Enhanced Chemotherapy Delivery by Intraarterial Infusion and Blood-Brain Barrier Disruption in the Treatment of Cerebral Metastasis

David Fortin, MD[1]
Cathy Gendron, MD[1]
Marie Boudrias, MD[1]
Marie-Pierre Garant, MD[2]

[1] Surgery Department, Division of Neurosurgery and Neuro-oncology, Universite de Sherbrooke, Quebec, Canada.

[2] Biostatistics, Centre Etienne Lebel, Centre Hospitalier Universitaire de Sherbrooke, Quebec, Canada.

Address for reprints: David Fortin, MD, Surgery Department, Neurosurgery and Neuro-oncology Division, Sherbrooke University, 3001 12e Ave. Nord, Sherbrooke, Quebec J1H 5N4, Canada; Fax: (819) 820-6452; E-mail: david.fortin@usherbrooke.ca

Received August 14, 2006; revision received October 26, 2006; accepted November 21, 2006.

BACKGROUND. Cerebral metastases are clinically significant in 10% to 30% of patients with neoplasia. Multiple cerebral metastases are typically treated with palliative radiotherapy. There is no consensus on the role of enhanced chemotherapy delivery as an adjuvant treatment modality in this disease. In this report, the authors detailed their experience with intraarterial (IA) chemotherapy infusion with and without blood-brain barrier disruption (BBBD) in patients with multiple cerebral metastases.

METHODS. From November 1999 to May 2005, 38 patients with multiple cerebral metastases were enrolled in a prospective study. Patients were treated with IA carboplatin, except for those with cerebral metastases of systemic lymphoma, who were administered IA methotrexate. Osmotic BBBD was offered to patients without the presence of a significant mass effect. These regimens were coupled with intravenous etoposide and cyclophosphamide. Cycles were repeated every 4 weeks.

RESULTS. Survival was calculated from study entry and radiologic response was based on MacDonald criteria. Kaplan-Meier estimates were generated for all subgroups. Mean and median survival obtained was as follows: 34 and 29.6 months for the whole group; 33.6 and 42.3 months for ovarian carcinoma; 15.3 and 13.5 months for lung adenocarcinomas; 8.3 and 8.8 months for small cell lung carcinoma; 8.9 and 8.1 months for breast carcinoma; and 24.8 and 16.3 months, respectively, for cerebral metastasis from systemic lymphoma.

CONCLUSIONS. Even with a small number of patients in each subgroup, the results obtained seem promising for multiple brain metastasis of ovarian carcinoma, adenocarcinoma of lung, small cell lung carcinoma, and systemic lymphoma. ***Cancer*** **2007;109:751–60.** © *2007 American Cancer Society.*

KEYWORDS: blood-brain barrier disruption, brain metastasis, chemotherapy.

Brain metastases are the most common intracranial tumors among adults. They occur in 20% to 40% of cancer patients, which represents over 170,000 new cases per year in the US.[1,2] The metastatic process to the central nervous system (CNS) usually implies an uncontrollable disease, and typically represents an exclusion criterion in most Phase II and III clinical studies. The emergence of cerebral metastasis significantly impacts the quality of life of the patient, producing neurological morbidity.[3] More so, it adversely impacts survival, as their presence entails per se a poor prognosis. According to the recursive-partitioning analysis (RPA) of the Radiation Therapy Oncology Group (RTOG), median survival of brain metastases patients ranges between 2 and 7.1 months, thus illustrating the poor prognosis observed in these patients.[4]

Most patients will present with multiple lesions.[5,6] Magnetic resonance imaging-based studies reveal that approximately 80% of patients

DOI 10.1002/cncr.22450
Published online 8 January 2007 in Wiley InterScience (www.interscience.wiley.com).

TABLE 1
Eligibility Criteria

Criteria
Histological confirmation of cerebral lesion
Previous radiotherapy and chemotherapy permitted
Dexamethasone permitted
Normal renal and hepatic functions
Normal cardiac and pulmonary functions
White cells $\geq 2.5 \times 10^3/mm^3$
Granulocytes $\geq 1.5 \times 10^3/mm^3$
Platelet $\geq 100 \times 10^3/mm^3$
Karnofsky 50–100

TABLE 2
Chemotherapy Regimens Used in Conjunction With the BBBD Procedure in This Study

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

BBBD indicates blood-brain barrier disruption; i.a., intraarterial; i.v. intravenous.
* Value in mg.

have more than 1 metastasis at presentation.[6] In these patients the approach is usually considered palliative, and whole-brain radiation therapy (WBRT) is offered in an attempt to briefly stabilize disease progression. However, the role of radiotherapy remains controversial.[7] Even though this treatment modality has been shown effective for local tumor control, survival benefits have been modest, ranging from 3 to 5 months.[4–6] More so, WBRT has been associated with significant side effects.[8,9]

Chemotherapy has been of limited use in patients with brain metastasis because of the blood-brain barrier (BBB). The delivery impediment of therapeutic molecules related to the physicoelectric characteristics of the BBB and the activity of efflux pump systems is such that a significant area under the curve is hard to maintain.[10–12] Based on the rationale of bypassing the BBB, different approaches have been proposed.[13] One such approach consists of increasing the effective concentration of a chemotherapy agent by intraarterial (IA) administration. By doing so, this regional delivery paradigm increases local plasma peak concentration and local area under the curve, ultimately translating into a 3 to 5.5 $\times$ factor increase in intratumoral concentration.[13,14] This strategy can also be augmented by manipulating the BBB permeability through different means.[15,16] To date, there is no consensus on the role of these approaches in the treatment of brain metastases. We hereby relate our experience with the IA administration of chemotherapy in cerebral metastatic disease, with and without osmotic blood-brain barrier disruption (BBBD).

MATERIALS AND METHODS

This prospective Phase II study was conducted at the Centre Hospitalier Universitaire de Sherbrooke (CHUS) from November 1999 to May 2005. The protocol was approved by the Institutional Review Board and informed consent was obtained in accordance with institutional regulations. Patients with histologically confirmed brain metastases were eligible. All histological subtypes were allowed, except notoriously chemoresistant histologies, such as hypernephromas and melanomas.

Eligibility criteria also included a Karnofsky Performance Status (KPS) >50 and measurable disease on initial contrast enhanced computed tomography (CT)/magnetic resonance imaging (MRI). Prior radiotherapy and chemotherapy was allowed. The complete list of inclusion criteria is detailed in Table 1. The primary endpoint of this study was survival.

After enrollment and initial evaluation, patients were treated every 4 weeks (1 cycle) for up to 12 cycles. The procedure was accomplished in a standardized way. After general anesthesia, a catheterization via transfemoral puncture of either the right or left carotid or vertebral artery was performed, the parent vessel(s) used depending on the tumor(s) location. Before appropriate vessel selection a diagnostic angiogram was obtained in the vessel(s) of interest. However, a 4-vessel angiogram was not performed routinely. The catheter was placed at the level of C1-C2 for carotid and at the level of C5-C6 for vertebral circulation. After determination of the adequate infusion rate for mannitol infusion to open the barrier, mannitol was infused at high flow over 30 seconds in the selected artery. During this infusion the whole vascular tree in the selected distribution was filled with mannitol, whereas reflux in the common and external carotid artery was kept to a minimum. The chemotherapy was then infused at a rate calculated to prevent streaming.[16]

Two different chemotherapy regimens were used based on tumor histology. Methotrexate (5 gm), for systemic lymphomas, or carboplatin (400 mg/m^2) for all other histologies, was infused via the catheter. Both regimens are detailed in Table 2. Leucovorin rescue was used with the methotrexate protocol. All patients received Neupogen (5 $\mu g/kg$ subcutaneous daily) for 7 days.

TABLE 3
Treatment Modality Detailed for Each Group of Patients

	Intraarterial (IA)	IA + BBBD
Ovary	1	4
Breast	1	3
Lung		
Adenocarcinoma	5	4
Oat cell	9	0
Systemic lymphoma	2	6
Others	0	3

TABLE 4
MacDonald Criteria[36]

Complete response (CR)	Complete disappearance of all enhancing tumor and no corticosteroid use other than physiologic doses with stable or improved neurological condition
Major partial response (MPR)	>75% reduction in enhancement
Partial response (PR)	>50% reduction in enhancement and stable corticosteroid use with stable or improved neurological condition
Progressive disease (PD)	>25% increase in contrast enhancement or any new tumor nodule, with or without neurological progression
Stable disease (SD)	Other circumstances

Because the procedure induces a transitory increase in intracranial pressure, only 1 vascular territory could be disrupted per session. Thus, patients with multiple metastases covering more than 1 vascular distribution were approached as follows: different vascular distributions were treated alternately from cycle to cycle. The presence of a significant mass effect, as exemplified by a closed quadrigiminal cisterna, dilatation of the contralateral ventricular system, or uncal herniation, represented an absolute contraindication to BBBD. Some patients presenting an excessive mass effect but otherwise meeting all the inclusion criteria were offered IA chemotherapy without BBBD (Table 3). In this setting, general anesthesia is not required, and as the BBB is not breached the chemotherapy dose was equally split between each vascular distribution treated, thus covering all lesions for each cycle.

All patients were monitored with complete blood and platelet counts every week. A biochemical, kidney and liver function profile, and electrolyte assessment was requested every 4 weeks. Neurological and general examination was performed before each cycle. Assessment of overall response was based on tumor evaluation from CT/MRI scans obtained before each treatment and interpreted according to the MacDonald criteria (Table 4). Data were prospectively collected from study entry and at every visit during the study.

TABLE 5
Groups Based on Histology

Histologic subtype	No. of cases	Average no. of metastases
Lung	18	5.1
Adenocarcinoma	9	
Small cell lung carcinoma (SCLC)	9	
Ovary	5	1.75
Carcinoma	1	
Adenocarcinoma	3	
Seropapillar	1	
Breast adenocarcinoma	4	5.5
Systemic lymphoma	8	1.3
Others	3	4.7
Hypernephroma	1	
Testicular seminoma	1	
Anal epidermoid carcinoma	1	

Statistical Analysis

Mean and median survivals from study entry were calculated from the first cycle of treatment to death or May 1, 2005. Based on these, Kaplan-Meier estimates were also extrapolated.

RESULTS

Descriptive Data

From November 1999 to May 1, 2005, 38 patients were accrued in this study and grouped in 5 distinct histological classes (Table 5).

The median age was 55, 9 years (20–74 years) for the whole group at enrollment, and there were 25 women (65.8%) and 13 men (34.2%). These 38 patients were submitted to 199 procedures (mean of 5.2 cycles per patient). Nineteen were exposed to BBBD, whereas the remaining 19 patients were treated with IA chemotherapy. On accrual, 63.2% of patients had received radiotherapy and 73.7% had already been exposed to chemotherapy for their primary disease (Table 6). The agents used were: carboplatin, cisplatin, etoposide, taxol, topotecan, 5FU, navelbin, vincristine, vinblastin, and adriamycin. In an attempt to characterize our study population prognostically, we stratified our patients according to the RTOG partitioning analysis classes. Three patients were stratified as class 1, 18 as class 2, and 17 as class 3. Overall, 92.1% of patients were in classes 2 or 3 (Table 7). The mean number of metastatic lesion was 3.5 lesions per patient.

Tumor Response, Time to Tumor Progression (TTP), and Overall Survival

The mean overall survival from diagnosis of brain metastases was 34 months, whereas median overall survival was 29.6 months. Mean and median overall survivals from study entry were, respectively, 19.9, and 13.5

TABLE 6
Previous Treatment Before Study Entry

	Systemic chemotherapy	Radiotherapy	Radiosurgery
Ovary	5	1	0
Breast	4	3	2
Lung			
Adenocarcinoma	6	8	3
SCLC	4	4	1
Systemic lymphoma	7	5	0
Others	2	3	1

SCLC indicates small-cell lung carcinoma.

TABLE 7
Distribution of Patients in RPA Classes

RPA classes	Criteria	No. of patients	Median survival time expected, mo
I	All of the following: 1. Karnofsky ≥70 2. Age ≤65 3. Controlled primary tumor with no extracranial metastases	3	7.1
II	1. Karnofsky ≥70 and at least 1 of the following 2. Age ≤65 3. Uncontrolled or synchronous primary tumor presence of extracranial metastases	18	4.2
III	Karnofsky <70	17	2.3

RPA indicates recursive-partitioning analysis.

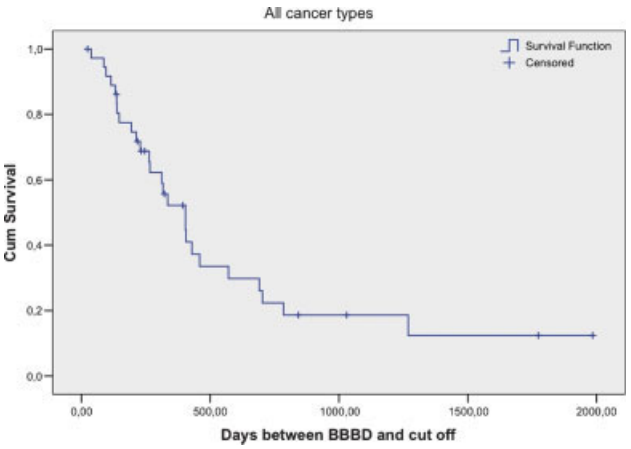

FIGURE 1. Kaplan–Meier survival curve (days) for the global group of metastasis patients, from study entry to death.

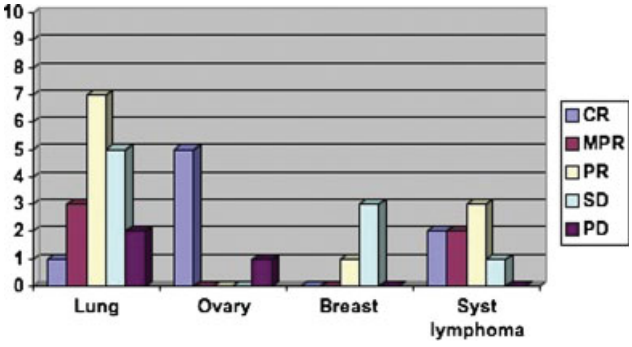

FIGURE 2. Best radiological response, according to the MacDonald et al.[36] criteria for each major histological subgroup analyzed in this study. CR indicates complete response; MPR, major partial response; PR, partial response; SD, stable disease; PD, progressive disease.

months, for the entire group of patients (Fig. 1). Figure 2 summarizes the assessment of best radiological response to the treatment for each group based on MacDonald criteria. Twenty-three patients (60%) progressed during treatment, for a mean TTP of 127 days. Interestingly, of 10 patients already exposed to systemic administration of drugs used in our regimen, 7 showed a response, 1 patient remained in stable disease (SD), and 2 progressed.

Lung Carcinoma (n = 18)

Lung metastases patients presented a median survival of 11.2 months. Two histological subgroups were identified and analyzed separately. Adenocarcinomas (n = 9) depicted a mean and median survival time of 15.3 and 13.5 months, respectively. The best response to treatment was 1 major partial response (MPR) and 4 partial response (PR). For small cell lung carcinoma (SCLC) patients (n = 9), we observed 1 complete response (CR), 2 MPR, and 3 PR, with 8.3 months of mean and 8.8 months of median survival (Fig. 3). As SCLC patients typically presented with multiple lesions and a significant mass effect related to peritumoral edema, all were treated with IA chemotherapy, without BBBD.

Lymphoma (n = 8)

Systemic lymphoma patients with brain metastasis presented an average and median survival of 24.8 and 16.3 months, respectively. Two patients completed the full treatment regimen (12 cycles), and are still in CR after 57.2 and 51.9 months (Fig. 4). Interestingly, 7 of 8 patients presented a response.

Ovarian Metastasis (n = 5)

This group showed an average and median survival of 33.6 and 42.3 months, respectively. These patients presented and all or non-behavior when studying radiological responses, in that 4 of them had a CR, whereas 1 progressed and died 8 months after treatment initiation.

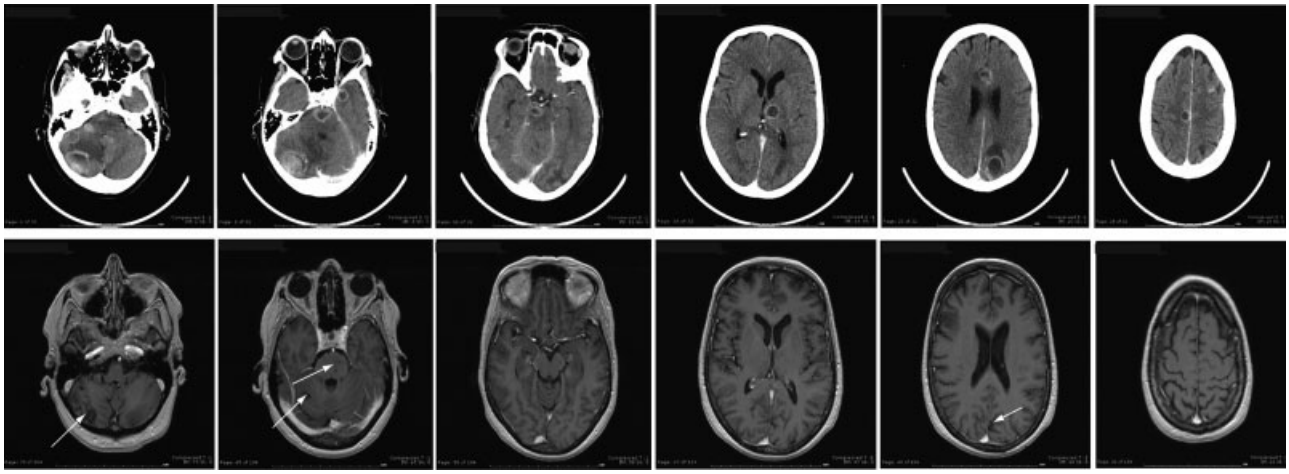

FIGURE 3. A 62-year-old woman with an initial presentation of headache, nausea, and dizziness. A computed tomography (CT) scan revealed the presence of multiple brain lesions (upper row). Systemic investigation revealed the presence of a pulmonary nodule and of numerous abnormal lymph nodes. A biopsy of 1 of these lymph nodes revealed the diagnosis of an oat cell carcinoma. The patient was exposed to 8 cycles of intraarterial chemotherapy and presented a complete response (CR) (lower row). The white arrows depict areas of hypointense signal related to encephalomalacia. These regions correspond to areas where significant tumor nodules were present before treatment; these nodules have now receded, thus producing encephalomalacia.

Two of these 5 patients are still in CR with a follow-up of 34.1 and 27.8 months (Fig. 5). None of the responders had been exposed to radiation therapy.

Breast Carcinoma (n = 4)

A mean and median survival of 8.9 and 8.1 months, respectively, were observed. Best radiological response observed was 1 PR. The 3 other patients progressed.

Complications and Adverse Events

For the present study, adverse events are classified in 2 distinct categories: hematologic toxicity and adverse events associated with the procedure itself. In terms of hematologic toxicity, we observed 1 grade 3 occurrence of anemia and 1 grade 4 thrombocytopenia according to the National Cancer Institute common toxicity criteria. Two occurrences of grade 3 and 1 of grade 4 neutropenia were also observed. Three adverse events related to the procedure were recorded. One occurrence of severe neck pain after perfusion of chemotherapy in the vertebral artery was observed in a patient treated with IA chemotherapy without BBBD. This syndrome was controlled with steroids. Two patients presented with a postinfusion orbital pseudotumor syndrome.[17] Their condition completely recovered after high-dose steroids.

DISCUSSION

Brain metastases occur in 20% to 40% of cancer patients and are associated with a dismal prognosis. Typically, patients with multiple brain metastases are exposed to WBRT as a palliative measure.[1,2,6] The rationale supporting the use of this approach relies on the demonstration that it has a high potency of controlling neurological symptoms.[18] However, survival improvement is modest, ranging from 3 to 5 months.[3,5] This survival has not been altered despite 3 decades of clinical research aimed at improving outcome for these patients.[6] The short median survival benefit has to be weighed against the possibility of inducing side effects such as fatigue, alopecia, and transient worsening of neurological symptoms.[5,6,8] More worrisome are the risks of inducing delayed toxicity such as diffuse cerebral injury, producing progressive dementia, gait ataxia, and sphincter dysfunction in the few patients presenting a long-term survival.[16] DeAngelis et al.[9] described an incidence of radiation-induced dementia of 1.9% to 5.1% in patients with brain metastases. This was probably an underestimate, as only the most severely affected patients were identified and no formal neurocognitive testing was accomplished. These side effects need to be considered in light of the palliative context.

The role of standard chemotherapy in the treatment of brain metastases has always been marginal, as penetration of the chemotherapy agent beyond the BBB is limited.[11] By way of its anatomic and physiologic properties, the normal BBB prevents passage of ionized water-soluble compounds with a molecular weight greater than 180 Da.[19] Although the integrity of the barrier is often compromised within or around tumors, this alteration in permeability is variable and heterogeneous, nonetheless greatly limiting drug penetration.[19] More

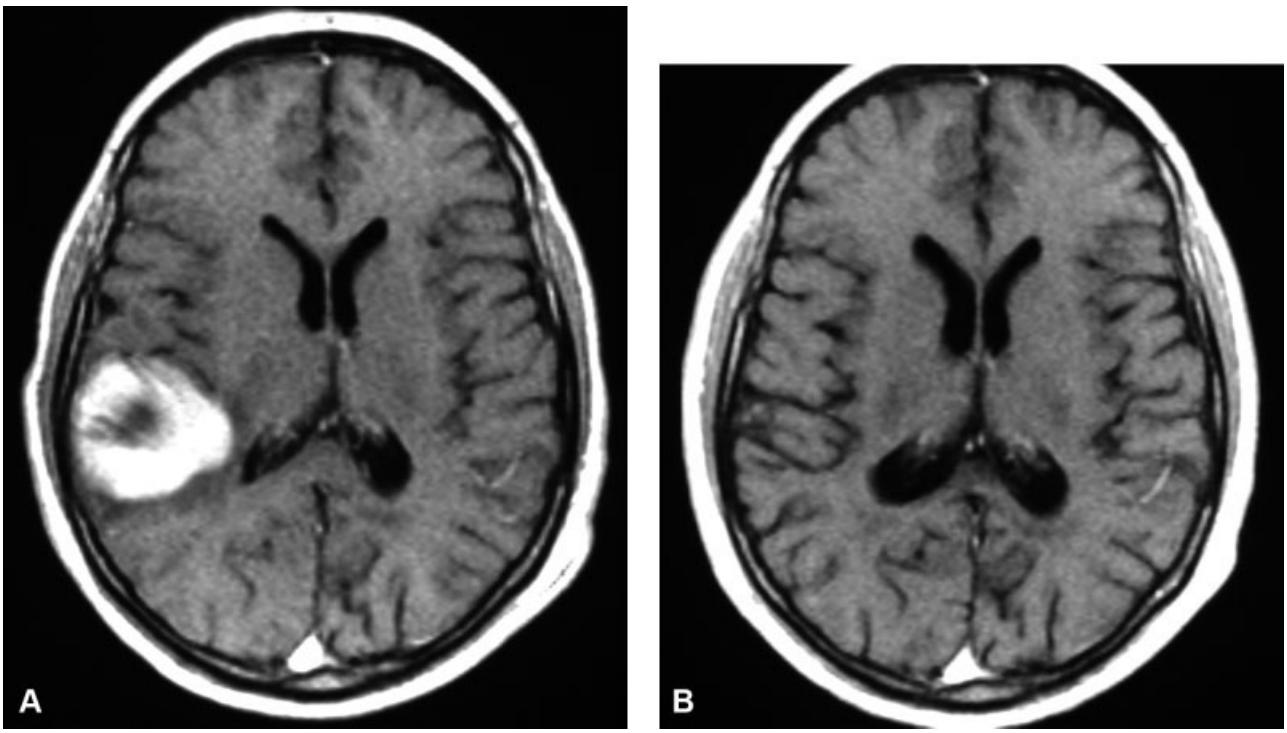

FIGURE 4. A 49-year-old man was diagnosed with a systemic non-Hodgkin B-cell lymphoma with an abdominal presentation. After having undergone 6 cycles of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) and abdominal radiotherapy, a positron emission tomography (PET) scan showed no residual disease. Two months after the completion of radiation therapy he presented a left-sided sensory seizure. After investigation, a right parietal lesion was uncovered (A), biopsied, and a confirmatory diagnosis of B-cell lymphoma was made. The patient was enrolled in our study and underwent 12 cycles of blood-brain barrier disruption (BBBD) in conjunction with the methotrexate regimen. At study cutoff he was still in complete response (CR), 51 months after his inclusion in the study (B).

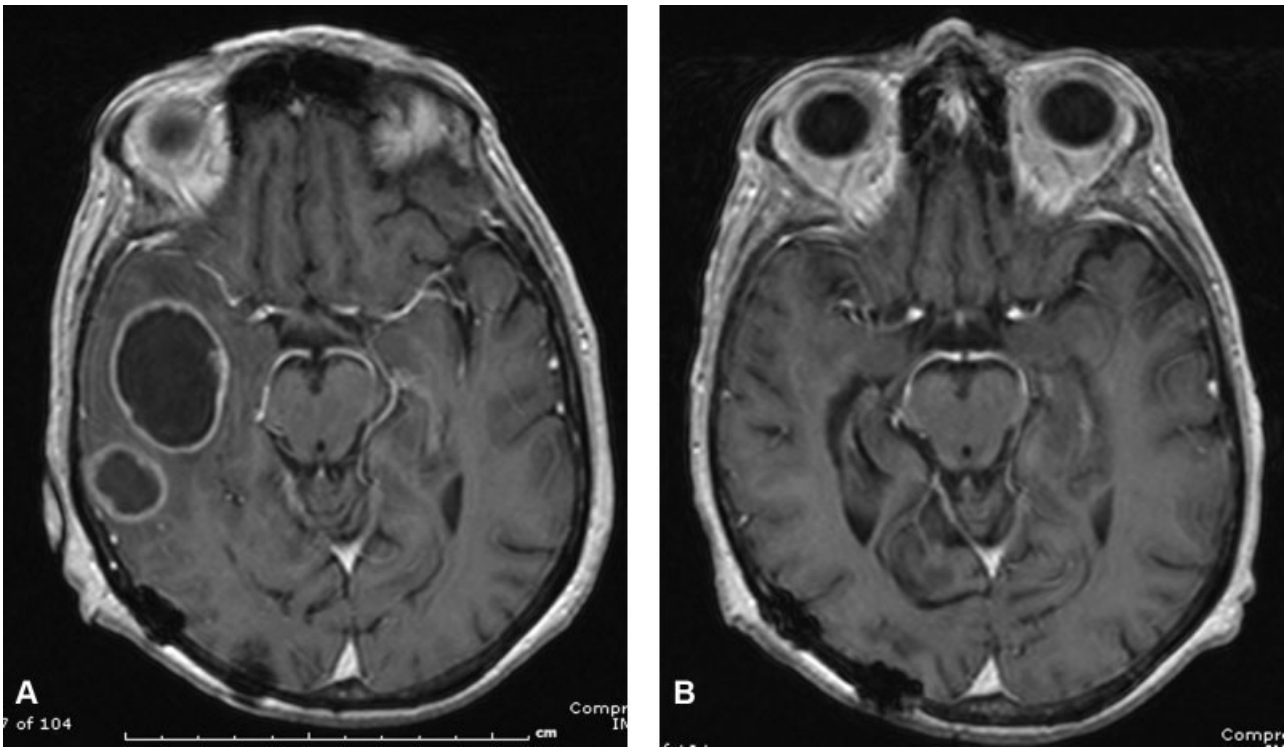

FIGURE 5. A 69-year-old woman was diagnosed with poorly differentiated ovarian adenocarcinoma in May 2001, at which time she underwent extensive abdominal and gynecologic surgery, followed by 6 cycles of taxol/carboplatin. She presented a seizure in May 2002 and a metastatic lesion was identified in the right parietal region. She underwent a craniotomy for tumor resection, followed by 8 cycles of the carboplatin regimen in conjunction with blood-brain barrier disruption (BBBD). She was considered in complete response (CR) after 2 cycles, and that condition was maintained until December 2005, when she experienced recurrence in the right temporal lobe. (A) BBBD treatments were resumed and she was considered in CR after 3 cycles (B).

so, drug distribution is uneven, with a preferential accumulation in the necrotic areas of the tumor.[5] Drug penetration at the edge of the tumor is nonexistent, as has been shown in a study using fluorescein as a marker of permeability.[20] The presence of the P-glycoprotein (P-gp) efflux pump at the luminal surface of the brain capillaries and the constant flow of cerebral spinal fluid (CSF) emanating from perivascular spaces further contribute to a decrease in the actual concentration and time of exposure of tumor cells to chemotherapy. Interestingly, despite the fact that this limitation in delivery imposed by the barrier is more and more acknowledged, it remains underdiscussed in the field of neurosciences.[11,12]

Intraarterial Chemotherapy and BBBD

Different approaches have been advocated to improve delivery across the BBB. One such approach has been extensively tested in the clinic, and is commonly used by our team, both in the preclinical and clinical setting. It involves the IA infusion of chemotherapy with or without prior administration of a hypertonic solution to produce a transient increase in permeabilization of the barrier in a given cerebrovascular distribution.[15,16] The so-called IA chemotherapy infusion refers to the regional delivery of chemotherapy to the CNS, which produces a significant increase in plasma peak concentration and in the area under the curve related to the first pass effect.[13] This translates in a significant increase in intra-tumoral chemotherapy concentration by a 3–5.5-fold factor, as most of these lesions are highly vascularized.[19] Newton et al.[13] reported their experience with IA chemotherapy in a group of 27 patients exposed to IA carboplatin and IV etoposide. All the patients in this series had been exposed to radiation before enrollment, and 67% had been exposed to chemotherapy. The authors reported a 54% response rate and a 20-week median survival from study initiation. This lead to an impressive TTP of 16 weeks in the cohort, thus validating this approach as promising in the treatment of this patient's population. Doolittle et al.[21] reported their results on brain metastases treatment as part of a broader series. Although not specified in the article, most of those patients had been treated by IA chemotherapy without BBBD. Thirteen patients with brain metastasis of unspecified histology were so treated with the following results: 3 CR, 2 PR, and 5 SD. However, no details as to the specific histology in relation to response and duration of response are given for this subset of patients, thus greatly limiting the reach of the results.

One way to further increase delivery is to add an osmotic manipulation of the BBB to the IA chemotherapy infusion. The permeation of the BBB is obviously transitory (30 minutes to 2 hours according to experimental data), but lasts for a sufficient time to allow the IA infusion of a therapeutic molecule.[19] The procedure would also allow a transient decrease in the function of the P-gp pump, thereby allowing for improved delivery of chemotherapy agents that are also known substrate of this pump.[22] Even if the barrier is breached in the tumoral tissue, its integrity remains virtually intact at the periphery of the tumor.[19] Sato et al.[20] elegantly demonstrated in vivo that the mannitol infusion increases the permeability of the barrier at the edge of the tumor, in the peritumoral area. Recently, we reported encouraging results obtained with malignant glioma patients using the BBBD procedure.[16] Fragmentary data were also available on a group of 10 patients with brain metastasis. The median survival time from study entry was 9 months. Interestingly, the extent of the increase in permeability has been shown to correlate with long-term survival in a population of lymphoma patients treated with the BBBD procedure combined with IA methotrexate infusion.[23] In that study the authors clearly established a relation between the clinical outcome of the patient and the intensity of delivery obtained by the procedure, emphasizing the relevance of improving delivery strategies.

As stated earlier, the selection of patients directed toward BBBD was partially based on the presence of a significant mass effect, and some patients were denied BBBDs but were offered IA chemotherapy based on that criterion. Because BBBD produces a significant increase in interstitial brain water content, patients with a significant mass effect could be at risk for herniation, and thus strict criteria are applied to exclude these patients from BBBD.[16] Unquestionably, this constitutes a huge bias factor in detriment of the IA cohort.

Recently, Newton et al.[14] reported on the importance of performing a 4-vessel angiogram before selecting the appropriate vessel(s) for treatment. In a series of 78 patients (39 with metastasis), those authors showed a 6.4% alteration in treatment plan after having performed a 4-vessel angiogram, and not just a diagnostic angiogram of the presumed vessel(s) of interest, as we do. The fact that the relevant vessel might not be selected is worrisome, even if the risk is fairly low (6.4%). As this instance can be easily avoided by a 4-vessel angiography before the final planning of the treatment, this appropriate measure should be implanted in every study on IA with or without BBBD. We intend to do so in future trials.

Overall Survival

The analysis of a heterogeneous group of patients as a whole, such as our series of brain metastasis, is always difficult and data can be influenced by many confounding factors. One way to limit these confounding factors is to stratify the patients according to validated prognos-

tic factors. The recursive-partitioning analysis (RPA) of the RTOG databases allows this stratification along 3 different prognostic classes.[4] According to these classes, median survival of patients with brain metastases ranges between 2 and 7.1 months (Table 7). As most of our patients (35 of 38, or 92.1%) fitted criteria of class 2 or 3, expected median survival for this group of patients would lean between 2.3 and 4.2 months. Thus, a mean and median survival of 19.9 and 13.5 months, respectively, compares favorably with this projection. It also allows us to preclude favorable survival biases as an explanation for these results.

Lung Metastasis

Lung is the primary source of metastasis to the brain. SCLCs and adenocarcinomas have similar frequencies of seeding to the brain, averaging a 30% incidence.[24] Overall, more than 50% of patients with brain metastases from lung cancer present with multiple lesions.[25]

A median survival of 4–8 months was reported for adenocarcinoma patients treated with either systemic chemotherapy regimens with and without prior WBRT.[24] The 9 patients with adenocarcinoma enrolled in the present study presented 13.5 months of median survival from study entry. All these patients were treated at recurrence, after having failed radiation therapy. Only 1 patient is still alive at 20.7 months.

The European Organisation for Research and Treatment of Cancer (EORTC) Lung Cancer Cooperative Group evaluated the efficacy of WBRT as the sole treatment for the SCLC subgroup and found a median disease-free survival of only 5.4 months, even though the reported stabilization or improvement in neurological status was 60%.[25] Systemic chemotherapeutic regimens have been used without prior WBRT with a median survivals ranging from 3 to 4 months.[26] Some prospective trials for the treatment of SCLC brain metastases have found median survival of 3–6 months when these regimens were used after WBRT.[24] In our series, a median survival of 8.8 months was obtained for this group, which demonstrates a limited advantage with respect to results obtained from the literature. Only 3 patients were treated with radiotherapy after having failed chemotherapy. From chemotherapy failure, these patients showed a median survival of 2.7 months.

Ovarian Metastasis

Brain represents a rare site of metastasis for patients suffering from an ovarian carcinoma. Autopsy series reported an incidence of CNS metastasis of 2% to 12%. This site thus represents only 0.7% to 1.8% in a large series of patients with brain metastasis.[27–29] Melichar et al.[28] found that a combination of surgery, radiotherapy, and conventional chemotherapy was associated with a median survival of 20 months and that surgery with chemotherapy resulted in a median survival of 15 months. However, because of the small cohort size (2–12 patients), extrapolation of these intervals is limited.[30] Our results are also marred by a small sample size of 5 patients, thus limiting the reach of our analysis. A median and mean survivals of 42.3 and 33.6 months, respectively, from study entry were obtained in these patients. More important, 2 of these 5 patients are still alive and in CR after having completed the entire course of treatment. All of the responders ($n = 4$) were exposed to chemotherapy alone, and thus were spared the side effects and discomfort related to radiation therapy. Even with a limited number of patients, we suggest that this treatment modality is an adequate substitute to radiation therapy in this particular histology, and should thus be considered up front.

Breast Metastasis

Ten to 15% of patients with advanced breast cancer will eventually present with CNS involvement. CNS metastases would be a major contributing factor in the death of 68% of these patients.[31] Patients are typically in an advanced stage of their disease and have already been exposed to multiple chemotherapy regimens.[32] The same can be said of our patients, who had all been exposed to radiation therapy and to multiple chemotherapy regimens (average of 4).

Fenner and Possinger[33] reviewed 8 trials on standard chemotherapy as treatment for brain metastasis of breast cancer. They concluded that median survival was 6 months and that this figure was similar to WBRT. Different investigators have tested temozolomide in pretreated and preirradiated patients and have obtained a median survival time of 4 to 7 months.[5,34] Similar results were produced in our series of 4 patients, with a median survival of 8.1 months. The best response obtained was 2 SD. One factor that could explain the poor results obtained in this group is the fact that all patients were heavily pretreated for their systemic disease before enrollment in our study. These results are in sharp contrast to the results published by Newton et al.,[13] who reported a CR/PR in 4 of 9 patients with breast cancer. Thus, a larger and more diverse cohort will be needed to study the impact of this treatment in this class of patient.

Systemic Lymphoma With Brain Metastases

Parenchymal brain metastases from systemic lymphoma have been reported infrequently. In a series of 498 patients with malignant non-Hodgkin lymphoma, only 30 presented a secondary CNS involvement. The prognosis of this condition is typically poor, with a mean survival with treatment of 3.5 months.[35] The

patients in our series presented a median survival of 16.3 months, with 2 patients still in CR at 57.2 and 51.9 months. These results represent a significant improvement over previously published series, and this approach should be considered in this rare occurrence.

Complications

Doolittle et al.[21] reported on the safety of this procedure, when performed in a standardized fashion, in a multicenter setup. Our data further support this contention.

Poor Response Factors

When reviewing the pretreatment radiological characteristics of each patient, we found 2 surrogates adversely impacting response: heavy tumor burden independent of the histological nature of the brain metastasis, and important bihemispheric edema. The nature of the edema may be vasogenic or postradiotherapy. All patients showing these features either alone or in combination achieved a poor or no response at all.

Conclusion

Even if the number of patients in each subgroup is small, the results obtained in this study seem promising for the following histologies: ovarian carcinoma, lung adenocarcinoma, SCLC, and lymphoma.

REFERENCES

1. Patchell RA. The management of brain metastasis. *Cancer Treat Rev.* 2003;29:533–540.
2. Soffietti R, Ruda R, Mutani R. Management of brain metastases. *J Neurol.* 2002;249:1357–1369.
3. Tsao MN, Sultamen K, Chiu D, et al. Supportive care management of brain metastases: what is known and what we need to know (NCIC). *Clin Oncol.* 2003;15:429–434.
4. Gaspar L, Scott C, Rotman M, et al. Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. *Int J Oncol Biol Phys.* 1997;37:745–751.
5. Tosoni A, Ermani M, Brandes AA. The pathogenesis and treatment of brain metastases: a comprehensive review. *Crit Rev Oncol Hematol.* 2004;52:199–215.
6. Metha MP, Khuntia D. Current strategies in whole-brain radiation therapy for brain metastases. *Neurosurgery.* 2005;57: s4–33–44.
7. Bezjak A, Adam J, Barton R, et al. Symptom response after palliative radiotherapy for patients with brain metastases. *Eur J Cancer.* 2002;38:487–496.
8. Andrews DW, Scott CB, Sperduto PW. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. *Lancet.* 2004;363:1665–1672.
9. DeAngelis LM, Delattre JY, Posner JB. Radiation-induced dementia in patients cured of brain metastases. *Neurology.* 1989;39:789–796.
10. Fortin D. La barriere hemato-encephalique: un facteur cle en neuro-oncologie. *Rev Neurol.* 2004;160:523–532.
11. Pardridge WM. The blood-brain barrier: bottleneck in brain drug development. *NeuroRx.* 2005;2:3–14.
12. Pardridge WM. Targeting neurotherapeutic agents through the blood-brain barrier. *Arch Neurol.* 2002;59:35–40.
13. Newton HB, Slivka MA, Volpi C, et al. Intra-arterial carboplatin and intravenous etoposide for the treatment of metastatic brain tumors. *J Neurooncol.* 2003;61:35–44.
14. Newton HB, Figg GM, Slone HW, Bourekas E. Incidence of infusion plan alterations after angiography in patients undergoing intra-arterial chemotherapy for brain tumors. *J Neurooncol.* 2006;78:157–160.
15. Kraemer D, Fortin D, Neuwelt EA. Chemotherapeutic dose intensification for treatment of malignant brain tumors: recent developments and future directions. *Curr Neurol Neurosci Rep.* 2002;2:216–224.
16. Fortin D, Desjardins A, Benko A, Boudrias M. Blood-brain barrier disruption enhanced chemotherapy in the treatment of malignant brain tumors: the Sherbrooke experience. *Cancer.* 2005;103:2606–2615.
17. Fortin D, Salame J, Desjardins A, Benko A. Technical modification in the intracarotid chemotherapy and osmotic blood-brain barrier disruption procedure to prevent the relapse of carboplatin-induced orbital pseudotumor. *Am J Neuroradiol.* 2004;25:830–834.
18. Duffey P, Chari G, Cartlidge NE, Shaw PJ. Progressive deterioration of intellect and motor function occurring several decades after cranial irradiation: a new facet in the clinical spectrum of radiation encephalopathy. *Arch Neurol.* 1996;53:814–818.
19. Kroll RA, Neuwelt EA. Outwitting the blood-brain barrier for therapeutic purposes: osmotic opening and other means. *Neurosurgery.* 1998;42:1083–1100.
20. Sato S, Kawase T, Harada S, Takayama H, Suga S. Effect of hypersomotic solutions on human brain tumour vasculature. *Acta Neurochir.* 1998;140:1135–1142.
21. Doolittle ND, Miner ME, Hall WA, et al. Safety and efficacy of a multicenter study using intra-arterial chemotherapy in conjunction with osmotic opening of the blood-brain barrier for the treatment of patients with malignant brain tumors. *Cancer.* 2000;88:637–647.
22. Hartz AM, Bauer B, Fricker G, Miller DS. Rapid modulation of P-glycoprotein-mediated transport at the blood-brain barrier by TNF-alpha and LPS. *Mol Pharmacol.* 2006;69:462–470.
23. Kraemer D, McAllister L, Fortin D, Doolittle N, Neuwelt EA. Association of drug delivery and clinical outcomes in human non-AIDS primary CNS lymphoma as a model to assess the impact of total dose intensity delivered to the CNS. *Neurosurgery.* 2001;48:1033–1041.
24. Ebert BL, Niemierko E, Shaffer K, Salqia R. Use of temozolomide with other cytotoxic chemotherapy in the treatment of patients with recurrent brain metastases from lung cancer. *Oncologist.* 2003;8:69–75.
25. Postmus PE, Haaxma-Reiche H, Gregor A, et al. Brain-only metastases of small cell lung cancer; efficacy of whole brain radiotherapy. An EORTC phase II study. *Radiother Oncol.* 1998;46:251–260.
26. Postmus PE, Smit EF. Chemotherapy for brain metastases of lung cancer: a review. *Ann Oncol.* 1999;10:753–759.
27. Anupol N, Ghamande S, Odunsi K, Driscoll D, Lele S. Evaluation of prognostic factors and treatment modalities in ovarian cancer patients with brain metastasis. *Gynecol Oncol.* 2002;85: 487–492.
28. Melichar B, Urminske H, Kohlova T, Nova M, Cesak T. Brain metastases of epithelial ovarian carcinoma responding to cisplatin and gemcitabine combination chemotherapy: a case report and review of literature. *Gynecol Oncol.* 2004;94:267–276.

29. Micha JP, Goldstein BH, Hunter JV, et al. Long-term survival in an ovarian cancer patient with brain metastases. *Gynecol Oncol.* 2004;92:978–980.
30. McMeekin SD, Kamelle SA, Vasilev SA, et al. Ovarian cancer metastatic to the brain: what is the optimal management? *J Surg Oncol.* 2001;78:194–201.
31. Boogerd G, Cuzzoni Q, Strada MR, et al. Response of brain metastases from breast cancer to systemic chemotherapy. *Cancer.* 1992;69:972–980.
32. Subramanian A, Harris A, Piggot K, et al. Metastasis to and from the central nervous system—the relatively protected site. *Lancet Oncol.* 2002;3:498–507.
33. Fenner MH, Possinger K. Chemotherapy for breast cancer brain metastases. *Onkologie.* 2002;25:474–479.
34. Christodoulou C, Bafaloukos D, Kosmidis P, et al. Phase II study of temozolomide in heavily pretreated cancer patients with brain metastases. *Ann Oncol.* 2001;12:249–254.
35. Hoerni-Simon G, Suchaud JP, Eghbali H, et al. Secondary involvement of the central nervous system in malignant non-Hodgkin's lymphoma. A study of 30 cases in a series of 498 patients. *Oncology.* 1987;44:98–101.
36. MacDonald DR, Cascino TL, Schold SC Jr, Cairncross JG. Response criteria for phase II studies of supratentorial malignant glioma. *J Clin Oncol.* 1990;8:1277–1280.