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Clinical Study

Intra-arterial carboplatin chemotherapy for brain tumors: A dose escalation study based on cerebral blood flow

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Summary

Purpose. To perform an intra-arterial dose escalation study of carboplatin based on hemispheric blood-flow estimation in patients with recurrent malignant glioma. The primary purpose was to determine the maximally tolerated intra-arterial dose. *Methods and patients*. Methods included: 1) selective intra-arterial delivery performed with modern microcatheters, 2) pulsatile infusion, and 3) dosage based on local cerebral blood-flow estimation (middle cerebral artery 60%, anterior cerebral artery 20%, posterior cerebral artery 15%, and anterior choroidal artery 5% of the hemispheric blood-flow). The deliveries were performed above the ophthalmic artery in the anterior circulation, or above the anterior inferior cerebellar arteries in the posterior circulation. The doses were escalated from 200 mg/hemisphere at 50 mg increments. Twenty-one patients were studied (14 with glioblastoma multiforme, five anaplastic astrocytoma, one aggressive low-grade glioma, one metastasis). Patients had recurrent glioma limited to one hemisphere and Karnofsky score of 50 or greater. Concomitant therapies were allowed. *Results*. Carboplatin was escalated to a dose of 1400 mg/hemisphere. One patient had a permanent neuromotor decline. The predominant toxicity was hematopoietic. The median time to tumor progression was 22 weeks, median survival 39 weeks, and the response rate 70% (50% SD and 20% PR) of 19 patients. *Conclusions*. Hemispheric blood-flow estimation allowed us to escalate the dose of intra-arterial carboplatin to twice what was previously considered safe. Responses compared favorably to previous studies. Further studies are needed to determine if this method will provide improved and durable responses.

Introduction

The prognosis of malignant glioma is extremely poor even with therapy using maximal surgical resection, radiation therapy, and chemotherapy. Many investigators have concluded that the efficacy of chemotherapy in malignant glioma is extremely limited, as confirmed in a recent meta-analysis [1]. Extensive research into the causes of drug resistance have found molecular resistance induced by multiple drug resistance genes such as the O6-methylguanine-DNA methyltransferase [2]. As hypothesized, dose intensification of chemotherapy may overcome molecular resistance and improve survival. This dose intensification can be obtained by high-dose intravenous chemotherapy while treating hematopoietic toxicity with granulocyte colony-stimulating factors or autologous bone marrow transplant [3]. However, these studies showed significant toxicity and mortality with large variation in response rates [3].

Another method of dose intensification for brain

tumors employs intra-arterial therapy. In theory, intra-arterial therapy is at its greatest advantage when first-pass extraction is significant (lipid-soluble drugs) and when the drug has a rapid systemic clearance [4]. However, even agents like cisplatin, which does not meet all these characteristics, have shown some advantages [4–9]. Intra-arterial chemotherapy can have neurologic, ophthalmologic, and otologic complications [10–15]. These complications may be due to: 1) improper technique and improper placement of the microcatheter, 2) slow infusion of the drug and laminar flow, with high concentrations of chemotherapy perfusing certain areas of the brain, and 3) improper basis of delivery (mg/m^2 or AUC vs. blood flow). To exploit the possibility of intra-arterial chemotherapy we associated the following factors: 1) selective intra-arterial delivery performed with modern microcatheters, 2) pulsatile infusion to overcome streamlining and heterogeneous delivery, 3) dosage based according to estimated local cerebral blood-flow (neither body surface area nor area-under-the-curve measurement). These factors allowed us, in a dose escalation study, to infuse very high doses of carboplatin while maintaining low toxicity.

Methods

This study was performed at the University of California, Los Angeles, with the first patient starting in January of 1994 and the last in August of 1995. The study was approved by the UCLA Human Subjects Protection Committee. The eligibility criteria included patients who were 18-year of age or older and had a malignant brain tumor with the contrast enhancement on MRI limited to one hemisphere. Only patients with recurrent or progressive disease were included. Recurrent or progressive diseases were defined by pathology obtained from a debulking surgery, or by tumor enlargement demonstrated on imaging studies.

The primary end-points were the dose escalation and the determination of toxicity. The secondary end-points included measurements of efficacy. The dose escalation of carboplatin started at 200 mg per hemisphere and reached 1400 mg per hemisphere. Pre-therapy evaluation included: history and physical, neurologic examination, Karnofsky score, magnetic resonance imaging, audiogram, complete blood count, liver function test, blood urea nitrogen, creatinine, lytes, magnesium, and routine urinalysis.

Procedures

Each procedure required a 2-day hospital stay. The evening prior to treatment, the patient was admitted, interim history and physical exam were obtained, and hydratation was started at 100 cc/hr. The next morning a foley or condom catheter was placed, ondansetron 30 mg intravenously was given for antiemitic prophylaxy, and the patient was transported to the angiosuite. In the angiographic suite, conscious sedation was given, and one femoral artery (alternatively right and left) was punctured and catheterized in a standard fashion. Five-thousand units of heparin were given intravenously. A 5 F guiding catheter (Medtronic-MIS, Sunnyvale, CA) was placed into the proximal internal carotid and/or the vertebral artery, and a baseline angiogram was performed. Using standard methods of micro-catheterization, a microcatheter (Jet Stream 18, Medtronic-MIS; or Tracker 18, Target Therapeutic, Fremont CA; or Magic 1.8, Balt, Montmorency, France) was placed at the chosen point of infusion. Several injection tests with contrast material were performed in a pulsatile fashion in order to: 1) define the territory so perfused, 2) to evaluate any inhomogeneity in the drug delivery, and 3) to determine the stability of the microcatheter. The microcatheter was repositioned as necessary to obtain the optimal delivery of carboplatin. Treatment planning used the data obtained from the angiogram and the MRI. The target area included the contrast enhancing area in T1-weighted sequences, and the area of high signal intensity in T2-weighted sequences that was estimated to represent tumor. The dose to each arterial territory was determined, and pulsatile infusion was started. The pulsatile infusion was performed by forceful injection of 0.5 to 1 cc boluses. The catheter was tested periodically by fluoroscopy to verify its position. At the beginning of

the study the rate of infusion was 3 cc per minute, and was increased progressively to 9 cc/min. Drug deliveries were performed supra-ophthalmic in the anterior circulation or above the anterior inferior cerebellar artery in the posterior circulation (mostly the P2-P3 segement of the posterior cerebral artery). After completing the delivery, the angiogram was repeated and the catheter was removed. Anticoagulation was reversed with intravenous infusion of protamine, and dexamethasone 10 mg IV was given. The patient was returned to the hospital ward with continued intravenous fluid for 4 hours, with frequent vital signs and neurologic checks. The next morning a neurologic exam was given and the patient was discharged with anti-emetics as needed. Toxicity was monitored by weekly complete blood count with differential and platelets and monthly neurologic exams. MRI scans and audiograms were obtained at baseline and after every two treatments. If significant hematopoetic toxicity occurred, the total dose of carboplatin was reduced by 25%.

Blood-flow estimation and treatment dosing

The treatment dosing was based on local cerebral blood-flow estimation using two hypotheses: 1) The total cerebral blood-flow, as the total brain weight, is fairly constant between adults, 2) The cerebral hemispheres are fed by the anterior cerebral artery (ACA), the middle cerebral artery (MCA), the posterior cerebral artery (PCA) and perforating arteries (PerfA) like the anterior choroidal artery, the posterior communicating artery and the lenticulostriate arteries. The proportion of hemispheric blood-flow from each of those arteries are empirically divided as follows: MCA 60%, ACA 20%, PCA 15%, and PerfA 5% (Table 1). If the angiography showed significant deviations from the above percentages due to interindividual variation of post-surgical changes, the angiographer had the option to change the major artery blood-flow percentages and deliver the drug in the appropriate proportions. Only one patient (Table 3, patient 7) had a variation in these proportions, due to significant filling of the middle cerebral artery territory by the posterior cerebral artery.

Table 1. Hemispheric blood flow estimate

Artery	% Hemispheric blood flow
Anterior cerebral artery	20%
Middle cerebral artery	60%
Posterior cerebral artery	15%
Anterior choroidal artery	5%

The hemispheric dose started at 200 mg/hemisphere and was escalated at 50 mg increments until 1400 mg/hemisphere. An example of delivery using the blood-flow-estimate approach is as follows: Patient X has a brain tumor in the anterior and middle cerebral arteries distribution as determined by the MRI. The microcatheter is placed in the internal carotid artery above the ophthalmic artery. If there is a large posterior communicating artery (P-com), the catheter is placed above it. If the P-com is insignificant the catheter is placed just above the ophthalmic artery. Eighty-five percent (MCA 60% + ACA 20% + PerfA 5%) of the hemispheric dose is delivered, which in a 300 mg/hemisphere dose is 255 mg.

Responses

The responses were characterized as follows: *Complete response*: A complete resolution of all abnormalities suggestive of tumor on MRI, plus an improved or normal neurologic examination without

Table 2. Patient characteristics

Total	21
Male	14
Female	7
Mean age	51 (20– 76)
Mean Karnofsky	71 (50–100)
Tumor types	
GBM	14
AA	5
ALG	1
MET	1

GBM : glioblastoma multiforme; AA: anaplastic astrocytoma; ALG: aggressive low grade astrocytoma; MET: metastatic tumor to brain.

steroid medication. *Partial response*: A greater than 50% reduction in the enhancing tumor pseudo-volume on MRI, plus a stable or improved neurological examination or decreased dose of steroids. *Progressive disease*: A greater-than-or-equal-t0 50% increase in the enhancing tumor pseudo-volume on MRI (compared to baseline on any MRI scan with no duration requirement). In addition, steroid dose should be stable or increased for a patient to be classified as having progressive disease. *Stable disease*: Patients were classified as having stable disease if they did not fall into any of the above three categories.

The time-to-tumor-progression (TTP) was determined by, 1) the time when the tumor pseudo-volume increased beyond 50% or, 2) the time when the tumor showed 50% increase from the 'best response' MRI scan after a partial response or, 3) when a new lesion clearly felt to be tumoral appeared.

A digital camera was used to copy MRI images. The MRI measurements of pseudo-volumes were performed using NIH Image version 1.59 software to measure areas. The slice thickness and skips were multiplied by the area and summed for pseudo-volume measurements.

Patient characteristics

Patient characteristics are detailed in Tables 2 and 3. All 21 patients were evaluable for toxicity. Twenty of the 21 patients were evaluable for response, since one patient with metastatic germ cell tumor was

Table 3. Study characteristics for all patients

Patient #	Age	Sex	Grade	KPS	Response	Con tx	Previous Tx	TTP	Survival	# Treatment	mg/hemisphere
1	48	F	AA	70	SD		rad chemo	111+	111+	6	300– 700
2	63	M	AA	80	PD	radsx	rad	9	53	3	450– 550
3	43	M	AA	80	SD		rad	86	96+	12	500– 750
4	27	M	GBM	70	SD		rad	15	25	3	600– 750
5	45	M	GBM	60	PD		rad chemo	6	14	1	700
6	20	M	AA	80	PR		chemo rad surg	122+	122+	12	200– 900
7	60	M	GBM	80	PD	radsx	chemo rad	22	29	5	500– 700
8	71	M	GBM	70	PD		rad	7	14	2	800– 850
9	76	M	GBM	70	SD	tam	rad	19	46	3	800– 900
10	59	M	GBM	70	SD	thio	rad chemo	15	35	2	900
11	52	F	ALG	70	PR	tam	rad tam	28	56	5	640– 900
12	45	M	GBM	50	PD	tam	rad tam	7	23	2	900– 950
13	51	F	GBM	80	SD	tam	rad	27	35	2	900
14	37	F	GBM	60	PR	tam	rad tam	31	39	6	900–1100
15	69	M	GBM	50	PD	tam	rad chemo	4	7	2	900– 950
16	53	F	GBM	70	SD	tam	rad tam	17	19	3	900–1000
17	69	F	GBM	70	PR		rad	33	48+	5	900–1000
18	47	M	GBM	80	SD		rad chemo	42+	42+	6	700– 900
19	44	M	GBM	80	SD	tam	rad	42+	42+	9	1000–1400
20	37	F	AA	80	PD		rad chemo	7	30	2	1000
21	33	M	MET	80	NE		rad chemo	na	na	1	750
										Total 92	

Age in years, grade'' AA – anaplastic astrocytoma; GBM – glioblastoma multiforme; ALG – aggresive low grade astrocytoma; MET – cerebral metastisis. KPS – Karnofsky performance status. Response: SD – stable disease; PR – partial response; PD – progressive disease; NE – not evaluable; Con tx – concomitant treatment); radsx – radiosurgery; thio – intracystic thiotepa; tam – tamoxifen. Previous tx – previous treatment; rad – radiation; surg – surgery prior to the carboplatin, chemo – one or multiple treatments with chemotherapy; tam – tamoxifen. TTP – time to tumor progression in weeks. Survival – in weeks. # treatment – total number of treatment with ia carboplatin. mg/hemisphere – milligrams of carboplatin per hemisphere.

taken off treatment due to the progression of systemic disease. Nineteen patients were evaluable for time-to-tumor-progression and survival, as one of the patients, who had stable disease, opted for surgical debulking of her tumor after 3 treatments (17 weeks). This patient later died of a pulmonary embolism at 19 weeks. Left hemisphere tumors predominated (12 left, 9 right), and two patients had contrast-enhancing tumor involving the contralateral side of the corpus callosum. All patients had prior radiation treatment; 11 had previous chemotherapy. Four patients (Table 3: 2, 6, 8, 18) had a subtotal resection prior to starting the study. One patient had 95% of the tumor removed (Table 3: 18). Two did not have an MRI within 48 hours of surgery (Table 3: 2, 8) and so a strict evaluation of their response was difficult. All patients had stable or decreasing doses of decadron two weeks prior to the baseline MRI except patient 13 and 16. Four patients were treated with tamoxifen prior to the study with evidence of tumor progression and continued on tamoxifen after enrolling. Four patients were placed on tamoxifen at their request at enrollment. During the study two patients received radiosurgery and one received intracystic thiotepa through an ommaya reservoir.

Results

Results are displayed in Table 3. Ninety-two procedures were performed in the 21 patients treated. Selective intra-arterial chemotherapies were performed 84 times in the supra-ophthalmic internal carotid artery, nine times in the middle cerebral artery, 26 times in the posterior cerebral artery, and 6 times in the supra-AICA basilar artery. The hemispheric dose was escalated from 200 to 1400 mg, corresponding to a total dose of 70 to 1200 mg. or to a dose of 65 to 625 mg/m^2.

Twelve deliveries were performed with a dose of 900–1000 mg/hemisphere and 20 with a dose of 1000–1400 mg/hemisphere. Fourteen deliveries were performed with a total dose of 900–1000 mg and 16 with 1000–1200 mg. Nine deliveries were performed with a dose of 450–500 mg/m^2, 18 with 500–600 mg/m^2, and 9 with 600–625 mg/m^2.

Overall toxicity was limited, the most severe complication being a permanent weakness in one patient. Eight patients experienced mild to moderate nausea for doses ranging from 600–1300 mg/hemisphere. Two patients vomited within 48 hours of treatment for doses ranging from 600–900 mg/hemisphere. Headaches occurred in four patients who were administered a broad range of doses. The majority of headaches occurred immediately after treatment and also recurred after subsequent deliveries.

Neurologic toxicity was uncommon. Eight seizures occurred in five patient within 48 hours of delivery for doses ranging from 350 to 1400 mg/hemisphere. All had frequent seizures at baseline, and post-treatment seizures were typical. One patient developed an hemiparesis three hours after the procedure. She recovered partially to 75% from baseline with dexamethasone. She had received a dose of 1000 mg/hemisphere and upon rechallenge there was no repeat of the event. Another patient receiving 1100 mg/hemisphere developed a transient weakness but fully recovered within 24 hours.

Five patients experienced significant hematologic toxicity which necessitated a decrease in carboplatin dosage or use of stem-cell growth factors. One patient who had multiple treatments with a dose of 1100 mg per hemisphere (500 mg/m^2) showed a neutrophil count grade 4 toxicity. Another patient who was treated with a dose of 850 mg per hemisphere (500 mg/m^2) developed a grade 3 toxicity with a 7-week recovery of counts requiring a decrease in dosage. Another patient treated with 900 mg per hemisphere (475 mg/m^2) developed a prolonged neutropenia requiring a decrease in carboplatin dosage to 700 mg per hemisphere. One patient who was treated with a dose of 900 mg per hemisphere (500 mg/m^2) developed a grade 3 hemoglobin toxicity and required a blood transfusion. Most platelet toxicities were grade 2, but in one patient treated with a dose of 900 mg per hemisphere (450 mg/m^2), thrombopenia was prolonged to 7 weeks, thus necessitating a decrease in carboplatin dosage. No neutropenic fevers occurred. Deep venous thrombosis occurred in three patients, all on high doses of tamoxifen. Procedure-related complications included minor foley catheter trauma of the

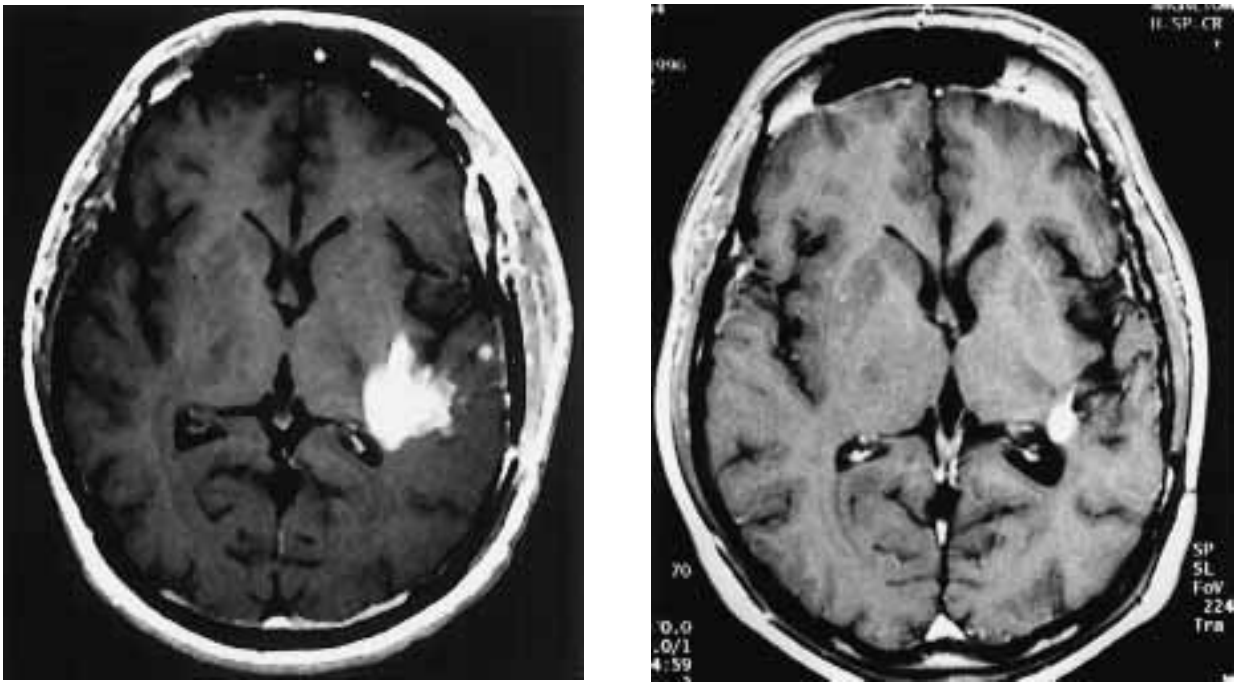

Figure 1. Patient 5 before treatment with seletive intraarterial carboplatin (1a) and after 12 treatments (1b).

urethra in two patients, and small hematomas at the groin in two other patients. Four patients required an extra hospital day for the following reasons: 1) sedation secondary to lorazapam treatment for seizure, 2) coffee grounds emesis, 3) neuromotor weakness, 4) seizures.

There were neither ophthalmologic nor otologic toxicity, nor stroke.

Response

Of the 20 patients evaluable for response, 14 (70%) had a stable disease or a partial response (Table 4). Stable disease was seen in 10 (50%) patients, two with anaplastic astrocytomas and eight with glioblastoma multiforme. Partial response was seen in 4 (20%) patients, one with anaplastic astrocytoma (Figure 1), one with aggressive low grade glioma,

Table 4. Carboplatin response in recurrent malignant glioma

Study	Route of delivery	Drug dosage	Response (SD + PR)	Stable disease	Partial response	MTTP (weeks)	Median survival (weeks)	MTTP responders (weeks)
Present study (20)	SIA	Dose escalation	70%	50%	20%	22*	39*	31
Warnick [21] (29)	IV	350 mg/M2	50%	na	na	13	36	19
Yung [20] (29)	IV	400– 450mg/M2	48%	34%	14%	11	32	26
Poisson [22] (19)	IV	450 mg/M2	40%	30%	10%	na	na	na
Follezou [23] (19)	IA	400 mg/M2	40%	30%	10%	na	26	na

Study – () indicates number of patients evaluable in studies; Route of delivery: IV – intravenous; IA – intraarterial; SIA – selective intraaterial; MTTP – median time to tumor progression; na – not available; SD – stable disease; PR – partial response; * – calculated using 19 evaluable patients for MTTP and MS – median survival.

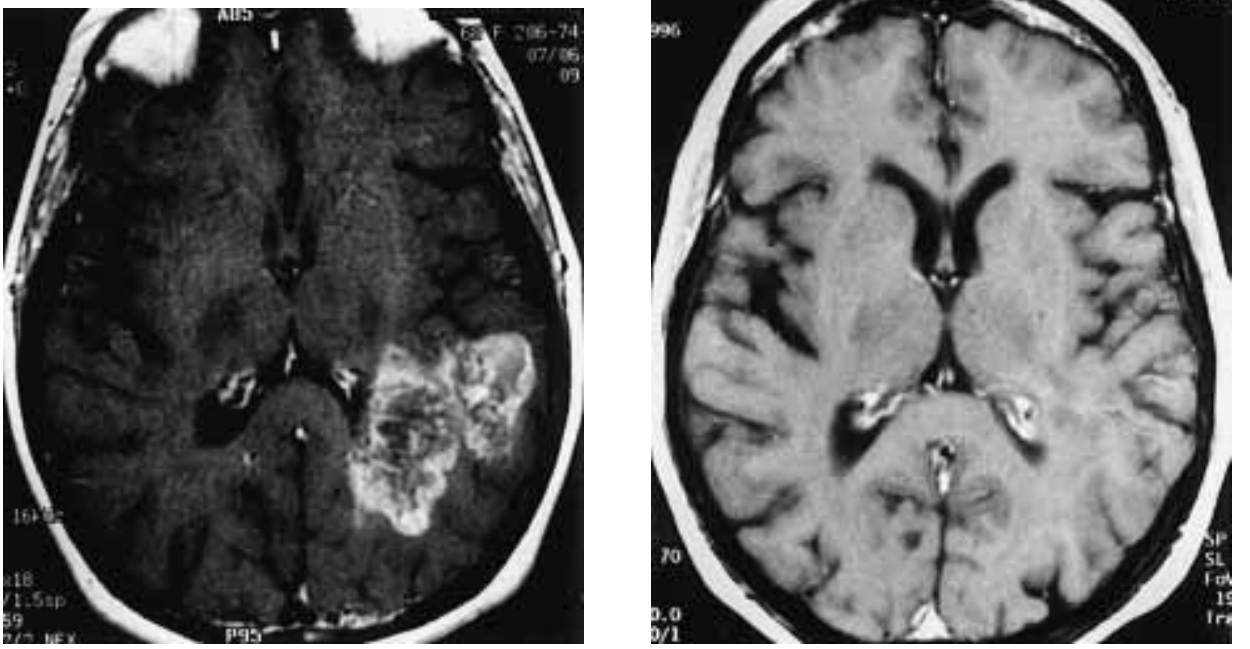

Figure 2. Patient 17 recurrent glioblastoma multiforme before (2a) and after (2b) 5 treatments of selective intraarterial carboplatin.

and two with glioblastoma multiforme (Figure 2). In the 19 patients evaluable for durability of response and survival, the Mean Time-to-Tumor-Progression (MTTP) was 22 weeks and the Median Survival (MS) was 39 weeks. The MTTP of the 13 evaluable responders was 31 weeks. Excluding patients who had received surgery without a 48 hours post-surgical baseline MRI, or those with concomitant treatment; only 8 patients were evaluable for response (1, 3, 4, 5, 6, 17, 18, 20). In that group these was 2 Partial responses, 4 Stable disease, and 2 Progressive disease.

Discussion

The main pharmocologic advantage of intra-arterial chemotherapy is the increased exposure of the tumor to the chemotherapeutic agent. However, intra-arterial chemotherapy has been criticized due to excessive toxicities without evidence of improved tumor response [11–15]. In this study, we attempted to address the problems of poor tumor response and high toxicity by choosing a drug more adapted to intra-arterial chemotherapy and by improving the technique of intra-arterial delivery.

Platinum-based compounds are water-soluble chemotherapy agents which have been used extensively for intra-arterial treatment of brain tumors. Previous studies have shown that, compared to intravenous delivery, intra-arterial delivery increased by 2–3 fold concentration of cisplatin in brain tumors [5–9]. Cisplatin has been used intra-arterially with some success in malignant glioma [16–18], but high doses have been difficult to use due to brain toxicity caused by cerebral arteritis and disruption of the blood-brain-barrier. In a previous study, significant toxicity was reported with intracarotid infusion of 60 mg/m^2 of cisplatin [19]. However, 60 mg/m^2 is roughly half the typical IV dose – a low dose which may obviate the advantage given by intra-arterial delivery.

We decided upon carboplatin (a cisplatin analog) because it has lower neuro- and nephrotoxicities than cisplatin [20]. Since both carboplatin and cisplatin are water-soluble substances with similar molecular weight, one can extrapolate that the in-

crease in tumor concentration obtained by intra-arterial delivery of cisplatin can be applied to carboplatin. Finally, carboplatin has been found to be effective with intravenous [21–23] as well as intra-arterial [24, 25] deliveries in recurrent malignant glioma.

The technique used for arterial delivery was improved by the use of the modern microcatheters, pulsatile infusion, and dosage of the drug based on cerebral blood flow. Modern microcatheters allowed for a safe approach of intracerebral microcatheterizations. All the patients could be catheterized and no catheter-related complication was observed. All the deliveries were performed above the supra-ophthalmic carotid artery in the anterior circulation, and above the anterior inferior cerebellar arteries in the posterior circulation, thus avoiding ophthalmologic and otologic toxicity. Another advantage of distal (intracranial) intra-arterial delivery over proximal intra-arterial delivery is that it may substantially increase drug exposure of the tumor [26].

All drug infusions were performed in a pulsatile fashion by forceful manual injection of small boluses, to avoid intravascular streaming and laminar flow associated with slow continuous infusion [27]. Intravascular streaming can lead to heterogeneous delivery of chemotherapy, with either high concentrations of chemotherapy and neurotoxicity, or low concentrations and inefficacy. As one study demonstrated, pulsatile infusion eliminated laminar flow in supra-ophthalmic carotid artery deliveries when a peak flow of over 1 ml/second was reached, even without using cardiac gating [27].

In oncology, the basic for proper dosage usually relates to the body size (mg/m^2) or to the clearance of the drug (AUC), and takes into account the systemic and bone marrow exposures. However, the situation for the brain is a particular one, as there are large inter-individual variations in the body surface area or the glomerular filtration rate, but small inter-individual variations in the weight and size of an adult brain. Therefore, in selective arterial delivery where the first passage of the drug is the most important for therapeutic effect as well as for toxicity, we deemed it more appropriate to base drug dosage on local cerebral blood flow. This approach had been previously suggested by other authors [25, 28]. In these studies toxicity was analyzed in relation to the major arterial branches (anterior cerebral, middle cerebral, and posterior cerebral arteries) given by the internal carotid artery where the infusion was performed. It was found that patients whose internal carotid artery branched off into two major cerebral arteries had shown an increase of cisplatin and carboplatin toxicity, as compared to patients whose internal carotid artery branched off into three major arteries. This finding related toxicity to blood flow [25, 28]. We estimated the blood flow in the major cerebral arteries by the amount of cerebral mass they vascularized. The middle cerebral artery was estimated to vascularize as a mean 60% of a cerebral hemisphere, the anterior cerebral artery 20%, the posterior cerebral artery 15% and the anterior choroidal artery 5%. At the beginning of our chemotherapy experience we tried to measure the blood flows in the major cerebral arteries (middle cerebral, anterior cerebral and posterior cerebral arteries) by measuring the arterial velocities and cross-sections. Arterial blood velocities were measured with intravascular Doppler (SmartWire. Cardiometrics, Inc. Mountain View, Ca) and with trans-cranial Doppler, while the arterial cross-sections were measured on MRI or during the angiograms. However, intra-arterial as well as trans-cranial Doppler measurements had a high interobserver variability, while the cerebral vessels had a diameter of one to three millimeters and their measurements on MRI or on angiogram were not very precise. Therefore, our blood-flow measurements had a margin of error of at least 100% and were quite time consuming. The blood flow measured into the middle cerebral artery was roughly three times bigger than in the anterior cerebral or posterior cerebral arteries. These measurements confirmed our method of estimating blood-flow in these arteries. Thus, these blood-flow estimations were used to determine the maximum dose of chemotherapy in every patient of this study.

Using these three technical points, we were able to reach a dose of 1400 mg/hemisphere of carboplatin without significant or consistent neurological toxicity, and we were limited only by the systemic

toxicity of carboplatin. This dose is almost double than that previously considered maximal for intra-arterial administration of carboplatin [25].

The most severe complication was permanent weakness in one patient, and the cause was unclear (patient 16). The weakness occurred 2 to 6 hours post-procedure. The follow-up MRI showed no change from baseline, and repeated delivery at 1000 mg was well tolerated. Possible causes included edema from IV hydration (the patient was given a diuretic after the second treatment, which was well tolerated) or carboplatin toxicity. Such focal neurological deficits, described in previous series of intra-arterial carboplatin deliveries, have been attributed to direct toxicity of carboplatin to the brain [25].

High doses of carboplatin could be delivered during this dose escalation study with limited hematologic toxicity, and intravenous hydration may account for this low toxicity. Hydration increases the creatinine clearance and, by inference, using the Calvert formula, increases the rate of free carboplatin clearance by renal excretion [29]. However, hematopoietic toxicity was the limiting factor in 5 patients. The result is the decrease of carboplatin exposure to the bone marrow, but on the other hand, it also decreases the brain tumor exposure to carboplatin offered by multiple passes. However, the potential loss of drug exposure may have little consequence during intra-arterial chemotherapy in which the primary advantage is high concentration of the first pass.

In this study there were no catheter related complications, stroke, otologic, or ophthalmologic toxicity. Careful and skilled catheterization technique, frequent fluoroscopic checks of the catheter position, and the use of heparin made intra-arterial chemotherapy a safe procedure.

Table 4 compares the response rates in this study with other studies using intravenous or intra-arterial delivery of carboplatin for recurrent brain tumor. Before a comparison can be made, differences in the studies must be considered: 1) Our series was a dose escalation evaluation in which some patients received less while others received more carboplatin than in other studies, 2) Concomitant therapy was allowed, 3) Intra-arterial chemotherapy may lead to more patients selection than intravenous chemotherapy and, 4) Measurements of tumor volume were used to determine response.

Still, some comparisons can be made with previous studies. In this study, the evaluable patients had a 70% response rate (10 stable disease, 4 partial response). This result compares favorably with studies of intravenous chemotherapy with carboplatin in which responses ranged from 50 to 48% [21, 22]. Median survival was favorable, and there was a clear improvement in the median time-to-tumor-progression. In addition, a selected group of patients had durable responses (patients 1, 3, 6). If the patient population is narrowed down to those meeting strict criteria for evaluation of response (eight patients), the percentage of stable disease and partial response is similar to the whole group. When comparing the responders of this study with two previous IV studies [21, 22] we see an improvement in the percentage of responders as well as an improvement in the median time-to-tumor-progression. This raises the possibility that patients who would not respond to intravenous chemotherapy may respond to intra-arterial chemotherapy, and patients who would respond to intravenous chemotherapy would benefit even more from intra-arterial chemotherapy. It also raises the question of whether further dose intensification will improve the durability and efficacy of responses.

In conclusion, we performed a dose escalation study of selective intra-arterial chemotherapy with a dosage of carboplatin calculated according to hemispheric cerebral blood-flow. This allowed us to reach doses twice the previous recommended dose of 300 mg/m^2 [25], without reaching the neurologically maximum tolerated dose. Since further dose escalation was limited by hematopoietic toxicities, we intend to use growth factors and stem cell rescue to reach this neurologically maximal tolerated dose in an attempt to improve the response rates and the durability of response. We are also considering blood-brain-tumor-barrier modification with RMP-7 [30], which is another way to intensify the dose of chemotherapy agents delivered into the tumor.

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