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Abbreviation:

ICA = internal carotid artery

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Intraarterial Chemotherapy for Brain Tumors by Using a Spatial Dose Fractionation Algorithm and Pulsatile Delivery¹

PURPOSE: To evaluate the cause of complications in intraarterial chemotherapy for brain tumors and validate a dosage algorithm based on arterial territory.

MATERIALS AND METHODS: Four hundred sixty-two procedures were performed in 113 patients. Technique included pulsatile infusion of a chemotherapeutic agent. Dosage was calculated per hemisphere and divided per arterial territory according to a spatial dose fractionation algorithm based on the vascular territories of major cerebral arteries: middle cerebral artery, 60%; anterior cerebral artery, 20%; posterior cerebral artery, 15%; and perforator arteries, 5%. Hospital charts of all patients were retrospectively reviewed for complications, with specific attention given to the angiograms to determine a cause. Then, subgroup analysis of the chemotherapy protocol with the largest patient population was performed to evaluate predictors of complications.

RESULTS: Six (1.3%) complications were asymptomatic; 12 (2.6%), transient neurologic; three (0.6%), permanent minor neurologic; three (0.6%), permanent major neurologic; and 32 (7.0%), seizures. In the subgroup analysis, the hemispheric dose administered according to the algorithm was strongly predictive of seizure and neurologic deficit.

CONCLUSION: Neurotoxicity of intraarterial cerebral chemotherapy can be minimized by using pulsatile injection and the described spatial dose fractionation algorithm.

The prognosis of patients with malignant brain gliomas is dismal, with a median survival after diagnosis of approximately 12 months. The standard treatment includes maximal surgical resection and radiation therapy; adjuvant chemotherapy has limited efficacy and is usually reserved for recurrent tumors (1,2). One way to increase the efficacy of chemotherapy is to increase the dose delivered to the tumor by using intraarterial delivery (3).

The substantial pharmacologic advantage of intraarterial delivery compared with intravenous cerebral chemotherapy has been proved in animal as well as clinical studies (4). Compared with intravenous injection, superselective injection of technetium 99m hexylmethylpropylene amineoxine into human cerebral arteries such as the middle, anterior, and posterior cerebral arteries has achieved a concentration of hexylmethylpropylene amineoxine in brain tissue 50 times higher (5). In other clinical studies of cerebral chemotherapy, the concentration delivered to the tumor by using intraarterial injection versus intravenous administration of chemotherapeutic agents was five times higher with hydrosoluble drugs (6) and up to 50 times higher with liposoluble drugs (7). Because of this pharmacologic advantage, intraarterial chemotherapy for brain gliomas has been performed for more than 15 years with the aim of improving the limited efficacy of intravenous chemotherapy by overcoming molecular resistance (8). Furthermore, intraarterial chemotherapy results in a more localized delivery than does intravenous administration

TABLE 1
Combination Therapies Prior to
Intraarterial Chemotherapy

Surgical Resection*	Radiation Therapy	Intravenous Chemotherapy	No. of Patients†
No	No	No	3 (2.7)
No	Yes	No	8 (7.2)
No	Yes	Yes	13 (11.7)
Yes	No	No	5 (4.5)
Yes	No	Yes	2 (1.8)
Yes	Yes	No	24 (21.6)
Yes	Yes	Yes	56 (50.4)

* Patients who did not undergo surgical resection underwent diagnostic biopsy only.

† Data are based on a total of 111 patients, because the prior treatment in two patients could not be determined precisely. The numbers in parentheses are percentages.

and thus is well suited for treatment of primary brain malignancies because these tumors rarely metastasize and most recurrences are local.

However, intraarterial chemotherapy is still controversial, because clinical study results have suggested but not proved its superior efficacy and because it can be particularly toxic (4,9–19).

We suspect that the neurotoxicity of cerebral intraarterial chemotherapy results mostly from inappropriate delivery secondary to inadequate dose and streaming of drug. In most intraarterial chemotherapy protocols, the drug dose is based on weight or body surface area. Such dosing methods, which are derived from intravenous chemotherapy protocols, may be poorly adapted to intraarterial chemotherapy, because in intraarterial chemotherapy the brain is exposed to the drug primarily during the first pass. This theory led us to develop the concept of hemispheric dosage, in which dose is based not on body weight or surface area but rather on cerebral vascular territories. Furthermore, heterogeneous drug delivery can occur during slow continuous chemotherapy infusion because of streaming. Streaming occurs when an infused substance does not mix with the flow of blood but rather remains an independent concentrate, which is preferentially delivered to one arterial branch over another. This results in an overdose to one area yet an inefficient dose to another. This led us to use a pulsatile injection technique to avoid streaming.

The purpose of our study was to evaluate the causes of complications in intraarterial chemotherapy for brain tumors and validate a dosage algorithm based on arterial territory.

MATERIALS AND METHODS

Total Patient Population

From March 1993 to June 1998, 113 patients (78 male, 35 female; mean age, 48 years; age range, 5–77 years) with progressive or recurrent malignant brain tumors were enrolled in six intraarterial chemotherapy protocols performed at our institution. All protocols were approved by the institutional review board, and informed consent was obtained from all patients. The mean pretreatment Karnofsky performance score was 78.6 (range 50.0–100.0). Most patients had glioblastoma multiforme ($n = 71$), followed by anaplastic astrocytoma ($n = 22$), metastases ($n = 11$), and other cancers ($n = 9$). The treatments performed before intraarterial chemotherapy are listed in Table 1. The various intraarterial chemotherapy protocols are listed in Table 2. Protocols 1–4 involved the blood-tumor barrier modifier lobaradimil (Cereport; Alkermes, Cambridge, Mass), a bradykinin analog that selectively increases the vascular permeability of tumor capillaries.

Intraarterial Chemotherapy Technique

Patients were brought to the angiography suite, where conscious sedation or, in uncooperative patients, general anesthesia, was induced. Catheterization was performed by using transfemoral arterial access and on alternating sides in patients undergoing multiple procedures.

The treatment area included the regions that were deemed at magnetic resonance (MR) imaging to represent tumor—that is, the enhancing area at T1-weighted sequences and the high-signal-intensity area at T2-weighted sequences. The arterial territory to be treated with the chemotherapy agent was determined by following basic knowledge of the arterial anatomy, so the entire treatment area was covered.

A set hemispheric dose or hemispheric dose escalation was defined for each protocol according to our knowledge of the toxicity of the drugs used (Table 2). The total dose was the dose actually delivered, that is, the injected fraction of the set hemispheric dose. The total dose was calculated according to the vascular territory of the major brain arteries by following the paradigm illustrated in the Figure and the specific examples in Table 3. The vascular territory of major brain arteries followed the paradigm middle cerebral artery, 60%; anterior cerebral artery, 20%; perforator arteries (including

the anterior choroidal artery, posterior communicating artery, recurrent artery of Heubner, and lenticulostriate arteries), 5%; and posterior cerebral artery, 15%.

Approximations of cerebral blood flow based on vascular territory were determined by means of consensus of four senior neuroradiologists (including Y.P.G., G.R.D., F.V.) on the basis of their experience with selective catheterization and anatomic knowledge of the vascular territories of the major brain arteries. For example, a patient with a large frontoparietal tumor, supplied by the anterior circulation, enrolled in a protocol in which a given drug was administered at a hemispheric dose of 100 mg would receive 85 mg of that drug in the supraorbital ICA—that is, 85% of the hemispheric territory. The hemispheric dose would be 100 mg; the total dose, 85 mg; and the surface area dose (in milligrams per meter squared), the total dose divided by the surface area. In some cases, with the spatial dose fractionation algorithm, patients with large tumors crossing the midline received more than 100% of the hemispheric dose. In these patients, the total dosage of chemotherapy was limited by the generally accepted toxic dose that was calculated by using the body surface area.

Selectivity was not the focus of treatment, but it was performed when it reduced the total dose. For example, superselective injections into a branch of the anterior, middle, or posterior cerebral arteries were avoided. A 5- or 6-F guide catheter was placed in the cervical ICA and/or the dominant vertebral artery. General anticoagulation was initiated with 5.0 IU of heparin. End-hole 1.7–2.5-F microcatheters were steam shaped in the desired configuration. Nonionic contrast material (iohexol [Omnipaque], 300 mg of iodine per milliliter; Nycomed Amersham, Princeton, NJ) was used. Catheterizations were performed with road-mapping fluoroscopic guidance. Once the microcatheter was in place, several test injections with 0.3–0.5 mL of a contrast material bolus with a 3-mL syringe were performed to test the stability of the microcatheter, the vascular territory opacified, and the absence of selective injection into a small branch or perforator artery. If the test injections were satisfactory, the drug was delivered by using strong injections of 0.3–0.5-mL boluses at a rate of 1–9 mL/min according to the specific protocol. The stability of the microcatheter was controlled periodically by using fluoroscopy (without injection of contrast material) during chemotherapy delivery. Microangiography was per-

TABLE 2
Intraarterial Chemotherapy Protocols

Protocol No.	Chemotherapy Agent	Blood-Tumor Barrier Modifier	Inclusion or Exclusion Criteria	No. of Patients	Treatment Status*
1	Carboplatin: 100 mg/hemisphere	Lobradimil: dose escalation from 10 to 300 ng/kg	Recurrent unilateral malignant gliomas, >18 years	12	Complete
2	Carboplatin: dose escalation from 300 to 600 mg/hemisphere	Lobradimil: 300 ng/kg	Recurrent unilateral malignant gliomas, >18 years	17	Complete
3	Carboplatin: 600 mg/hemisphere	Lobradimil: 300 ng/kg	Recurrent unilateral malignant gliomas, >18 years	9	Complete
4	Carboplatin: 400 mg/hemisphere	Lobradimil: 300 ng/kg	Metastatic tumors to the brain	7	Active
5	Carboplatin: dose escalation from 200 to 1,400 mg/hemisphere	None	Malignant glioma or metastases	62	Active
6	Thiotepa	None		6	Active

Note.—Treatment status at the time article was written.

formed if microcatheter movement was suspected.

After chemotherapy, follow-up angiography and neurologic examinations were performed. Dexamethasone (10 mg) was administered intravenously. The patients were given continuous intravenous fluid for 4 hours, frequently checked for vital signs and neurologic status in the neurologic ward, and discharged the following morning. The antiemetic drug ondansetron hydrochloride (8 mg) was administered intravenously and systematically 30 minutes before the procedure, and 8 mg was administered every 8 hours for 24 hours after chemotherapy.

The intraarterial chemotherapy cycles were repeated monthly. MR imaging was performed between the second and third cycles and then between each cycle. Intraarterial chemotherapy was continued in cases of tumor regression (ie, decrease of tumor volume, >50%) or stable disease (ie, change in tumor volume, <50%) at MR imaging. Intraarterial chemotherapy was discontinued in cases of progressive disease at MR imaging (ie, increase of tumor volume, >50%) or clinical deterioration. In these cases, the patient was either enrolled in another protocol or placed on supportive therapy.

Complications in the Total Patient Population

The hospital charts of all patients were retrospectively reviewed. For each chemotherapy procedure, the agent, dose, arteries treated, procedural angiograms, MR images, intraprocedural events, and postprocedural events were reviewed. Complications included (a) any clinical symptoms that occurred after the procedure, including headache, seizure, neurologic deficit (transient or permanent; new or

increased preexistent deficit), and hematologic abnormalities; (b) asymptomatic events that were identified at MR imaging performed prior to the next cycle; or (c) purely technical complications that occurred during the procedure.

Subgroup Analysis of Variables Predictive of Complications

Patient population.—To evaluate the relationship between independent variables and chemotherapy-related complications, we analyzed the largest subgroup of patients ($n = 62$), that which underwent protocol 5 (Table 2). Four patients were excluded from this retrospective analysis because the necessary data could not be extracted from their charts. Thus, 40 male and 18 female patients (mean age, 48 years; age range, 6–77 years) were included in this analysis. Patients underwent one to 12 cycles, with an average of four.

The treatment consisted of a dose escalation of intraarterial carboplatin, from 200 to 1,400 mg per hemisphere, which was fractionated and delivered according to the methods described previously (see Intraarterial Chemotherapy Technique section).

Chart review.—Patient charts were retrospectively reviewed for age, sex, height, weight, baseline symptoms, number of cycles, total dose (based on vascular territory as explained previously), hemispheric dose (defined by the protocol), and symptomatic complications. Body surface area was determined from an equation based on height and weight. Surface area dose (in milligrams per meter squared) was calculated as the total dose divided by the surface area. Complications were excluded if they were related to the angiographic procedure or the catheterization technique, because the intent of this analysis was to

evaluate the correlation between chemotherapy-related complications and independent predictors—primarily dose. The included complications were seizure, headache, and neurologic deficit (either new or increase in previous deficit).

Complications were analyzed, per patient, with independent variables such as dose (hemispheric, total, per body surface area) averaged. Stepwise logistic regression analysis was performed with poor outcome defined as seizure, headache, or neurologic deficit alone and with complications grouped together—that is, seizure plus deficit or seizure, headache, and neurologic deficit.

RESULTS

A total of 462 procedures were performed in 113 patients (mean, four procedures per patient; range, one to 12). The majority of procedures consisted of selective catheterization of the ICA, alone or associated with selective catheterization of the posterior cerebral artery (Table 4). Three chemotherapy procedures were not performed. One patient had carotid spasm with distal embolus into the middle cerebral artery; this was treated with intraarterial thrombolysis, which resulted in complete angiographic and clinical recovery. A second patient had asymptomatic ICA dissection with 50% stenosis due to the guide catheter. A third patient had severe atherosclerotic stenosis of the ICA. One selective catheterization of the anterior cerebral artery could not be performed because of tortuous anatomy, and the drug was delivered through the ICA.

Detailed clinical results are not reported in this article, which focuses on the technical aspects and complications of intraarterial chemotherapy among several patho-

logic entities and chemotherapy protocols. The clinical results of protocols 1 and 5 have been reported previously (8,20).

Complications in the Total Patient Population

The complications are summarized in Table 5. There were six (5.3% of 113 patients, 1.3% of 462 procedures) asymptomatic (ie, technical) complications, one of which was detected at routine follow-up MR imaging, 12 transient neurologic complications in nine patients (8.0% of patients, 2.6% of procedures), three permanent minor neurologic complications (2.6% of patients, 0.6% of procedures), three permanent major complications (2.6% of patients, 0.6% of procedures), five transient hematologic complications (4.4% of patients, 1.1% of procedures), and six other transient complications (5.3% of patients, 1.3% of procedures). Thirty-two seizures occurred in 17 patients (15.0% of patients, 7.0% of procedures) within 24 hours after intraarterial chemotherapy. Although there was a high rate of seizures, these were in only those patients who had seizures before treatment. Sixty patients (53% of patients, 13% of procedures) experienced nausea, vomiting, and/or headache within 24 hours after the procedure. Complications were divided into (a) toxicity of chemotherapy agent, (b) catheterization and/or angiography complications, and (c) hematologic toxicity.

Chemotherapy Toxicity Due to Technical Mistake

Five complications (4.4% of 113 patients, 1.1% of 462 procedures) were attributed to a local overdose of chemotherapeutic agent in a small artery due to misplacement of the microcatheter. These symptoms developed following the procedure. Two patients developed a nerve III palsy—one was permanent, and the other regressed over 2 months. In one, the microcatheter was placed in the ICA, with the tip pointing toward the posterior communicating artery; the result was subselective injection of the chemotherapeutic agent into this small vessel. In the second case, the microcatheter was placed in the posterior communicating artery itself. A third patient developed an asymptomatic infarct in the anterior choroidal artery territory that was depicted at routine MR imaging performed before the next cycle. Retrospective review of the angiogram showed that the microcatheter had been pointing toward the anterior choroidal artery, with subselec-

tive contrast material injection within this vessel. The fourth patient developed a midbrain infarction that manifested as nausea, diplopia, and permanent left-side numbness after the entire hemispheric dose of chemotherapeutic agent was mistakenly delivered into the P1 segment of the right posterior cerebral artery. The fifth patient experienced transient ocular pain, hyperemia, and eyelid swelling after a procedure performed with the positron emission tomography scanner, due to displacement of the microcatheter and infusion of chemotherapy agent into the ophthalmic artery. There was no immediate gross change in visual acuity, and the patient died from brain herniation secondary to tumor 1 month after the procedure, before his visual acuity was checked again.

Chemotherapy Toxicity Despite Appropriate Technique

Thirty-two seizures (7.0% of procedures) occurred in 17 (15.0%) patients within 24 hours after intraarterial chemotherapy. The seizures were associated with nausea and vomiting six times. One seizure, which was complicated by Todd paralysis that resolved completely, required an extra hospital day. Nausea, vomiting, and/or headache occurred following 60 (13.0%) procedures in 30 (26.5%) patients. Only one complication involved nausea and vomiting that were severe enough to increase the length of hospital stay.

Ten (2.2%) procedures in six (5.3%) patients were followed by a transiently increased preexistent neurologic deficit, which returned to baseline less than a week after the procedure. Two (0.4%) procedures (1.8% of patients) were followed by a permanent increase in a preexistent deficit. One of these patients had an increase in a preexistent paresis that recovered almost to baseline in the following weeks; the other did not recover from upper extremity paresis.

Other Complications

Two patients experienced major allergic reactions. One of these patients developed a Stevens-Johnson syndrome that resolved, but no further intraarterial chemotherapy was administered. The second patient developed cortical blindness after intraarterial chemotherapy in the basilar artery; this regressed totally within 24 hours, and additional intraarterial chemotherapy performed without contrast material was well tolerated.

Two patients each had a thromboem-

bolic complication (0.4% of procedures, 1.8% of patients) that was detected at intraprocedural angiography. Both patients had embolic occlusion of the middle cerebral artery: In one patient, the occlusion was due to carotid artery spasm around the catheter, and in the other patient, the occlusion was unexplained. Immediate intraarterial thrombolysis was performed, and neither patient developed deficits, despite the development of a small infarcted area that was depicted at CT in one case.

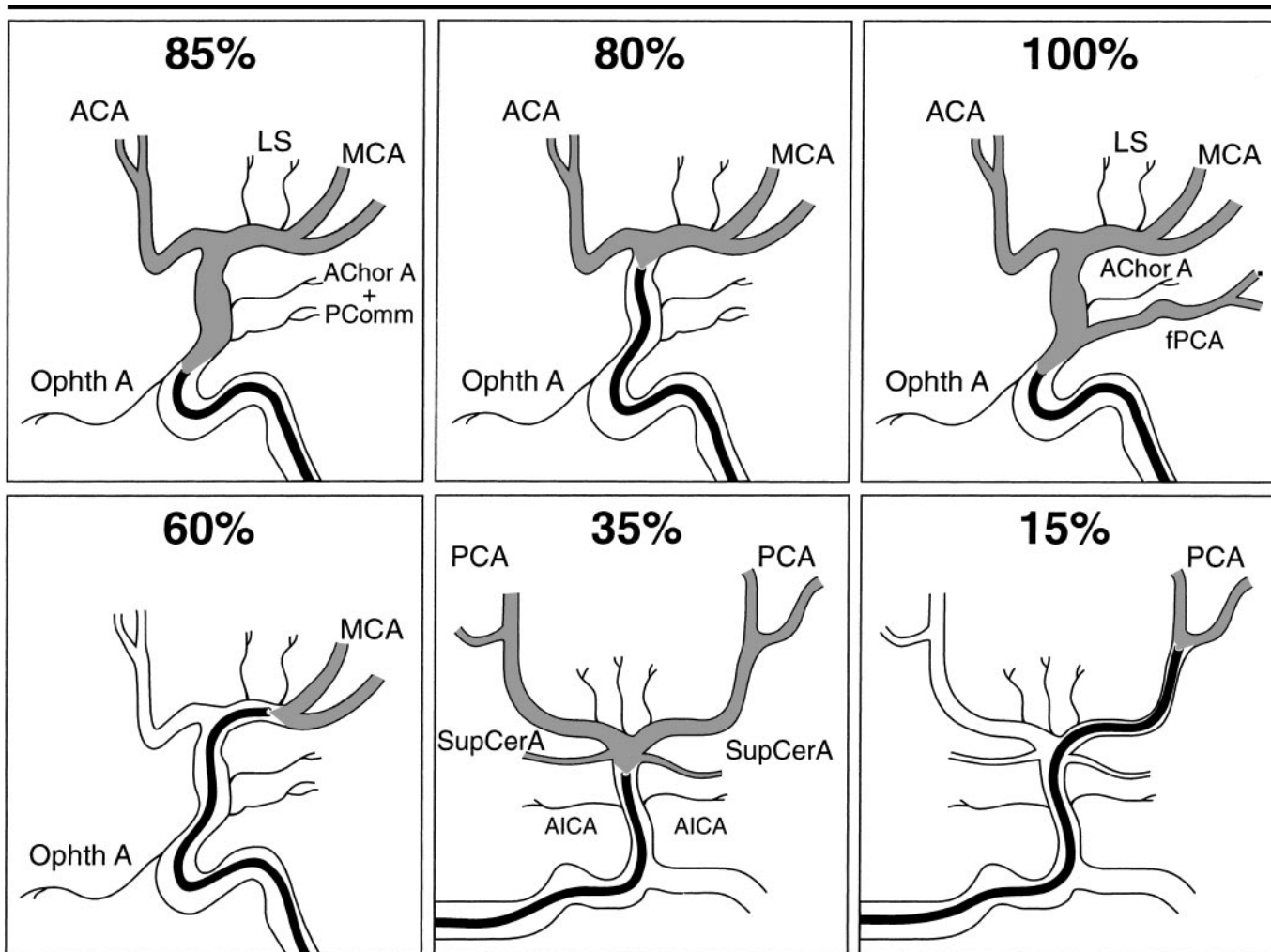
In one intraarterial delivery to the right posterior cerebral artery, lethargy, right-arm paresis, and short-term memory loss were noted at neurologic examination after the patient awakened from general anesthesia. CT and a new angiographic examination were performed immediately; both studies were normal. Follow-up CT depicted bilateral posterior thalamic infarction. Retrospective review of the angiograms showed a large thalamic perforating artery arising from the right P1 segment and supplying both thalami. Because symptoms were noticed immediately after the procedure and the chemotherapy infusion was distal to the origin of the thalamic perforator artery, the complication was attributed to temporary occlusion of the thalamic perforating artery by the microcatheter. The lethargy and motor deficit resolved, but the patient had permanent debilitating short-term memory loss.

Three ICA spasms were seen on intraprocedural angiograms: Two were asymptomatic, and one was symptomatic with aphasia. Two resolved spontaneously, and one was treated by injection of papaverine before the procedure was continued.

One asymptomatic dissection occurred, with 50% stenosis of the ICA. The procedure was stopped, heparin therapy was not reversed, and the patient was given antiplatelet therapy. The dissection resolved, and further intraarterial chemotherapy cycles were uneventful.

There were three hematomas at the groin puncture site, but none required treatment or additional hospital stay.

Five (4.4%) patients (1.1% of procedures) developed substantial hematologic toxicity after receiving high-dose carboplatin. Further intraarterial chemotherapy was delayed, and subsequent doses were lowered. One patient developed anemia that was substantial enough to require transfusion.



Diagrams illustrate the concept of hemispheric dose with spatial dose fractionation based on arterial territory: middle cerebral artery (MCA), 60%; anterior cerebral artery (ACA), 20%; posterior cerebral artery (PCA), 15%; perforator arteries (anterior choroidal [AChor A], posterior communicating arteries [PComm], lenticulostriate arteries [LS], and artery of Heubner), 5%. The percent of hemispheric dose delivered to each location is stated at the top of each diagram. The microcatheter is depicted in black, and the infused agent is depicted in gray. *Ophth A* = ophthalmic artery. Top left: For a large frontoparietal and mesiotemporal tumor, the microcatheter is positioned in the supraophthalmic internal carotid artery (ICA) below the origin of the posterior communicating artery. Eighty-five percent of the predetermined hemispheric dose is delivered to this location in the anterior cerebral artery, middle cerebral artery, and perforator arteries. Top middle: For a large frontoparietal tumor, the microcatheter is positioned in the ICA above the origin of the anterior choroidal artery. Eighty percent of the predetermined hemispheric dose is delivered to this location. Top right: For a patient with a fetal origin of the posterior cerebral artery (fPCA) and a large hemispheric tumor, the microcatheter is positioned in the supraophthalmic ICA below the origin of the posterior cerebral artery. One hundred percent of the predetermined hemispheric dose is delivered to this location. For a patient with the same large hemispheric tumor but a regular origin of the posterior cerebral artery from the basilar artery, the dose delivered is that depicted in the top left diagram (85%) plus that depicted in the bottom right diagram (15%), for a total hemispheric dose of 100%. Bottom left: For an insular tumor, the microcatheter is positioned in the M1 segment of the middle cerebral artery. Sixty percent of the predetermined hemispheric dose is delivered to this location. Bottom middle: For a tumor crossing the midline posteriorly, both posterior cerebral arteries must be treated. The microcatheter is positioned in the basilar artery above the origin of the anteroinferior cerebellar arteries (AICA). Thirty-five percent of the predetermined hemispheric dose is delivered to this location. The superior cerebellar arteries (SupCerA) are estimated to 2.5% of the hemispheric blood flow each. Bottom right: When one posterior cerebral artery is treated, the microcatheter is positioned in the P2 segment of the artery, and 15% of the predetermined hemispheric dose is delivered to this location. Because most of the patients enrolled in these protocols have large recurring tumors, delivery as depicted in the bottom middle and bottom right diagrams most often was used in conjunction with delivery in the anterior circulation, as depicted in the top left, top middle, or bottom left drawings.

Subgroup Analysis of Variables Predictive of Complications

Subgroup analysis in the group of patients treated with protocol 5 was performed to investigate correlations between independent variables—including age, sex, prior seizures, prior headaches, prior nausea or vomiting, prior neuro-

logic deficits, mean total dose, mean hemispheric dose, and mean surface area dose (range, 1.0–2.4 m²)—and symptomatic complications. Symptomatic complications included seizure ($n = 9$), headache ($n = 12$), and neurologic deficit ($n = 6$). Thirty-one patients experienced no complications. In multiple analyses, the mean

hemispheric dose was found to be predictive of complications. Mean hemispheric dose was of borderline significance ($P = .021$) in predicting all symptomatic complications combined ($n = 27$). None of the other predictive variables was predictive of all the symptomatic complications combined.

TABLE 3
Sites of Infusion and Dose Fractionation Based on Tumor Location and Arterial Territory

Tumor Location	Arterial Territories*	Dose to Sites of Infusion†	Total Dose (%)‡
Insular	MCA (60)	60% to MCA	60
Frontoparietal (+/- anterior temporal)	MCA (60) + ACA (20)	80% to supra Ach ICA	80
Frontoparietal (+/- anterior temporal) and mesiotemporal	MCA (60) + ACA (20) + Ach (5)	85% to supra Oph ICA	85
Hemispheric	MCA (60) + ACA (20) + Ach (5) + PCA (15)	100% to large Pcom, supra Oph ICA 85% to small Pcom, supra Oph ICA 15% to PCA	100
Frontoparietal (+/- anterior temporal) and mesiotemporal and crossing midline anteriorly	MCA (60) + ACA (20) + Ach (5) + contralateral ACA (20)	85% to supra Oph ICA 20% to contralateral ACA	105
Hemispheric and crossing midline posteriorly	MCA (60) + ACA (20) + Ach (5) + PCA (15) + contralateral PCA (15)	85% to supra Oph ICA 30% to supra AIC basilar artery	115
Hemispheric and crossing midline anteriorly	MCA (60) + ACA (20) + Ach (5) + PCA (15) + contralateral ACA (20)	85% to supra Oph ICA 15% to PCA 20% to contralateral ACA	120

Note.—ACA = anterior cerebral artery, Ach = anterior choroidal, AIC = anterior inferior cerebellar, ICA = internal carotid artery, MCA = middle cerebral artery, Oph = ophthalmic, PCA = posterior cerebral artery, Pcom = posterior communicating artery.

* The numbers in parentheses are percents of hemispheric blood flow.

† The dose is given as the percent of hemispheric dose.

‡ Total percent of hemispheric dose.

TABLE 4
Sites of Infusion and Dose Fractionation in 462 Procedures Performed in 113 Patients

Site of Infusion*	Percent of Hemispheric Dose†	No. of Procedures‡
ICA supraorbital artery	85 if small Pcom, 100 if large Pcom	270 (58.5)
ICA supra Ach	80	32 (6.9)
ICA + PCA	85 + 15 = 100	70 (15.2)
ICA + basilar artery	85 + 30 = 115	23 (5.0)
MCA + PCA	60 + 15 = 75	14 (3.0)
MCA + ACA	60 + 20 = 80	12 (2.6)
MCA (M1 segment)	60	12 (2.6)
ICA + contralateral ACA	85 + 20 = 105	10 (2.2)
Other arteries	Variable	19 (4.1)
Total		462 (100)

* ACA = anterior cerebral artery, Ach = anterior choroidal artery, ICA = internal carotid artery, MCA = middle cerebral artery, PCA = posterior cerebral artery.

† All numbers are percentages. Pcom = posterior communicating artery.

‡ The numbers in parentheses are percentages.

When complication was defined as neurologic deficit alone or seizure combined with neurologic deficit, the mean hemispheric dose was highly predictive, with a *P* value of .001 or .005, respectively. Hemispheric doses ranged from 525 to 1,530 mg per hemisphere (mean, 944 mg per hemisphere). Older age also was significant in predicting neurologic deficit (*P* = .04) as well as seizure combined with neurologic deficit (*P* = .051). The mean total dose and mean surface area dose were not predictive of complications. Total doses ranged from 350 to 1,300 mg (mean, 845 mg); surface area doses ranged from 246 to 812 mg/m² (mean, 446 mg/m²). When com-

plication was defined as either headache alone or seizure alone, no factors were predictive.

DISCUSSION

The toxicity of drugs delivered intravenously is well known and, individual susceptibility aside, predictable. In contrast, neurotoxicity of cerebral intraarterial chemotherapy occurs with a wide range of chemotherapeutic doses (12,21,22). The goal of this study was to explain the seemingly arbitrary nature of neurotoxicity of intraarterial chemotherapy. In this article, we reviewed the complications of

our institution's intraarterial chemotherapy protocols with (a) dose calculation by using a spatial dose fractionation algorithm, a method we think is more appropriate for intraarterial delivery, and (b) pulsatile injection delivery to prevent streaming and subsequent focal toxicity.

Our aim was to understand why each complication occurred and whether and/or how each could have been prevented. Results of an additional subgroup analysis indicated that the complications of seizure and neurologic deficit were related to the hemispheric dose, not the total dose or surface area dose. With use of hemispheric dosage and pulsatile delivery, neurotoxicity did not occur by chance with a wide range of chemotherapy doses as it did in previous intraarterial delivery trials (12,21,22), but rather it could be predicted and thus prevented. The correlation between neurotoxicity and hemispheric dose supports the effectiveness of the spatial dose fractionation method.

Spatial Dose Fractionation

The drug dosage for intravenous chemotherapy is calculated according to the body surface area, body weight, or drug clearance rate. These variables can vary greatly among individuals. However, cerebral weight, volume, and blood flow differ little among individuals (although there is a known decrease in brain weight and cerebral blood flow with aging (23) and a 10% lower weight in female individuals). For example, the body surface

TABLE 5
Complications of 462 Intraarterial Chemotherapy Procedures Performed in 113 Patients

Complications	Asymptomatic*	Transient	Permanent Minor	Permanent Major
Neurologic	Two emboli treated by using immediate thrombolysis, one infarction of anterior choroidal artery, two ICA spasms, one ICA dissection	Ten increases in a preexisting deficit in six patients, one nerve III palsy, one aphasia, 32 seizures in 17 patients, 60 cases of nausea, vomiting, and/or headache	Two mild increases in a preexisting hemiparesis, one nerve III palsy	One short-term memory loss, one upper extremity paresis, one hemianesthesia
Hematologic		Five, one of which requiring blood transfusion		
Other		Two cases of allergy Three groin hematomas One case of ocular symptoms		

area in healthy individuals usually varies from 1.5 to 2.4 m². If one administers intraarterially 100 mg/m² of a given drug, a large patient will receive 240 mg, whereas a small patient will receive 150 mg (a factor of 240/150 = 1.6), yet the cerebral weight of the two patients is similar. Furthermore, the vascular territory of major intracranial arteries varies greatly.

In our algorithm, we supposed that the posterior cerebral artery supplies approximately 15% of the total cerebral volume, whereas the middle cerebral artery supplies 60%. Therefore, delivery of the same dose into the posterior cerebral artery versus into the middle cerebral artery differs by a factor of four (60%/15%). Together, these factors combine to create a large dose variation between two patients with similar cerebral weights, even if they are given the same surface area dose. More specifically, infusing the posterior cerebral artery in a large patient with a body surface area of 2.4 m² could potentially deliver 6.4 (1.6 × 4.0) times more chemotherapeutic agent than could infusing the middle cerebral artery in a small patient with a body surface area of 1.5 m². This could explain complications that appear to be random because they occur in one patient but not in another, even though both patients received the same surface area dose of chemotherapeutic agent.

Previous intraarterial chemotherapy trials have involved intravenous dosing methods. However, neurotoxicity is due primarily to the highest dose delivered to the target brain tissue; this occurs during the first pass through the arterial circulation. Therefore, toxic dose is directly related to blood flow through the infused artery—a concept suggested in previous studies (24,25). Neurologic complications were increased when infused carotid arteries were abnormally small (24) or the infused artery had two branches com-

pared with three or more (25). In one study (19), selective intracranial infusion of a standard dose of cisplatin (75 mg/m²) carried a higher risk than did ICA infusion. The body surface area dose was divided when several intracranial arteries were infused, but it was not reduced when only one artery was infused; the entire dose could be delivered selectively into one intracranial branch. The increased neurotoxicity with selective infusions was probably due to the higher hemispheric dose.

In multiple analyses, performed in our subgroup analysis, hemispheric dose predicted toxicity, whereas total dose or surface area dose did not. This finding supports the effectiveness of spatial dose fractionation: The appropriate drug dose for intraarterial chemotherapy should be based on the arterial territory, not the body weight or surface area. In the current study, hemispheric dose predicted outcome when poor outcome was defined as any complication, seizure plus neurologic deficit, or neurologic deficit alone, but not when poor outcome was defined as headache alone or seizure alone. This may have been due to the fact that the groups of patients with headaches (*n* = 12) and seizures (*n* = 9) were small. Therefore, if even a few patients had headaches or seizures unrelated to chemotherapy, statistical analysis would not have enabled us to detect the significance. These variables could have been significant in a larger patient population since most of the headaches and seizures were chemotherapy related. The group of patients with neurologic deficits also was small (*n* = 6), but the causal relationship with the procedure was relatively certain. Therefore, even in such a small group of patients, analysis enabled us to detect highly significant *P* values.

Also interesting in our subgroup analysis was the significance of age in predict-

ing seizure and neurologic deficit. Previous study results have suggested that neurotoxicity is increased in older patients (24), possibly because of the known decreased cerebral blood flow. A limitation of our model was that factors that are known to lessen cerebral blood flow were not taken into account when calculating dose. Brain weight is 10% smaller in female individuals than in male individuals (23). Older age, high dose radiation, and previous surgical resection all decrease cerebral blood flow. Although the capability of our spatial dose fractionation algorithm to predict chemotherapy toxicity is a posteriori proof of its validity, this algorithm could be improved by adjusting the hemispheric dose according to all of these factors.

Delivery Technique: Pulsatile Injection for Homogeneous Delivery

Numerous in vitro and in vivo models have demonstrated the phenomenon of streaming (22). This occurs because of the laminar flow of arterial blood. Infused substances become part of the laminar flow instead of mixing in homogeneously. In a transparent human ICA model, slow infusion resulted in concentrations in given branches that were up to five times higher than the expected concentrations (26). In an in vivo study with rhesus monkeys, slow infusion of iodoantipyrine into the ICA resulted in a 13-fold difference in the concentration of tracer in the cortex, white matter, and basal ganglia, as compared with a rapid infusion rate (27). When the infused substance is a drug, the consequence of uneven distribution is overdose and toxicity in one area and inefficacious delivery in another. If we assume that heterogeneity due to streaming can cause up to a five-fold increase in drug delivery and we

combine this with the variations (described previously) due to body surface area (1.6-fold) and intraarterial chemotherapy without using spatial dose fractionation (fourfold), we arrive at a 32-fold ($5.0 \times 1.6 \times 4.0$) difference. This may explain the seemingly random complications observed with a wide range of doses in previous intraarterial chemotherapy trials (12,21,22).

Various recommendations have been made to improve mixing of the injected agent with blood. For example, diastole-phased pulsatile injection has substantially decreased heterogeneous drug delivery clinically (28,29). Another variable that affects streaming and toxicity is delivery location. Cervical (compared with supraophthalmic) ICA delivery reduces streaming, because there is more time and distance for mixing of blood and drug before arrival at the target tissue (22). Accordingly, if pulsatile injection is not used, supraophthalmic ICA injection has more neurotoxicity than does cervical ICA injection (16). To our knowledge, few authors have discussed delivery in a region as distal as the ICA branches. Positioning the microcatheter distally is an interesting technical point. One theoretic benefit is that arterial flow is slowed by the presence of the microcatheter; prolonged transit time increases tumor exposure to the chemotherapeutic agent during the first pass. On the other hand, the surrounding normal brain tissue also is subjected to this increased drug exposure, which can lead to neurotoxicity. In reality, the utility of this controversy is negated by the patient population; most such patients have large tumors that involve several arterial territories and thus will not benefit from superselective infusion (30).

In the chemotherapy protocols described in this article, numerous measures were taken to ensure homogeneous delivery. First, the microcatheters were steam shaped so that the tip was pointed toward the center of the artery to avoid perforator vessels. Before delivery, a test angiogram was obtained to check for uniform perfusion of contrast material. Then, the chemotherapy agent was delivered through end-hole microcatheters with strong injections of 0.3–0.5-mL boluses at a rate of 1–9 mL/min according to the specific protocol. Although multiple side-hole microcatheters may improve mixing, end-hole microcatheters were used, because they allow a more precise injection site, which is important in the intracranial circulation.

Analysis of Complications

Previous reports of intraarterial chemotherapy have described a wide range of complications depending on the infusion protocol, agent used, and catheter-related technique (10,12,14,15,21,31,32).

The complications in this study can be divided in several ways. First, they may be considered in terms of severity: asymptomatic ($n = 6$), transient ($n = 115$), permanent minor ($n = 3$), or permanent major ($n = 3$). Second, they may be classified by probable cause: technical mistake ($n = 5$), chemotherapy toxicity ($n = 110$), or catheterization or angiographic complication ($n = 12$). Neurotoxicity may be due not only to the chemotherapeutic agent but also to the intraarterial injection of the contrast material, and, as in protocols 1–4, to the use of the blood-tumor barrier modifier lobradimil. The high rate of transient and chemotherapy toxicity was due to the inclusion of all complications—including seizure ($n = 32$); nausea, vomiting, and/or headache ($n = 60$); anemia ($n = 5$); transient increase in preexistent deficit ($n = 10$); and groin hematoma ($n = 3$)—which are commonly accepted as unavoidable with aggressive chemotherapy protocols and considered to be relatively minor in light of the prognosis. The six permanent complications—two increases in a preexisting hemiparesis, one nerve III palsy, one short-term memory loss, one upper extremity paresis, and one hemianesthesia—are listed in Table 5. Among these, two were preventable: In the case of the nerve III palsy, the microcatheter placed in the supraophthalmic ICA was pointing toward the posterior communicating artery, and toxic overdose in that artery occurred. In the case of hemianesthesia from a middle brain infarct, the protocol was not respected, and, thus, the entire hemispheric dose—instead of a fractionated dose—was delivered to the P1 segment of the posterior communicating artery. Although these cases may be anecdotal, they illustrate the point that severe complications must be carefully analyzed to learn how to avoid them.

In summary, this article scrutinizes the severities and causes of complications with several intraarterial chemotherapy protocols performed at our institution. In addition, results of statistical analysis of the protocol with the largest number of patients showed that hemispheric dose—not total dose or surface area dose—was a significant predictor of neurotoxicity. We conclude that most complications are

preventable by using appropriate technique and the method of spatial dose fractionation according to arterial territory. Dose fractionation based on arterial territory is an interesting concept that potentially could be applied to intraarterial delivery of other drugs—for example, selective intraarterial neuroprotective agents in the treatment of stroke.

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