain had postinjection angiographic demonstration of increased orbital vascularity and vasodilatation, sometimes associated with arteriovenous shunting. Subjective orbital discomfort reported by the patients during chemotherapy correlated with this orbital hyperemia. Some therapeutic suggestions for managing this undesirable effect of BCNU chemotherapy are discussed.

The purpose of this communication is to describe the various orbital angiographic abnormalities that appear just after intracarotid 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) chemotherapy for cerebral neoplasms and to discuss some therapeutic implications.

Subjects and Methods

Our clinical material comprises 13 internal carotid angiographic examinations from seven patients with biopsy-proven malignant gliomas of the brain who entered the University of Michigan experimental intraarterial BCNU chemotherapy protocol [1]. Briefly stated, immediately after transfemoral catheter placement in the appropriate internal carotid artery, BCNU is dissolved in ethanol (100 mg BCNU per 0.75 ml ethanol) and added to 47 ml of normal saline. This mixture is hand-injected through a three-way stopcock in 2.5 ml increments, the BCNU mixture alternating with simple normal saline flush. Five to ten min after completion of chemotherapy, routine internal carotid angiography is performed, using 7 ml of Conray-60 (meglumine iothalamate 60%) for every examination.

Thirteen separate chemotherapeutic applications were administered to the seven patients at different times. The orbital pain during chemotherapy was treated with varying doses of morphine sulphate given intravenously, using an average total dose of about 20 mg/patient. Dexamethasone was used as clinically indicated [1]. Radiation therapy also was administered in the seven cases (table 1).

The BCNU protocol described above differs from our original BCNU protocol, in which angiography was done *before* and *not after* BCNU administration. The last 35 internal carotid angiograms obtained before instituting our present protocol were reviewed also.

Results

All 13 angiograms obtained immediately *after* internal carotid BCNU chemotherapy demonstrated apparent ipsilateral increase in orbital vascularity and vasodilatation (fig. 1). Intraorbital arteriovenous shunting was seen also in two patients. In those patients who received intracarotid BCNU therapy on more than one occasion (i.e., cases 1 and 6 had three cycles each 6–8 weeks apart), the degree of orbital vascular abnormality was essentially unchanged between the individual examinations, despite increasing doses of the drug (table 1). The degree of orbital vascular abnormality correlated well with subjective discomfort. In no case were any similar cerebral vascular abnormalities seen.

Received November 22, 1982; accepted after revision July 21, 1983.

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***AJNR* 5:55–58, January/February 1984**
0195–6108/84/0501–0055 $00.00
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TABLE 1: **Summaries of Patients with Malignant Gliomas Studied by Arteriography after BCNU Chemotherapy**

Case No.	Glioma Location, Grade	Prechemotherapy Irradiation in Rads (Gy)	Orbital Pain during Chemotherapy	Arteriographic Orbital Plethora	Arteriovenous Shunting	BCNU Dose (mg/m²)
1	Right frontoparietal, III	5000 (50)	++	++	0	250
			+++	+++	++	300
			+++	+++	++	300
2	Right temporoparietal, III	0	++	++	0	300
3	Right frontoparietal, II	0	++	++	0	250
			++	++	0	300
4	Left parietal, III	0	++	++	0	250
			++	++	0	300
5	Left parietal, III	0	+++	+++	+	250
6	Right parietooccipital, III	0	++	++	0	250
			++	++	0	300
			++	++	0	300
7	Left parietooccipital, IV	6500 (65)	++	++	0	300

Note.—+ = minimal; ++ = moderate; +++ = marked.

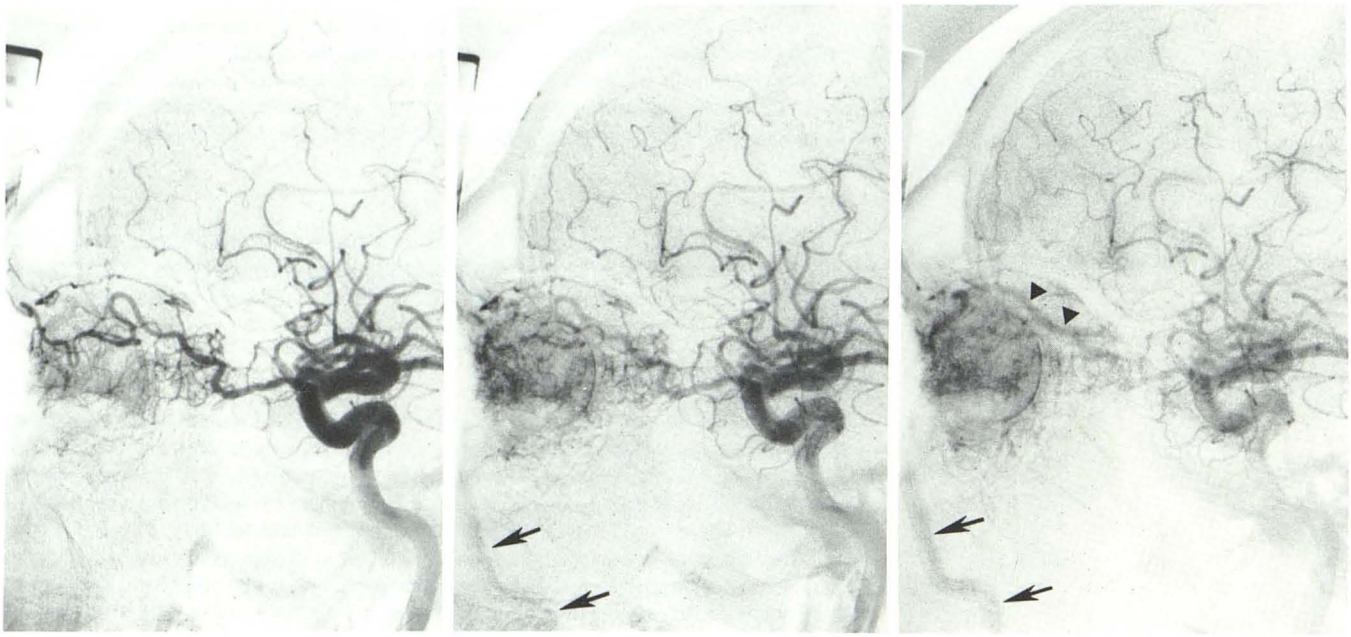

Fig. 1.—Case 1. **A**, Selective right internal carotid angiogram after BCNU chemotherapy, cycle 3. Marked increase in orbital vascularity. Apparent large size of ophthalmic artery and its branches indicates vasodilatation. **B**, 0.5 sec later. Arteriovenous shunting into angular vein (*arrows*) and pronounced intraorbital vascular "stain." **C**, 0.5 sec later. Moderate arteriovenous shunting into superior orbital vein (*arrowheads*) in addition to angular vein (*arrows*).

The 35 internal carotid angiograms obtained just *before* BCNU infusion showed no orbital abnormalities. These studies included patients receiving multiple cycles of chemotherapy. The delay between chemotherapeutic cycles was 6–8 weeks [1] (fig. 2).

Discussion

BCNU is an alkylating chemotherapeutic agent that has been shown to have efficacy in the direct intraarterial treatment of malignant gliomas [1–3]. As clinical awareness of such therapy increases, increasing use may be expected. The most severe known toxic effect associated with this treatment has been ipsilateral retinal vasculitis resulting in transient or permanent loss of vision [1–4]. This alarming side effect appears to be dramatically reduced by decreasing the ethanol concentration in the BCNU mixture [1]. Nevertheless, orbital pain remains a significant problem. BCNU is known to be slightly soluble in a 5% dextrose/water (D5W) solution. A clinical investigation comparing administration of BCNU dissolved in dilute ethanol with BCNU dissolved in D5W, prepared by rapid agitation and filtration, has been initiated as a result of this study.

In our earlier intracarotid BCNU protocol, internal carotid angiography was performed routinely just *before* infusion of the chemotherapeutic agent. At that time, administration of

Fig. 2.—Selective right internal carotid angiogram *before* second course of intracarotid BCNU chemotherapy. No orbital abnormalities are seen.

radiographic contrast material before BCNU infusion was believed to possibly enhance tumor exposure to BCNU by transient alteration of the blood-brain barrier (BBB) in the tumor [5, 6]. More recent evidence suggests that tumor exposure to BCNU after intracarotid administration of hyperosmolar solutions (mannitol) actually may decrease because of increased drug delivery to the normal part of the brain [7]. In a similar manner, hyperosmolar radiographic contrast material transiently opening the BBB of the normal brain also may divert some of the BCNU from the tumor. Disruption of the normal BBB after intraarterial injections of modern contrast agents is well known [8–12]. Therefore, angiography is now performed only *after* BCNU infusion.

No individual patient's treatment was in progress when the protocol change was made from pre- to postchemotherapeutic angiography. Therefore, pre- and postchemotherapeutic angiograms from the same patient are not available for comparison. However, review of the last 35 internal carotid angiograms obtained just *before* intracarotid BCNU therapy revealed no intraorbital abnormalities. Some of these patients had multiple cycles of chemotherapy. If orbital abnormalities had persisted longer than 6–8 weeks, they should have been apparent on at least some of the angiograms obtained *before* second or third BCNU therapy cycles. None were demonstrated.

As an example, figure 2 represents angiography performed just *before* a second course of BCNU chemotherapy. This particular patient suffered significant subjective orbital discomfort during her first course of BCNU, which was 6 weeks earlier. Effectively, this "follow-up" study was 6 weeks "delayed". If orbital abnormalities had persisted 6 weeks, they would have been demonstrated on this study. None are apparent, nor were they on the angiogram just *before* the patient's first course of BCNU.

The dramatic differential dilatory response to BCNU therapy in cerebral versus orbital vascularity is consistent with the well known differences in regulatory mechanisms for cerebral versus extracerebral blood flow [13]. It leads to speculations on the use of chemical and/or mechanical manipulation to transiently decrease orbital (including ocular) perfusion and, it is hoped, to reduce BCNU-induced retinal complications. This was attempted in two patients who had suffered mild ocular toxicity after previous BCNU therapy. Retrobulbar nerve block was administered with 0.5% Marcaine (3 ml) and 2% lidocaine (1 ml). During BCNU or saline infusion, intermittent scleral pressure was applied with a cotton swab to occlude the central retinal artery blood flow for 30 sec. This occlusion was verified and continuously monitored with indirect ophthalmoscopy. All infusions, either BCNU or saline flush, were interspersed with release of scleral pressure for 50 sec periods to allow normal retinal arterial flow while no BCNU or saline was being injected. These maneuvers appeared to be successful in these patients in that no further retinal toxicity occurred, and orbital pain was significantly reduced.

To date, no chemical manipulation has been attempted, but topical or subconjunctival administration of a vasoconstrictor that is absorbed predominantly by the vitreous humor would be a logical approach. Extremely low doses of intraarterial catecholamines may also be reasonable in view of the known poor physiologic response to intraarterial catecholamines in the normal cerebral circulation [13].

The optimal BCNU delivery would seem to be via balloon-directed or coaxial catheter systems [14–18]. These systems permit perfusion of the internal carotid artery distal to the ophthalmic artery origin. Unfortunately, these systems are not without their own risks of complications [16, 17]. Thus, in addition to the added expense and time involved in using such systems, there is the possibility of exchanging one complication for others.

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