Enhanced Chemotherapy Delivery by Intraarterial Infusion and Blood-Brain Barrier Disruption in Malignant Brain Tumors

The Sherbrooke Experience

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BACKGROUND. The treatment of malignant brain tumors is hampered by the presence of the blood-brain barrier, which limits chemotherapy penetration to the central nervous system (CNS). In recent years, different strategies have been designed to circumvent this physiologic barrier. The osmotic blood-brain barrier disruption (BBBD) procedure is one such strategy, and has been studied extensively in preclinical and clinical studies. The authors detail their experience so far with the procedure in the context of an open Phase II study in the treatment of malignant brain tumors.

METHODS. Patients with histologically proven malignant gliomas, primitive neuroectodermal tumors, primary CNS lymphomas, and metastatic disease to the brain were eligible. Patients enrolled were treated every 4 weeks (1 cycle) for $\leq$ 12 cycles. A methotrexate-based regimen was offered to patients with lymphomas, whereas a carboplatin-based regimen was offered to patients with all other histologies. Before intraarterial chemotherapy infusion, patients were submitted to an osmotic BBBD procedure.

RESULTS. Seventy-two patients were included in the current report. The overall median survival times (MST) from treatment initiation for glioblastoma multiforme (GBM), anaplastic oligodendrogliomas, primary CNS lymphomas, and metastases were, respectively, 9.1, 13.9, not reached, and 9.9 months, whereas time to disease progression was 4.1, 9.2, 12.3, and 3.3 months. The MST from diagnosis was 32.2 months for GBM.

CONCLUSIONS. These encouraging results prompted the authors to further refine their knowledge of the potential contribution of this procedure in the treatment of brain tumors. These authors designed a randomized Phase III study for patients with GBM that is now open. ***Cancer* 2005;103:2606–15.**

KEYWORDS: malignant brain tumors, blood-brain barrier, blood-brain barrier disruption, chemotherapy, gliomas, brain metastases, primary central nervous system lymphomas.

The standard therapeutic arsenal available for the treatment of malignant brain tumors includes a combination of surgery, radiotherapy, and chemotherapy. Unfortunately, in most cases, complete disease remission remains elusive.[1] Primary brain tumors are infiltrative lesions, often without a clear margin between the tumor and normal brain tissue.[2,3] This reduces the likelihood of both complete resection at surgery and successful local treatment. Responses to radiotherapy are invariably transitory, despite attempts at maximizing the responses obtained in the initial randomized studies.[4,5] After

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more than three decades of research and clinical trials, these lesions remain invariably lethal. This observation has led some authors to suggest that patients diagnosed with malignant brain tumors should be enrolled in experimental studies, given the lack of improvement obtained with standard treatments.[6]

Metastatic brain lesions represent a different problem. The spread of these lesions to the brain from a primary site usually means loss of control of the primary disease and, often, widespread diffusion. However, when the metastatic process is limited to the brain, viable therapeutic approaches can be suggested to the patient. Total excision will be the procedure of choice in patients with a suspected single metastasis. For patients with multiple metastases, the approach is usually palliative and patients often receive radiotherapy to stabilize the disease for a short interval. Disease progression eventually follows.[7] The metastatic process to the central nervous system (CNS) usually suggests an uncontrollable disease, and typically represents an exclusion criterion in most systemic chemotherapy protocols.[1]

Although some studies have shown that the use of adjuvant chemotherapy after surgery prolongs survival in a selected group of patients, these improvements have generally been modest, and the majority of patients do not achieve disease remission.[1] Limited therapeutic success in the treatment of CNS neoplasia with chemotherapy is generally attributed to two factors: natural or acquired resistance to chemotherapy expressed by tumor cells, and delivery impediment related to the blood-brain barrier (BBB).[8]

The BBB is functionally situated at the brain capillary endothelium layer, and covers a surface area of 12 m^2/g of brain parenchyma.[8,9] The normal BBB prevents passage of ionized water-soluble compounds with a molecular weight $>$ 180 daltons (D). Most currently available effective chemotherapeutic agents have a molecular weight of 200–1200 D.[10] The function of the BBB is complex, and is derived from different anatomic and physiologic components, among which are the tight junctions, the efflux pumps, the basal membrane, and the astrocytic podophilic projections.[8,11]

Therefore, a strategy to increase dose intensity to the CNS must take into account the impediment imposed by the BBB, and somehow, bypass it. It is with that knowledge that the concept of transiently "opening" the BBB was developed (Fig. 1). Rapaport et al.[12] reported on the first animal experiments, and Neuwelt[13] pioneered and standardized the first human procedures. After a series of Phase I studies had been completed successfully, Phase II studies were initiated, and are still underway, paving the way for Phase III studies. Using a standard technique of

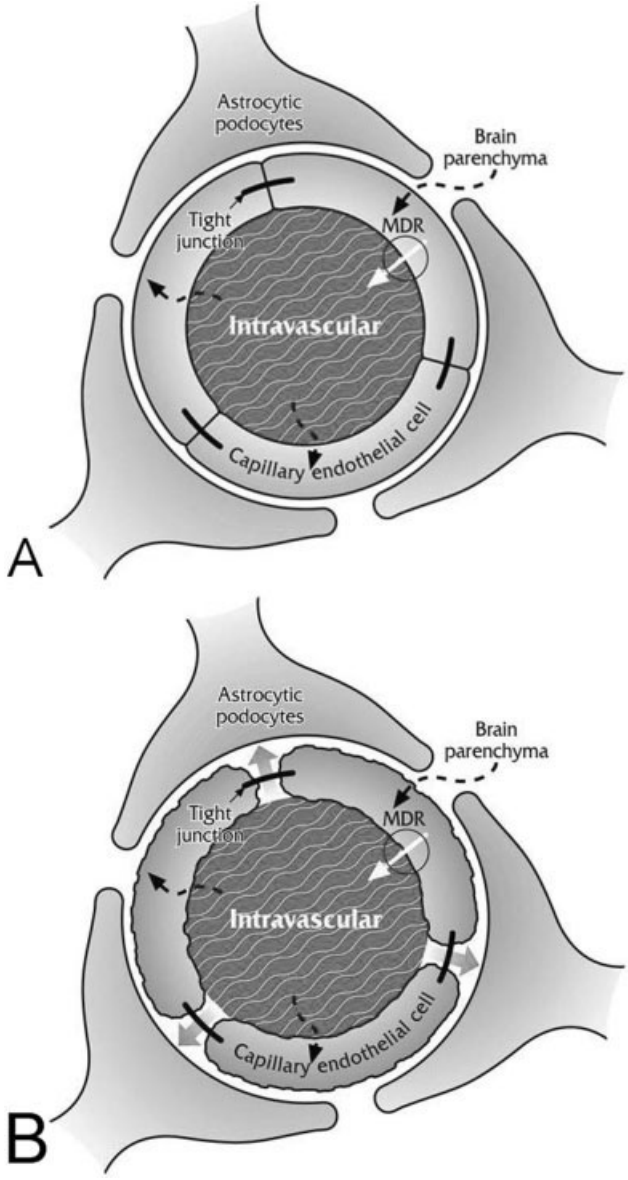


FIGURE 1. Schematic overview of the blood-brain barrier (BBB). Graphic sketch illustrating the hypothesis concerning the modification. (A) The tight junctions are devoid of any anatomic space between the endothelial cells. Moreover, the multidrug resistance (MDR) gene product, or p-gp efflux pump, is also illustrated as it is integral to the mechanism of the BBB. The osmotic blood-brain barrier disruption procedure induces a retraction in the cell membrane, as well as a physical opening between the endothelial cells (B) accompanied by a modification of the Ca metabolism in the cell.

osmotic blood-brain barrier disruption (BBBD) to enhance chemotherapy delivery with 3 different chemotherapy protocols, $>$ 6000 procedures have been performed in $>$ 400 patients across the BBB consortium, which includes 6 university centers.[14] The Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke University (Sherbrooke, Quebec, Canada) joined the consortium in November 1999, and

used an altered version of the Phase II protocols standardized across the BBB consortium. The current study reports our experience with this procedure thus far, with a description of the modifications we designed, and their implications.

MATERIALS AND METHODS

The protocol used in the current study was approved by the institutional review board, and informed consent was obtained in accordance with institutional regulations. Patients with histologically proven malignant gliomas (astrocytomas Grade 3 and 4, gliosarcomas, anaplastic oligodendrogliomas), primitive neuroectodermal tumors (PNET), primary central nervous system (PCNS) lymphomas, and metastatic disease to the brain were eligible. One additional patient with a diagnosis of malignant ganglioglioma was also included in the group of patients with malignant gliomas.

Eligibility criteria also included a Karnofsky performance score (KPS) $>$ 50, measurable disease on initial contrast-enhanced computed tomograpy/magnetic resonance imaging (CT/MRI) scans, and absence of a significant mass effect as exemplified by an open quadrigiminal cisterna, absence of dilatation of the contralateral ventricular system, and absence of uncal herniation. These radiographic criteria represented absolute contraindication to the procedure. Previous radiotherapy and chemotherapy were allowed.

After enrollment and initial evaluation, patients were treated every 4 weeks (1 cycle) for $\leq$ 12 cycles. The procedure was accomplished in a standardized way. After general anesthesia, selective catheterization via percutaneous transfemoral puncture of either the left carotid artery, right carotid artery, left vertebral artery, or right vertebral artery was performed, the parent vessel used related to the tumor location in the brain. The catheter was placed at the level of C1–C2 for the carotid circulation, and at the level of C5–C6 for the vertebral circulation.[8,14] After determination of the adequate infusion rate for mannitol infusion to open the BBB, the anesthesiologist prepared the patient for the BBBD. The mannitol was then infused at high flow over 30 seconds in the previously selected artery. During this infusion, the whole vascular tree in the selected distribution was filled with mannitol while reflux in the common and external carotid artery was kept to a minimum. After angiographic confirmation of the position of the catheter, the chemotherapy protocol was infused via the same catheter at a rate calculated to prevent streaming.[15,16]

In some patients in whom the mass effect was judged to be too important for the procedure, intraarterial chemotherapy was offered when the other inclusion criteria were met. In this situation, general anesthesia was not needed and chemotherapy infusion was accomplished after transfemoral catheterization of the appropriate vessel.

TABLE 1
Chemotherapy Regimens Used in Conjunction with the BBBD Procedure

Chemotherapy agents	Doses (mg/m^2)
Carboplatin protocol	
Carboplatin i.a.	400 mg/m^2
Etoposide i.v.	400 mg/m^2
Cyclophosphamide i.v.	330–660 mg/m^2
Methotrexate protocol	
Methotrexate i.a.	5000 mg
Etoposide i.v.	150 mg/m^2
Cyclophosphamide	500 mg/m^2

BBRD: blood brain barrier disruption; i.a.: intraarterially; i.v.: intravenously.

In the event of a tumor located in more than one cerebral artery distribution (large glioma, multiple metastases, or multicentric lymphomas), different vascular distributions were treated alternately from cycle to cycle.

Two different chemotherapy regimens were used based on tumor histology. Malignant gliomas, PNET, and brain metastases were treated using the carboplatin regimen, whereas a methotrexate-based regimen was used to treat PCNS lymphomas and systemic lymphomas with CNS involvement. Both regimens are detailed in Table 1.

All patients were monitored with complete blood and platelet counts every week. A biochemical evaluation, kidney and liver function profile, and electrolyte assessment were requested every 4 weeks. A comprehensive neurologic and general examination was performed before each cycle. Objective assessment of overall response was based on tumor evaluation from CT/MRI scans, interpreted according to the Macdonald et al. criteria,[17] in light of corticosteroid use. Briefly, a complete response (CR) suggested the complete disappearance of all enhancing tumors on consecutive CT/MRI scans $\geq$ 1 month apart, and no corticosteroid use other than physiologic doses, with stable or improved neurologic condition. A partial response (PR) suggested a $>$ 50% reduction in enhancement for measurable lesions and stable corticosteroid use, with stable or improved neurologic condition. Progressive disease suggested a $>$ 25% increase in contrast enhancement or any new tumor nodules, with or without neurologic progression. Stable disease (SD) applied to all other circumstances.

Data were prospectively collected at study entry and at every visit during the study.

TABLE 2
Breakdown of Histologic Subtypes

Histologic diagnosis	No. of patients (%)
Malignant astrocytomas	31 (28)
Glioblastoma multiforme	20
Anaplastic astrocytomas	6
Malignant ganglioglioma	1
Brainstem glioma	1
Optic glioma	1
Pleomorphic xanthoastrocytoma	1
Gliosarcoma	1
Anaplastic oligodendrogliomas	17 (24)
PNET	2 (3)
Primary CNS lymphoma	8 (11)
Systemic lymphoma	4 (6)
Metastasis	10 (14)
Breast	4
Ovarian	1
Testicular	1
Lung	4

PNET: primitive neuroectodermal tumors; CNS: central nervous system.

Statistical Analysis

Time to disease progression (TTP) intervals and overall survival intervals were calculated from the first cycle of treatment to, respectively, first radiologic or clinical sign of disease progression according to the Macdonald et al. criteria, and to death.[18,19]

RESULTS

Descriptive Data

From November 1999 to June 2002, 81 patients were accrued and treated in the current study. At the time of the report, nine patients had been exposed to a single cycle of treatment, and were therefore excluded from the statistical analysis. Of the remaining 72 patients, 34 (47%) were women and 38 (53%) were men. At enrollment, patients had a median age of 44 years (range, 8–72 years). The mean KPS for the series was 63. Before enrollment, all patients had histopathologic confirmation of diagnosis. Table 2 summarizes the number of patients by histologic diagnosis. A significant number of patients in this series were referred from other institutions after having failed to respond to previous treatment. At accrual, 44 patients (61%) had already been exposed to radiotherapy, and 36 (50%) had been exposed to chemotherapy.

A total of 353 treatment cycles were administered to patients, for a mean number of 4.9 cycles per patients. Of these, 243 treatment cycles represented BBBD-enhanced chemotherapy, and 110 treatment cycles represented intraarterial chemotherapy.

Tumor Response

The best radiographic response to treatment according to the Macdonald et al. criteria is reported in Table 3. It is noteworthy that 58% of patients with malignant astrocytomas (2 CR and 16 PR of 31 patients) achieved a response. However, and much to our disappointment, only 52% of patients with anaplastic oligodendrogliomas (9 PR of 17 patients) showed a response to treatment, without obtaining a single CR. Ten of these 17 patients with anaplastic oligodendroglioma had been treated with at least one other chemotherapy regimen before accrual in our protocol.

TABLE 3
Best Radiologic Responses by Macdonald Criteria

Characteristics	No.	CR	PR	SD	PD
Malignant astrocytomas	31	2	16	12	1
Anaplastic oligodendrogliomas	17	0	9	6	2
Primary CNS lymphomas	8	3	5	0	0
Systemic lymphomas	4	2	2	0	0
Metastasis	10	1	6	3	0
PNET	2	0	0	1	1

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; CNS: central nervous system; PNET: primitive neuroectodermal tumor.

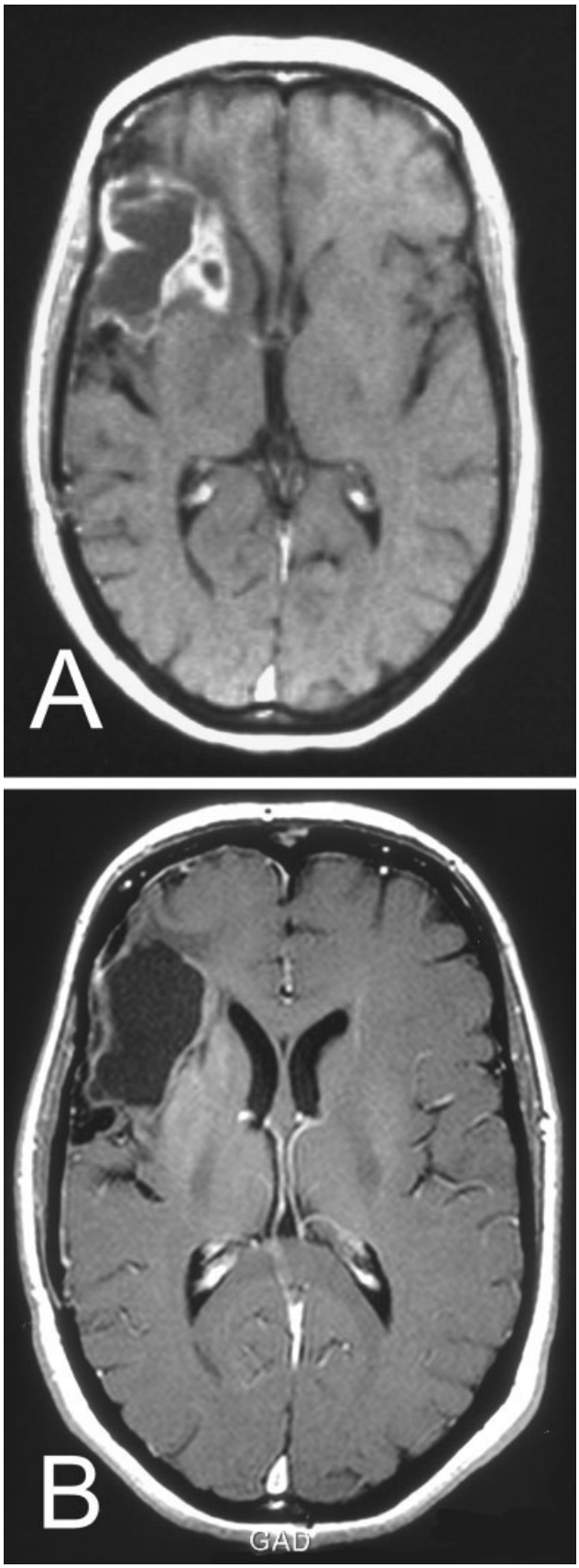
As depicted in Table 3, all patients with PCNS lymphomas responded with 4 CR and 4 PR. In this last group of patients, two patients who had a PR had previously been exposed to systemic chemotherapy and one had been submitted to radiotherapy, before enrollment. These patients were therefore treated for disease recurrence. Of 4 patients with systemic large B-cell lymphomas with CNS seeding, 2 patients obtained a CR, as documented by a cerebral MRI scan and a systemic positron emission tomography scan, and still maintain this response (Figs. 2,3).

Patients with different histologic types of metastatic disease were included in our study (see Table 2 for histologic subtypes). Of 10 patients, 7 achieved a response (1 CR, 6 PR), whereas the other 3 patients had SD for variable intervals (Fig. 4).

Overall Survival and Time to Disease Progression Interval

Overall survival and TTP data for each histologic subtype are presented in Tables 4 and 5.

For clarity's sake in reporting the results, patients with glioblastoma multiforme were analyzed as a separate group, excluding patients with other malignant astrocytic tumors. In this group, 15 patients presented with de novo tumors, whereas 5 patients had been diagnosed in the past with lower grade lesions that had subsequently transformed. Eighteen patients had been exposed to radiotherapy before accrual in the current study, and 10 had received previous chemotherapy, in the form of temozolomide ($n = 8$) or PCV ($n = 2$). None of the patients received radiosurgery or brachytherapy. In this group, 6 patients had under-



gone only 1 procedure at study accrual, whereas 14 underwent a second surgical procedure before accrual. These reoperations were proposed to patients in whom the mass effect from the recurrent tumor was excessive, or in whom a diagnostic query was present (e.g., a tumor progressing from a lower grade). When using the Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis classes for malignant gliomas, the patients would have been classified as follows: 3 with Class III, 8 with Class IV, 8 with Class V, and 1 with Class VI.[20]

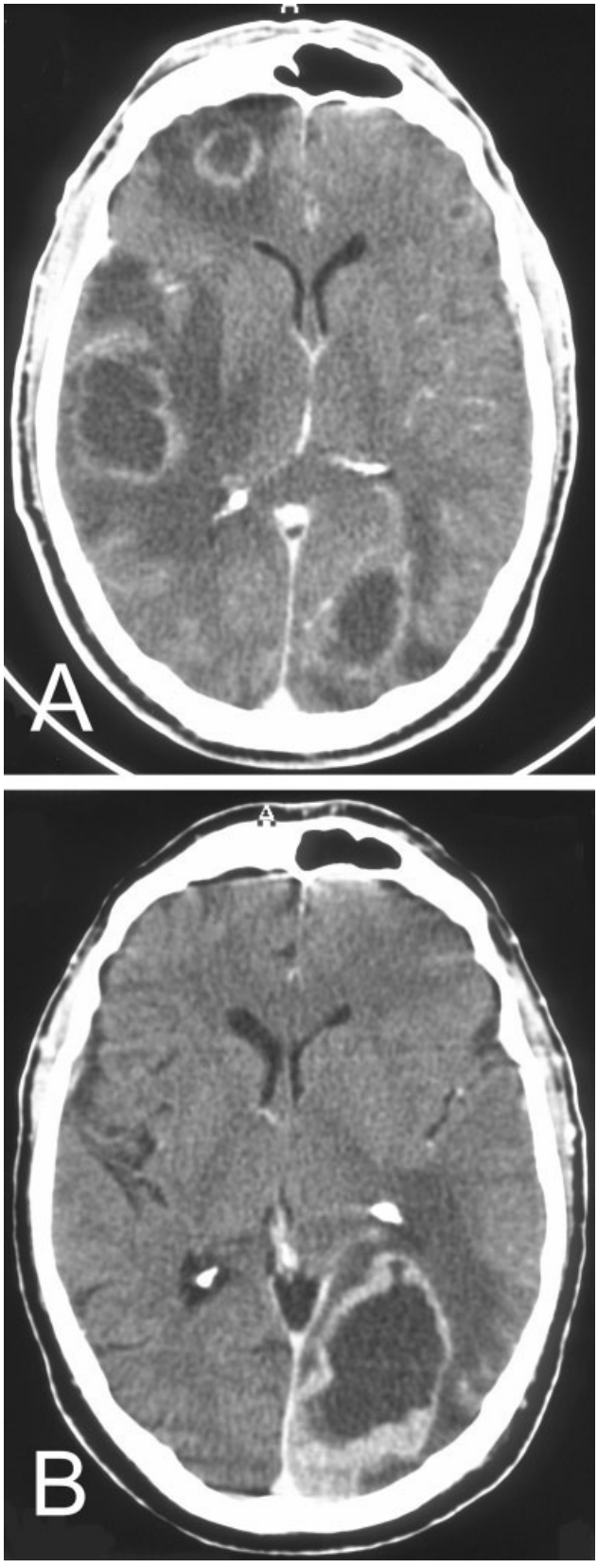
The overall median survival time (MST) from treatment initiation for glioblastoma multiforme was 9 months (38.6 weeks) and the TTP was 4.1 months (17.4 weeks). The overall MST from diagnosis was 32.2 months (138 weeks). For anaplastic oligodendrogliomas, the MST from study entry was 13.9 months (60 weeks) and the TTP was 9.2 months (39.3 weeks). The overall MST from diagnosis was 60 months (260 weeks).

The overall MST for PCNS lymphoma was not yet reached at the time of the current report and the TTP was 12.3 months (52.7 weeks) (Fig. 5). Although metastatic cerebral disease represented a heterogeneous group of histology, it was analyzed as a whole, given the small sample of patients. The overall MST from study entry was 9.9 months (42.6 weeks) and the TTP was 3.3 months (14.1 weeks).

Difference between Intraarterial and Blood-Brain Barrier Disruption Treatment Modality

The current study was obviously not designed to explore the difference between intraarterial chemotherapy, and intraarterial chemotherapy enhanced by osmotic BBBD. Hence, differences in outcomes observed between these two modalities cannot be interpreted as an indication of the superiority of one modality compared with the other. However, one is struck by this difference in all groups, even though, given the small sample size, it is statistically significant only in the metastasis group (Tables 4,5).

FIGURE 2. A 45-year-old woman was diagnosed in 1997 with a right-sided frontotemporal oligodendroglioma. She received a partial resection of the tumor and was followed up until 2000, when she developed disease progression. A biopsy showed a transformation to anaplastic oligodendroglioma, and PCV treatment was initiated. She was referred to our institution after having failed to respond PCV treatment. (A) An axial T1 gadolinium-enhanced magnetic resonance imaging scan obtained before blood-brain barrier disruption (BBBD) treatment initiation in this patient. Notice the recurrent tumor in the resection cavity. (B) After eight cycles of the BBBD-carboplatin tridrug regimen, a major partial response can be appreciated.



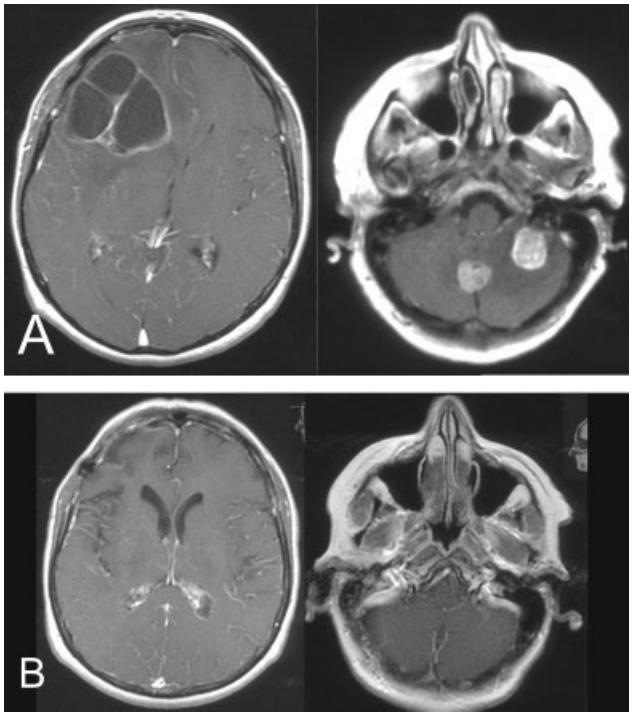


FIGURE 4. A 63-year-old woman with ovarian carcinoma developed a severe bifrontal headache rather suddenly. A year before, she had received aggressive resection of her primary disease, and had completed 2 months prior to the onset of symptoms, 6 cycles of intravenous carboplatin/paclitaxel before symptom emergence. (A) An axial T1 gadolinium-enhanced magnetic resonance imaging (MRI) scan displays 3 lesions: a right frontal ring-enhancing cystic lesion surrounded by vasogenic edema and producing a significant mass effect, and 2 homogeneously enhancing posterior fossa tumors producing 4th ventricular compression. The right frontal tumor was resected, and the patient was exposed to carboplatin tridrug blood-brain barrier disruption treatment in the vertebrobasilar distribution. The patient presented with a complete response (CR) after 12 cycles of treatment, and still maintains this CR as shown on a follow-up MRI scan $>$ 1 year after treatment discontinuation (B).

Complications and Adverse Events

Adverse events can be classified in two broad categories, i.e., those related to the chemotherapy hematologic toxicity and those related to the procedure itself. Complications are reported according to the National Cancer Institute common toxicity criteria.

FIGURE 3. A 55-year-old man was examined in the emergency room for a decrease in sensorium noticed by family members. (A) A contrast-enhanced computed tomography scan depicted multiple ring-enhancing lesions surrounded by vasogenic edema. Investigation revealed small cell lung carcinoma. Treatment was initiated with blood-brain barrier disruption in the right carotid artery, because tumor burden was maximum in this distribution. (B) After three cycles in the right carotid artery, a complete regression of the lesions in this vascular distribution was achieved. However, the left occipital tumor grew significantly, emphasizing the importance of delivery.

TABLE 4
Overall Survival Time per Histologic Breakdown from Diagnosis

Characteristics	No.	Average (weeks)	Median (weeks)	95% CI
Glioblastoma multiforme	20	178	138	50–226
BBBD	15	179	154	83–225
IA	5	158	90	56–124
Anaplastic oligodendroglioma	17	221	257	—
BBBD	15	192	257	0–519
IA	2	—	—	—
Primary CNS lymphoma	8	139	—	—
PNET	2	314	72	—
Metastasis	10	117	115	47–183
BBBD	5	157	115	56–174
IA	5	75	51	27–76

CI: confidence interval; BBBD: blood brain barrier disruption; IA: intraarterial chemotherapy; PNET: primitive neuroectodermal tumor; CNS: central nervous system.

TABLE 5
Time to Disease Progression Data for Each Histologic Subtype

Characteristics	No.	Average (weeks)	Median (weeks)	95% CI	*P*
Glioblastoma multiforme	20	23	17	13–22	
BBBD	15	24	17	12–23	0.4897
IA	5	18	14	0–31	
Anaplastic oligodendroglioma	17	39	39	0–78	
BBBD	15	39	39	24–54	
IA	2	26	10	—	
Primary CNS lymphoma	8	42	53	12–94	
PNET	2	11	3	—	
Metastasis	10	34	14	0–32	
BBBD	5	43	24	3–46	0.3877
IA	5	15	9	1–17	

CI: confidence interval; BBBD: blood brain barrier disruption; IA: intraarterial chemotherapy; CNS: central nervous system; PNET: primitive neuroectodermal tumor.

Hematologic toxicity was exceedingly unusual with these protocols, with four occurrences of a Grade 3 and 4 thrombocytopenia, and two Grade 3 and one Grade 4 neutropenia. Only one occurrence of neutropenic fever was encountered. No Grade 3 or 4 gastrointestinal toxicity occurrence was observed.

As reported by the BBB international consortium, hearing loss was adequately protected in all patients treated with carboplatin with the use of sodium thiosulfate, administered 4 hours after treatment.[21,22] No occurrence of Grade 3 or 4 hearing toxicity was observed.

Preprocedural seizures occurred in 5% of procedures, an observation similar to that reported by the BBB consortium.[14] Most seizures were observed in the group of patients who received methotrexate. Four patients experienced postprocedural seizures with a long-lasting postictal state. Two patients suffered from postinfusion orbital myositis. Their condition completely recovered after high-dose corticosteroids. Finally, two patients suffered from carotid thrombosis occurring in the interval between two treatment sessions. In one patient, this complication was related to an important spasm during the previous treatment session that was not completely relieved when mannitol was infused, whereas in the other patient, no spasm was documented. These carotid thromboses produced only minimal morbidity, with an ipsilateral monocular blindness in one patient, and a transitory contralateral paresis that completely recovered in the other patient.

DISCUSSION

The impact of the BBB on CNS therapeutic molecule delivery is a matter of great controversy. Only recently has this topic received the attention it deserves.[23] In recent years, numerous preclinical and clinical studies have addressed this issue, and different delivery strategies have been proposed.[1] The osmotic BBBD approach, as standardized by Neuwelt and his group,[10,13] has been studied extensively in Phase I and II designs. More than 6000 procedures in $>$ 400 patients have been accomplished thus far. As reported previously, the procedure has been shown to be relatively safe given its complexity.[14]

Preclinical and clinical data have convincingly demonstrated the potency of this approach to increase delivery of chemotherapy and of other molecules to the CNS.[23–32] One frequently cited objection against this approach is the well known fact that the BBB in a patient with a malignant brain tumor is frequently already leaky.[8] Although the integrity of the barrier is often compromised within the tumor, this alteration in permeability is variable and dependent on the tumor type and size.[10] Moreover, it is extremely heterogeneous in a given lesion.[8] Although the BBB is frequently leaky in the center of malignant brain tumors, the well vascularized actively proliferating edge of the tumor, in the brain adjacent to tumor area, has been shown to have variable and complex barrier integrity.[10] By steeply reducing the concentration of intravenously administered chemotherapeutic agent at the periphery of the tumor, the phenomenon of the sink effect is yet another mechanism that can contribute to a decrease in the area under the curve and can eventually lead to chemotherapy failure in CNS neoplasm treatment.[10]

Because of the transitory increase in intracranial pressure produced during the procedure, only one vascular distribution can be disrupted per session. As designed by the BBB consortium, the procedures are performed with two daily consecutive treatment ses-

sions.[14] The obvious advantage of this approach is to allow the treatment in two different vascular distributions per cycle. However, the logistic required to do so can be demanding.

The principal interest of the current study is to show that with minor alterations to the protocol regarding logistics (one treatment session per cycle at full dose instead of two consecutive daily treatments at one-half dose in two different vascular distributions per cycle), this approach can be used with success. Our results with glial tumors would even prompt us to suggest the use of this modification in future protocol designs investigating the efficacy of the BBBD approach in gliomas across the consortium. However, because of the chemosensitive and widespread nature of lymphoma disease, and because we experienced more precocious disease recurrence with this disease than the Oregon Health Sciences University series, the two-consecutive treatment sessions per cycle should be maintained for the treatment of this disease in future protocol designs.[33]

Our results with high-grade astrocytomas are encouraging. Looking at the whole series ($n = 31$), the MST from treatment initiation was 9.2 months, and 9 months for the glioblastoma multiforme subgroup ($n = 20$) (Fig. 6). It is noteworthy that the MST for the patient treated by BBBD was 10.5 months, compared with 6.4 months for the group treated by intraarterial infusion without BBBD ($P = 0.07$). It is presumed that the sample size will explain the reason why these data did not reach statistical significance. Moreover, as stated earlier, this difference could be explained by inclusion bias. Based on the presence of a significant mass effect, some patients were denied BBBD but were offered intraarterial chemotherapy. Unquestionably, this constitutes a huge bias factor. However, when studying KPS between the two groups, no significant difference was detected. To convincingly solve this issue, a randomized study will have to be proposed.

The MST of 138 weeks for the glioblastoma multiforme subgroup and 196 weeks for the whole malignant astrocytoma group is superior to the results reported by Kreamer et al.[1] This group reported a MST of 90 weeks for a series of 41 malignant astrocytomas. These authors used a standard BBBD approach with a dual dose of carboplatin (200 mg/m^2 $\times$ 2) equally divided in 2 different vascular territories in 2 treat-

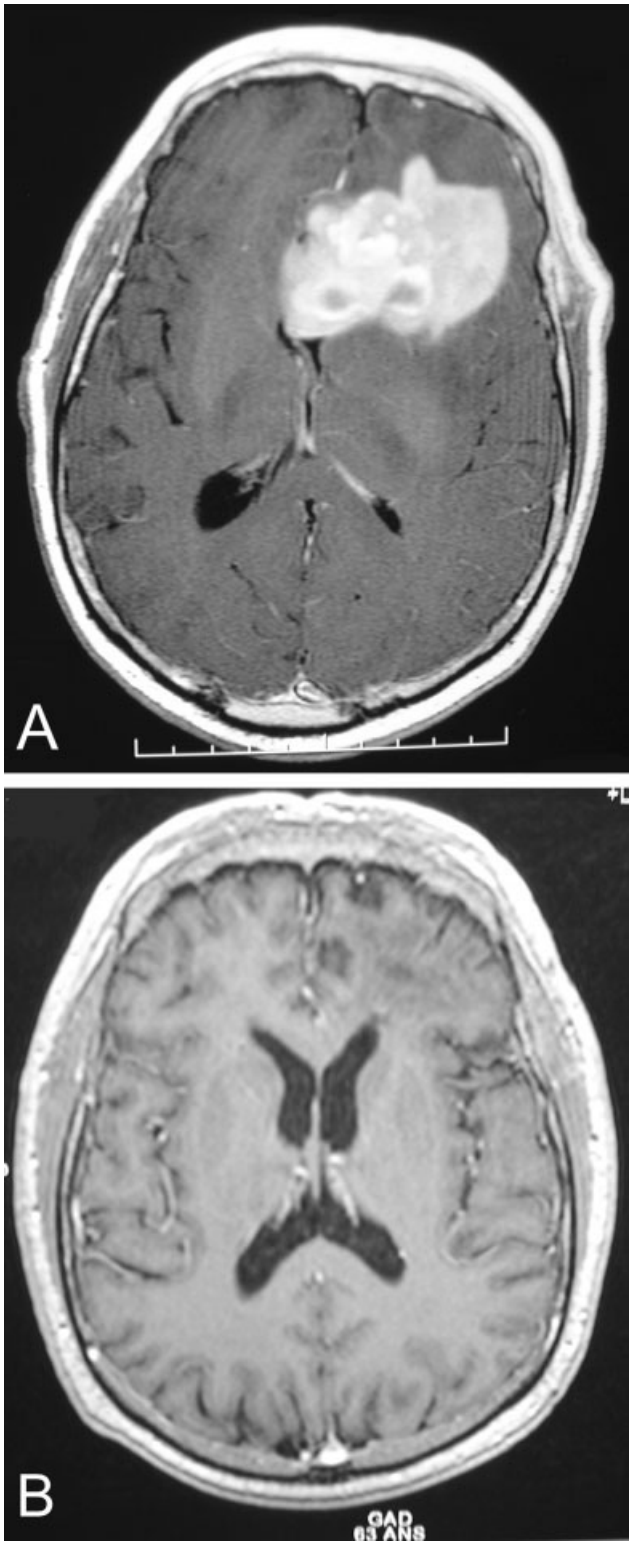


FIGURE 5. A 66-year-old man diagnosed with primary central nervous system lymphoma progressed after 3 cycles of an intravenous high-dose methotrexate regimen and was referred to our institution. (A) An axial T1 gadolinium-enhanced magnetic resonance imaging scan (MRI) depicted a left frontal tumor with extension in the anterior portion of the corpus callosum and septal area. This lesion exerted significant mass effect with a midline shift and distortion of the ventricular system. (B) An axial T1 gadolinium-enhanced MRI scan after 4 cycles of blood-brain barrier disruption-enhanced carboplatin tridrug regimen treatment. The patient is in complete response.

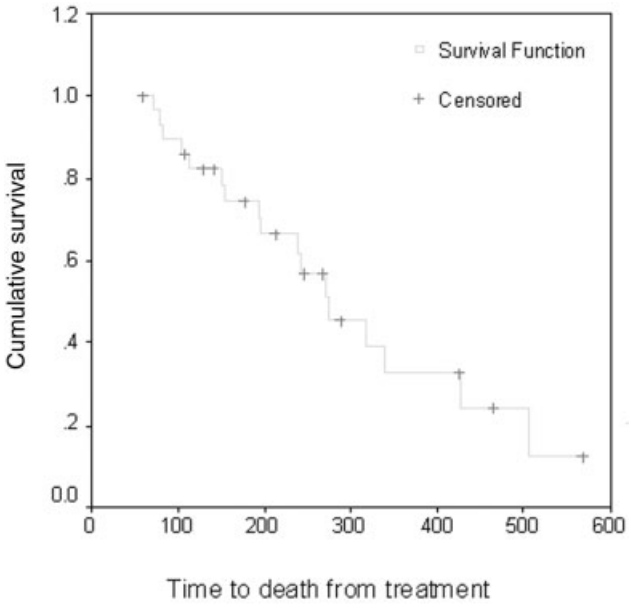


FIGURE 6. Kaplan–Meier survival curve (days) for patients with glioblastoma multiforme, from study entry to death

ment sessions at 24-hour intervals, whereas, as mentioned earlier, we used a single infusion of carboplatin (400 mg/m^2) in 1 vascular territory per cycle. Although the two series are different, and thus hardly comparable, we speculate that the modified protocol we used could favor survival and explain, in part, these disparities. Our approach might increase the area under the curve at the expense of a more limited treated distribution, therefore increasing the exposure of the more actively proliferating neoplastic cells. An analysis based on the RTOG regressive partition analysis criteria allows the breakdown of patients according to the most significant known selection criteria.[20] These data provide convincing evidence that the results are not entirely explained by selection biases, as most of our patients were classified as Class IV (n = 8) or Class V (n = 8). Survival per class was not calculated, as the data would have been of limited interest because of the small sample size for each class.

The results with the group of patients with anaplastic oligodendroglioma were not as satisfying as we had anticipated. The overall MST from diagnosis was 60 months. This compares with results previously reported in the literature.[3,34,35] Fifty-nine percent of these patients had previously been treated with chemotherapy, frequently with more than one regimen. We nevertheless obtained a median TTP from treatment initiation of 9.1 months, a demonstration that this treatment is active even in previously treated patients and can represent an adequate salvage option.

The improvement in delivery obtained with this procedure basically allows the decrease of the total systemic dose administered to the patient. This is reflected by the low hematologic complication rate in the current series. The most significant complication we encountered was related to endoluminal vessel injury, probably from infusing mannitol at high injection rates for a prolonged period of time in a vessel with residual spasm. This complication occurred in two patients. For one of these two patients, the spasm was documented before mannitol infusion. Endothelial injuries were presumably inflicted through a subintimal tear during the high-rate infusion of mannitol.

After analysis of these two patients, it was decided not to administer intraarterial mannitol in the presence of residual spasm. When severe spasms occur, all patients are now infused with 250 μg of intraarterial nitroglycerine to relieve the spasms. This approach has been successful in all patients (n = 8) who experienced such an occurrence of spasm.

The osmotic BBBD strategy is an adequate vehicle to increase chemotherapy dose intensity to the CNS. The increase in permeability has been documented in numerous preclinical and clinical studies, and its safety has been established by numerous reports, including the current study. The delivery strategy has now to be optimized with adequate therapeutic molecules in well designed randomized studies. The encouraging results obtained in our patients with high-grade gliomas have stimulated the design of a randomized Phase III study that will assess the contribution of the BBBD approach in the treatment of these lesions.[36]

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