

**ORIGINAL
RESEARCH**

E.C. Bourekas
H.B. Newton
G.M. Figg
H.W. Slone

Prevalence and Rupture Rate of Cerebral Aneurysms Discovered during Intra-Arterial Chemotherapy of Brain Tumors

BACKGROUND: During the administration of intra-arterial (IA) chemotherapy for the treatment of brain tumors (BTs), angiography may demonstrate asymptomatic, incidental cerebral aneurysms. The prevalence and complication rate of incidental aneurysms in patients undergoing IA chemotherapy remains unknown. It remains unclear whether the presence of an aneurysm represents an increased risk or a contraindication to this form of treatment.

METHODS: We performed a chart and angiography review of BT patients receiving IA chemotherapy over the previous 16 months. Seventy-eight patients were identified with primary (39) and metastatic (39) BTs.

RESULTS: The cohort consisted of 40 men and 38 women, with a mean age of 47.8 years (range, 22–80 years). During initial angiography, 8 patients (10.3%) were identified with incidental cerebral aneurysms. The aneurysms were saccular and varied in size from 2–4 mm (mean, 3 mm). Seven of the 8 patients continued IA chemotherapy after detection of the aneurysm, for a total of 35 IA procedures. Of these 7 patients, 5 expired from nonaneurysmal complications (mean survival, 5.4 months; range, 2–10 months); 4 from the primary tumor, and one from an infected craniotomy site. Two patients continue to survive; one remains in treatment, and the other has completed 12 months of IA therapy. There were no aneurysmal complications during or after IA treatment in any of the BT patients.

CONCLUSION: Incidental aneurysms may be more common in patients with BTs than the general population. In our patient population, there was no indication that an incidental aneurysm was reason to preclude or delay the use of IA chemotherapy.

Primary and metastatic brain tumors (BTs) affect between 120,000 and 170,000 new patients each year in the United States.^{1,2} The morbidity and mortality of these tumors remains very high, with length of survival ranging between 6 and 18 months for most patients. The use of innovative, dose-intensive treatment strategies may be of benefit in selected patients. One such treatment option is to administer chemotherapy by the intra-arterial (IA) route, which can potentially increase the intratumoral concentration of certain drugs by a factor of 5× to 10× over the intravenous route.^{3–6} During the administration of IA chemotherapy to BTs, angiography may demonstrate asymptomatic, incidental cerebral aneurysms. The prevalence of aneurysms in the general population is approximately 5%.^{7,8} The prevalence of incidental aneurysms in patients undergoing IA chemotherapy, however, remains unknown. It also remains unclear what the complication rates are of patients undergoing IA chemotherapy procedures who have an incidental aneurysm.

In this study, we will perform a retrospective angiographic and chart analysis of patients who have received IA chemotherapy for primary (PBT) and metastatic (MBT) to determine the prevalence of incidental aneurysms. In addition, we will attempt to determine whether the presence of an incident-

tal aneurysm increases the risk for IA chemotherapy procedures and if an aneurysm should be considered a contraindication to this form of BT treatment.

Materials and Methods

A chart and angiography review was performed of BT patients receiving IA chemotherapy from the neuro-oncology service during the previous 16 months at the James Cancer Hospital. During this interval, 78 patients with various types of BTs were identified. The treatment protocol consisted of IA carboplatin 200 mg/m²/day and intravenous etoposide 100 mg/m²/day on days 1 and 2 every 3–4 weeks (most patients were on a 4-week schedule).^{3–6} The white blood cell count had to be >2000/mm³ and the platelet count had to be >100,000/mm³ to receive treatment. The carboplatin was administered through the left or right internal carotid or vertebral arteries, or both (on separate days), on the basis of the predominant vascular supply of the tumor as judged from MR imaging scans. On the first day of the patient's first cycle of treatment, before the administration of chemotherapy, a complete cerebral angiogram was obtained to define the cerebral anatomy and confirm that the vascular territory to be treated was appropriate for the patient's tumor. For subsequent treatments, before administration of chemotherapy, a diagnostic arteriogram was obtained of only the vessel to be treated, to confirm that the vascular territory was intact and safe to proceed. For the carotid territory, the catheter was placed in the internal carotid artery at approximately the C2 level (once the bifurcation had been evaluated). For vertebral injections, the catheter was placed at approximately the C6–C7 level. Following the diagnostic arteriogram, carboplatin (dissolved in 150 mL D5W) was infused over 15 minutes by using intravenous tubing with an in-line disk filter. The etoposide (dissolved in 200–250 mL 0.9% NaCl) was administered intravenously by rapid infusion, over 5–10 minutes, after the arterial infu-

Received November 1, 2004; accepted after revision February 17, 2005.

From the Section of Neuroradiology (E.C.B., H.W.S.), Department of Radiology, Division of Neuro-Oncology and Dardinger Neuro-Oncology Center (H.B.N., G.M.F.), Department of Neurology, Ohio State University College of Medicine and Public Health and the James Cancer Hospital and Solove Research Institute, Columbus, Ohio.

This work was presented in part in poster format at the Society for Neuro-Oncology meeting, November 2003, Keystone, Colorado.

Address correspondence to Eric C. Bourekas, MD, Department of Radiology, Ohio State University Medical Center, 623 Means Hall, 1654 Upham Drive, Columbus, OH 43210.

sion was completed and the patient had returned to their hospital room. Following the chemotherapy infusion, the catheter was removed and hemostasis was obtained.

The arteriograms of all 78 patients were reviewed for evidence of an incidental aneurysm. All patients with an aneurysm were further evaluated (ie, hospital and clinic charts) for any complications related to the aneurysm due to the IA procedure and/or chemotherapy administration.

Results

The IA treatment cohort consisted of 40 men and 38 women, with a mean age of 47.8 years (range, 22–80 years). There were 37 patients with PBTs, including glioblastoma multiforme ([GBM] 17), astrocytoma grades II and III (13), medulloblastoma (2), oligodendroglioma (3), unspecified glioma (2), primary CNS lymphoma (1), and gliosarcoma (1). Forty-one patients had MBTs, including primary tumors originating from the breast (12), lung (12), nasopharyngeal region (2), kidney (1), ovary (1), esophagus (1), lower limb osteosarcoma (1), non-Hodgkin lymphoma (1), fallopian tube (1), melanoma (1), head and neck (1), and metastasis of unknown origin (1).

On review of initial staging angiography, 8 patients (10.3%) were identified with incidental cerebral aneurysms. Of this subgroup, one patient had a GBM, whereas the remaining cohort had metastatic tumors (lung, 4; breast, 2; esophagus, 1); the sex distribution was equal between men and women. The aneurysms were saccular and varied in size from 2 to 4 mm (mean, 3 mm). Seven of the 8 patients continued IA chemotherapy after detection of the aneurysm, for a total of 35 IA procedures. The eighth patient expired from systemic complications of lung cancer very quickly after the initiation of IA chemotherapy. Of the 7 patients who continued IA chemotherapy, 5 have died of nonaneurysmal complications, with survival ranging from 2 to 10 months (mean, 5.4 months). Four patients died from their primary tumor (GBM, 1; breast, 1; lung, 2), whereas another died of an infected craniotomy site. Two patients continue to survive. One patient (lung carcinoma) is on hiatus from IA chemotherapy after the completion of 12 months of treatment, and the other continues treatment after 3 cycles. There have not been any aneurysmal complications (eg, rupture, sentinel leak) during or after the administration of IA chemotherapy in any of the BT patients.

Discussion

IA chemotherapy has been shown to extend the time to progression and survival of patients with progressive or recurrent PBT and MBT, with minimal procedural morbidity.^{3–6} In general, the technique is well tolerated, with an incidence of procedural complications (eg, stroke, vasospasm, dissection, groin hematoma) ranging from 0.04% to 1.5% in a combined cohort of 52 patients and 432 IA treatment procedures.^{3–5} For the group of 25 patients with recurrent and progressive non-GBM gliomas, IA chemotherapy was associated with objective responses (ie, complete or partial response) in 20% of the cohort, whereas another 60% demonstrated stable disease.⁴ The overall median time to progression and survival for the recurrent PBT cohort were 24.2 weeks and 34.2 weeks, respectively. In 27 patients with symptomatic residual or progressive MBT, IA chemotherapy demonstrated objective responses in 54.2%

of the cohort, and another 32% had disease stabilization.⁵ The median time to progression of the MBT cohort was 16.0 weeks overall and 30.0 weeks in responders, with an overall median survival of 20.0 weeks from the time of initiation of IA chemotherapy.

During the course of angiography for IA chemotherapy administration, usually at the time of the first diagnostic angiogram, incidental aneurysms are often noted, raising the question of whether these aneurysms pose a risk when contemplating this form of treatment. In the general population, aneurysms are common, with prevalence at autopsy reported to be 2.0%–9.1% and at angiography to be 0.4%–8%.^{7,8} The mean prevalence of an aneurysm is approximately 5%, which means that as many as 14 million Americans currently have or will develop an aneurysm. Incidental aneurysms appear to be slightly more common in patients with BTs than the general population, with a reported prevalence at angiography of 0.9%–8.8%.^{9–15} The prevalence of aneurysms in our patient population of 10.3% is higher than previously reported. Before our study, the highest reported prevalence was 8.8% in patients with nonfunctioning pituitary adenomas.¹⁴ All of the aneurysms found in our study were small, measuring <5 mm. It is now well established that not all aneurysms rupture and it certainly appears that small aneurysms have a very low risk of rupture.^{16–18} The International Study of Unruptured Intracranial Aneurysms consortium evaluated the natural history of unruptured aneurysms during a 5-year period and concluded that the rupture rates of aneurysms in the anterior circulation measuring ≤ 7 mm was 0% and for the posterior circulation 2.5%.¹⁹ The annual incidence of subarachnoid hemorrhage in the United States ranges between 6 and 16 per 100,000, with an approximate mean of 10 per 100,000, which corresponds to roughly 28,000 episodes of subarachnoid hemorrhage per year. Because there are more than 14 million Americans with aneurysms, these numbers would suggest that most aneurysms do not rupture. Our results would indicate that IA chemotherapy does not increase the risk of aneurysmal rupture, though these conclusions are somewhat limited by the small size of our cohort, the abbreviated length of follow-up in some cases, and the shortened life expectancy of patients with CNS malignancies. There were no aneurysm-related complications, such as subarachnoid hemorrhage or sentinel leak, in any of our patients related to the angiographic procedure or the infusion of IA chemotherapy.

In conclusion, IA chemotherapy is a safe procedure to perform in BT patients with small incidental aneurysms. In our patient population, the use of IA chemotherapy was not associated with an increased occurrence of aneurysm rupture.

References

1. Newton HB. Primary brain tumors: review of etiology, diagnosis, and treatment. *Am Fam Phys* 1994;49:787–97
2. Newton HB. Neurological complications of systemic cancer. *Am Fam Phys* 1999;59:878–88
3. Gelman M, Chakeres DW, Newton HB. Brain tumors: complications of cerebral angiography accompanied by intraarterial chemotherapy. *Radiology* 1999;213:135–40
4. Newton HB, Snyder MA, Stevens C, et al. Intra-arterial carboplatin and intravenous etoposide for the treatment of recurrent and progressive non-GBM gliomas. *J Neurooncol* 2002;56:79–86
5. Newton HB, Snyder MA, Stevens C, et al. Intra-arterial carboplatin and intravenous etoposide for the treatment of brain metastases. *J Neurooncol* 2003;61:35–44

6. Newton HB, Stevens C, Santi M. **Brain metastases from fallopian tube carcinoma responsive to intra-arterial carboplatin and intravenous etoposide: a case report.** *J Neurooncol* 2001;55:179–84
7. King JT. **Epidemiology of aneurysmal subarachnoid hemorrhage.** *Neuroimag Clin North Am* 1997;7:659–68
8. Schievink WI. **Intracranial aneurysms.** *N Engl J Med* 1997;336:28–40
9. Pia HW, Obrador S, Martin JG. **Association of brain tumors and arterial intracranial aneurysms.** *Acta Neurochir* 1972;27:189–204
10. Jakubowski J, Kendall B. **Coincidental aneurysms with tumours of pituitary origin.** *J Neurol Neurosurg Psych* 1978;41:972–79
11. Wakai S, Fukushima T, Furihata T, et al. **Association of cerebral aneurysm with pituitary adenoma.** *Surg Neurol* 1979;12:503–507
12. Atkinson JLD, Sundt TM Jr, Houser OW, et al. **Angiographic frequency of anterior circulation intracranial aneurysms.** *J Neurosurg* 1989;70:551–55
13. Takahashi T, Saitoh K, Suzuki S. **Coincidental cerebral aneurysm with brain tumor: report of three cases.** *No Shinkei Geka* 1985;13:675–79
14. Pant B, Arita K, Kurisu K, et al. **Incidence of intracranial aneurysm associated with pituitary adenoma.** *Neurosurg Rev* 1997;20:13–17
15. Delfini R, Domenicucci M, Ferrari M. **Association of intracranial meningiomas and aneurysms: report of three cases and review of the literature.** *J Neurosurg Sci* 1990;34:51–56
16. Wiebers DO, Whisnant JP, Huston J, et al., for the International Study of Unruptured Intracranial Aneurysms Investigators. **Unruptured intracranial aneurysms: risk of rupture and risks of surgical intervention.** *N Engl J Med* 1998;339:1725–33
17. White PM, Wardlaw JM. **Unruptured intracranial aneurysms.** *J Neuroradiol* 2003;30:336–50
18. Johnston SC, Gress DR, Kahn JG. **Which unruptured cerebral aneurysms should be treated? A cost-utility analysis.** *Neurol* 1999;52:1806–15
19. International Study of Unruptured Intracranial Aneurysms Investigators. **Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment.** *Lancet* 2003;362:103–10