Complications associated with intraventricular chemotherapy in patients with leptomeningeal metastases

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The authors studied complications associated with intraventricular chemotherapy in patients with leptomeningeal metastases (LM). One hundred twenty consecutive patients with LM (71 females and 49 males) ranging in age from 10 to 72 years (median 42 years) were treated with involved-field radiotherapy and intraventricular chemotherapy using an Ommaya reservoir and intraventricular catheter system. The diagnosis of LM was determined by a combination of clinical presentation (114 patients); cerebrospinal fluid cytological studies (100); or neuroradiographic studies (42). Systemic tumor histological findings included breast (34 patients); non-Hodgkin’s lymphoma (22); melanoma (16); primitive neuroectodermal tumors including medulloblastoma (10); glial neoplasms, leukemia, small cell lung, nonsmall cell lung, and colon (six each); prostate and kidney (three each); and gastric cancers (two). Sixteen patients, all with non-Hodgkin’s lymphoma, also had acquired immune deficiency syndrome.

Patients received one to four (median two) chemotherapeutic drugs and underwent a total of 1110 cycles of intraventricular chemotherapy (median 10). Intraventricular chemotherapy administration and diagnostic Ommaya reservoir punc- tures totaled 4400, with a median of 46 per patient. Complications included aseptic/chemical meningitis (52 patients); myelosuppression due to intraventricular chemotherapy (21); catheter-related infections (nine); unidirectional catheter obstruction (six); intraventricular catheter malpositioning (two); Ommaya reservoir exposure (two); leukoencephalopathy (two); and chemotherapy-related myelopathy (one). There were no treatment-related deaths; however, seven patients (6%) required additional surgery for either catheter repositioning (two) or reservoir removal (five). Seven patients with catheter-related infections were treated successfully with intraventricular and systemic antibiotic drugs, thereby preserving the Ommaya system.

The authors conclude that Ommaya reservoirs are convenient and pharmacologically rational systems for administering intraventricular chemotherapy. Overall, serious complications requiring surgery are infrequent (6%) and most often secondary to catheter infections, Ommaya reservoir exposure, or initial catheter malpositioning. In the majority of instances, catheter infections may be managed medically, as may the most common complications of intraventricular chemotherapy including aseptic meningitis (43% of patients) and myelosuppression (18%).

KEY WORDS • Ommaya reservoir • intraventricular chemotherapy • complications

Leptomeningeal metastases (LM) have become increasingly common as anticancer therapies become more effective. Approximately 5% of all patients with solid tumors ultimately develop LM, a metastatic central nervous system (CNS) complication with profound implications for the affected patient. The average survival time following a diagnosis of LM is 4 to 6 months; however, some groups of patients, such as those with breast or hematological cancers, may have considerably longer survival times. Notwithstanding the limited life expectancy of individuals with LM, patients are frequently offered radiation and chemotherapy to palliate the effects of the disease. A common practice in many institutions is the use of radiation therapy directed at symptomatic or bulky signs of disease followed by the administration of intracerebrospinal fluid (CSF) chemotherapy.

Shapiro, et al., in a seminal paper about intra-CSF drug distribution, demonstrated that intralumbar administration of methotrexate (MTX) results in variable and often subtherapeutic cytotoxic drug levels in the lateral ventricles as compared with intraventricular MTX administration. As a consequence, a common practice in North American medical centers is the placement of an intraventricular catheter and subgaleal reservoir to facilitate intraventricular chemotherapeutic drug administration.

We present the 10-year experience at the University of California, San Diego, Neuro-Oncology Service, which includes 120 patients with LM treated by means of an intraventricular catheter and a particular subgaleal reservoir, the Ommaya reservoir, and report complications associated with the use of these devices.

Clinical Material and Methods

Study Population

One hundred twenty patients with LM (49 males and 71 females) were treated between July 1986 and June 1996 at the University of California, San Diego Gildred Cancer
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Center. These patients ranged in age from 10 to 72 years (median 42 years). Approximately 80% of these cases have been reported previously in a variety of papers discussing various aspects of evaluating and treating LM.5,8,10–12,17 All patients, or their guardians, gave informed consent and were treated prospectively in a similar manner. Inclusion criteria for entry into the study consisted of 1) Karnofsky performance scale (KPS) score28 greater than 60%; 2) expected survival time greater than 3 months; 3) diagnosis of LM made by compatible clinical or neuroradiographic findings with or without a positive CSF cytological study; 4) no prior intra-CSF therapy; and 5) desire of the patient for further therapy. Approximately 20% of patients evaluated for entry in the study were excluded for failing to meet these criteria. The KPS score for patients tested at the time of diagnosis of LM ranged from 70 to 100% (median 80%). One hundred patients had cytologically documented LM that required one (76 patients), two (20 patients), or three (four patients) lumbar punctures for diagnosis. In the remaining 22 patients, LM was documented by CSF abnormalities and a clinical syndrome or neuroradiographic findings consistent with LM. The disease was diagnosed in all patients after an initial systemic tumor presentation ranging from 2 to 28 months (median 6 months) after the primary tumor presentation. Patients presented with a variety of primary tumors including: breast (34 patients); non-Hodgkin’s lymphoma (22); melanoma (16); primitive neuroectodermal tumors (10); glial neoplasms, leukemia, small cell lung, nonsmall cell lung, and colon (six each); prostate and kidney (three each); and gastric cancers (two). In 16 of the patients with non-Hodgkin’s lymphoma the acquired immune deficiency syndrome was a comorbid diagnosis.

The presenting neurological examination included the following findings: headache (84 patients); solitary or multiple cranial neuropathies (78); ataxia (42); cauda equina syndrome (34); myelopathy (16); meningismus (12); radiculopathy (eight); and confusion (six). The extent of systemic disease was characterized as follows: in 19 patients, the primary tumor was in remission (that is, relapse manifested as isolated LM) and therefore only regional chemotherapy and limited-field CNS radiation were used. In the remaining 101 patients, LM occurred in the context of active systemic disease for which a variety of tumor-specific systemic chemotherapies were used in 60 patients) in addition to regional chemotherapy and limited-field CNS radiation. No patient had received high-dose systemic MTX, cytosine arabinoside (ara-C), or thio- triethylene phosphoramidate (TEPA) regimens with activity against LM.1,2,9,36

Imaging Techniques

All patients underwent placement of an intraventricular catheter and subgaleal reservoir, after which an extent-of-disease evaluation (CNS staging) was undertaken. This evaluation included the following: 1) cranial contrast-enhanced computerized tomography (CT) or magnetic resonance (MR) imaging; 2) spinal contrast-enhanced MR or CT myelography if clinically indicated (by myelopathy, radiculopathy, or back pain) or if CSF flow studies documented a spinal subarachnoid block; and 3) indium-111-diethylene triamine pentaacetic acid (111In-DTPA) CSF flow study following Ommaya reservoir placement.5–8,10–12,17

Gamma Imaging. As previously described,5–7,10,11 imaging was performed with a gamma camera (Elscint, Tel Aviv, Israel) equipped with a medium-energy collimator. Static images were acquired in a 128 X 128-pixel matrix using a dedicated computer. Studies were conducted using a large field of view camera with dual energy windows using a 20% window centered over 174 keV and 247 keV gamma-ray peaks of indium-111. Each image was acquired for either 2 minutes or 100,000 counts.

Following sterile precautions, 0.5 ml of 111In-DTPA (median dose 0.5 mCi) was injected into the intraventricular reservoir by means of a 25-gauge butterfly needle. After the radionuclide was injected, the catheter system was flushed with 2 ml of autologous CSF. No barbotage of the intraventricular reservoir was performed. Thereafter images were obtained every 5 minutes for 60 to 90 minutes, repositioning the patient and the scintillation camera as necessary. Abnormal radionuclide flow studies were categorized according to location of the CSF flow abnormality and defined by the CSF compartment at which radionuclide block occurred.5–10,11

Imaging With MR and CT Methods. Cranial CT scans were obtained using a commercial scanner (GE 9800; General Electric, Milwaukee, WI). Contiguous 10-mm-thick axial sections were obtained from the foramen magnum to the vertex before and after intravenous administration of iodinated contrast medium (Conray 43; Mallinckrodt, Inc., St. Louis, MO). Cranial MR examinations were performed on a 1.5-tesla MR imager with a superconducting magnet (Sigma; General Electric). After intravenous administration of 0.01 mmol/kg of gadolinium (Gd)-DTPA dimeglumine (Berlex Laboratories, Cedar Knolls, NJ), coronal and axial T1-weighted sequences (TR 600 msec/TE 25 msec) were obtained. All postcontrast images were obtained within 30 minutes of Gd infusion.

The spine MR images were obtained using the same 1.5-tesla superconducting magnet. Images were acquired before and after the intravenous administration of Gd-DTPA dimeglumine in a dosage of 0.1 mmol/kg of body weight. All postcontrast images were obtained within 30 minutes of Gd infusion.

Drug Schedule

All patients received intra-CSF chemotherapy according to a fixed sequence. Methotrexate was administered initially followed by cytosine arabinoside (ara-C) or thio-TEPA if clinically appropriate, and patients also received thio-TEPA if clinically appropriate.

Methotrexate. As previously reported,24,6,7,18,20,25,38 at the completion of limited-field irradiation MTX was administered intraventricularly in a concentration × time (C × T) drug schedule without use of systemic folinic acid. Administration consisted of 1) induction; 2 mg MTX in 5 ml nonbacteriostatic normal saline daily for 5 consecutive days every other week for 8 weeks (20 drug administrations, total dosage of MTX 40 mg); with or without 2) maintenance; 2 mg MTX in 5 ml normal saline daily for 5 consecutive days every 4 weeks until disease progression. Maintenance MTX was administered only to patients with a cytologically confirmed complete response and stable or
improved clinical disease following induction of intraventricularly administered MTX.

Cytosine Arabinoside. As previously reported,2,6,7,18,20,23,25,38 ara-C was administered intraventricularly on a C × T drug schedule following cytological relapse or failure to respond to intraventricular MTX. Administration consisted of 1) induction; 25 mg ara-C in 5 ml normal saline daily for 3 consecutive days every week for 4 weeks (12 drug administrations, total dosage of 300 mg); or 2) maintenance; 25 mg ara-C in 5 ml normal saline daily for 3 consecutive days once every 4 weeks until disease progression. Induction ara-C was administered only to patients demonstrating failure to respond, cytologically confirmed relapse, or clinical disease progression following intraventricularly administered MTX. Maintenance ara-C was administered only to patients with cytologically confirmed response and stable or improved disease after induction of intraventricularly administered ara-C.

Thio-TEPA. As previously reported,2,6,7,18,20,23,25,38 thio-TEPA was administered intraventricularly on a C × T drug schedule after failure to respond, cytologically confirmed relapse, or clinical disease progression following intraventricular MTX or ara-C chemotherapy. Administration consisted of 1) induction; 10 mg thio-TEPA in 5 ml normal saline daily for 3 consecutive days every week for 4 weeks (12 drug administrations; total dosage of thio-TEPA, 120 mg); or 2) maintenance; 10 mg thio-TEPA in 5 ml normal saline daily for 3 consecutive days once every 4 weeks until disease progression. Induction thio-TEPA was administered only to patients with cytologically confirmed relapse or disease progression following intraventricularly administered MTX or ara-C. Maintenance thio-TEPA was administered only to patients with cytologically proven complete response and stable or improved disease after induction of intraventricularly administered thio-TEPA.

Response Criteria

Cytological response criteria are defined based on CSF cytology as follows:6–8 1) complete response (CR), two consecutive negative CSF cytological examinations (on both ventricular and lumbar sampling) at least 1 week apart and sustained for at least 1 month; 2) partial response (PR), conversion from positive to suspicious on two consecutive CSF examinations (both ventricular and lumbar sampling) at least 1 week apart and sustained for at least 1 month; and 3) progressive disease (PD), conversion from negative on two prior consecutive examinations to positive or two consecutive positive or suspicious cytological examinations. All patients underwent weekly ventricular CSF cytological examinations and a lumbar CSF cytological examination was conducted at the conclusion of induction therapy. Clinical response criteria were based on sequential neurological examination as follows: 1) CR, resolution of all neuroradiographic signs; 2) PR, incomplete resolution of neuroradiographic signs; 3) stable disease, no change in neuroradiographic signs (<25% decrease in lesion size); and 4) PD, worsening of preexisting or new neuroradiographic signs. Neuroradiographic responses were determined following completion of involved-field radiotherapy and at the conclusion of induction intra-CSF chemotherapy.

Ommaya Reservoir Placement

Reservoir placement was performed after all patients had received a local anesthetic and 1 g of a prophylactic cephalosporin antibiotic medication intravenously prior to the skin incision. Semilunar skin incisions were made in the mid-pupillary line over the right coronal suture. Preassembled Ommaya reservoirs (Baxter, Heyer-Schulte, Deerfield, IL) with a catheter measuring 7.5 cm from the outer table of the skull were placed through a single burr hole. The wounds were closed in two layers. Ommaya reservoirs were used as soon as 4 hours after implantation.

Results

One hundred twenty patients underwent 1110 cycles of intraventricular chemotherapy with a median of 10 cycles per patient. Among the entire cohort, 4400 Ommaya punctures were performed with a median of 46 (range 10–86) Ommaya punctures per patient. Complications associated with the use of an Ommaya system can be divided into two separate domains: those related to time of surgical placement of the device (within 30 days of reservoir placement) and those occurring subsequently during instillation of intra-CSF chemotherapy.

Two patients (2%) were found to have malpositioned catheters (one in the brain parenchyma and one in the cerebral convexity subarachnoid space) and consequently required removal and replacement of the catheter system. Six patients (5%) developed a unidirectional catheter obstruction that stopped CSF from being withdrawn from the subgaleal reservoir but which allowed administration of intra-CSF drug therapy. In patients so affected, the intraventricular catheter continued to be used, but alternative CSF sampling sites were necessary to permit assessment of response to therapy. Imaging studies performed in these patients demonstrated normal CSF radioisotope flow dynamics. However, the ventricle within which the catheter system resided was coopted, suggesting ventricular wall collapse as the cause of the unidirectional catheter obstruction. Two patients (2%) developed a delayed pressure necrosis of the skin overlying the Ommaya reservoir, resulting in exposure. This occurred 2 and 6 months, respectively, after surgical placement and necessitated removal and replacement of the Ommaya system. Neither of these patients had subsequent bacterial infections.

Sixty-two (51%) of the 120 patients developed meningitis. In 52 patients (43% of the patient population) the meningitis was demonstrated to be aseptic and occurred in relationship to intra-CSF drug administration consistent with drug-induced chemical meningitis. Clinical findings
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in these patients included some combination of low-grade fever, headache, nausea, vomiting, meningismus, photophobia, and a sterile CSF pleocytosis in all patients. This was a self-limited condition in all cases and was easily managed by the coadministration of oral steroid medications. No patient required hospitalization or delay in initiating the next cycle of chemotherapy because of chemical meningitis. However, approximately 13.5% of all episodes of aseptic chemical meningitis (seven patients) required outpatient administration of intravenous fluids to mitigate dehydration seen as a consequence of nausea and vomiting. The incidence of aseptic meningitis was similar regardless of the intra-CSF agent used (MTX, ara-C, or thio-TEPA). No patient was treated with concomitant intra-CSF hydrocortisone.

In nine patients (7.5%), bacterial meningitis occurred as a consequence of catheter infection. In four instances these episodes were related to placement of the Ommaya system and occurred within 30 days of surgery, and five episodes were secondary to the iatrogenic introduction of bacteria during regional chemotherapy administration. In all nine cases, Staphylococcus epidermidis was cultured from the CSF. Following bacteriological documentation, sterilization of CSF in the first two patients encountered was achieved by removal of the Ommaya system and treatment with intravenous antibiotic drugs. Sterilization of CSF was achieved in the remaining seven patients by a combination of intravenous (vancomycin), oral (rifampin), and intraventricular (vancomycin) antibiotic drugs. In all seven patients treated in this manner the Ommaya system was preserved; however, antibiotic therapy necessitated a 2- to 3-week delay in initiating or continuing regional chemotherapy.

Twenty-one patients (18%) developed Grade III or IV myelosuppression (Common Toxicity Scale of the Cancer and Leukemia Group B), and six patients (5%) required transfusion. None of these patients developed bacterial meningitis while suffering myelosuppression. Four patients required red blood cell transfusion, and all six required platelet transfusion. All of these episodes were ascribed to complications of intra-CSF thio-TEPA therapy; however, concomitant administration of systemic chemotherapy was a factor in two instances, thereby confounding causality. No treatment-related deaths occurred. No myelosuppression was seen in patients treated with either intra-CSF MTX or ara-C unless concomitant systemic chemotherapy was administered. Systemic folic acid was not given to patients treated with intra-CSF MTX on the C × T schedule.

Three patients developed neurotoxicity directly related to chemotherapy, with permanent neurological consequences. In two patients (2%) this was manifested as a leukoencephalopathy wherein it appeared that intra-CSF chemotherapeutic materials had backed up through the brain via the track created by the intraventricular catheter. The surrounding brain was injured in a focal manner in both cases within the nondominant frontal lobe, resulting in a frontal lobe syndrome. In the third patient (1%) a presumed chemotherapy-related myelopathy developed that manifested as a spastic paraparesis. This patient displayed no evidence of LM progression either on CSF analysis or neuroimaging studies. In addition, although this individual suffered from paraplegia for many months before ultimately dying of systemic cancer, no evidence of recurrent LM was demonstrated at postmortem examination. The overall incidence of permanent neurological toxicity directly related to intraventricular chemotherapy was 3%.

Discussion

Several issues are pertinent to use of the Ommaya system for intraventricular chemotherapy administration in patients with LM. One issue involves decisions regarding appropriate candidates for intra-CSF drug therapy, which are problematic. A general consensus among neurooncologists regarding which patients with LM are candidates for aggressive combined-modality therapy include: 1) life expectancy greater than 3 months; 2) KPS scores greater than 60, implying patients are to a reasonable extent independent in activities of daily living; and 3) a patient’s desire for further therapy. Although the median survival time in patients with a diagnosis of LM is limited, the CNS may be relatively spared by CNS-directed therapies. For example, in selected women with breast cancer and LM, aggressive combined modality therapy arrests LM progression, and in the majority of such women death is a consequence of systemic organ failure.

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C × T drug schedule wherein small doses of MTX (1–2 mg) are administered every 12 to 24 hours over 3 to 5 days as compared with the standard high-dose (10–15 mg) twice-weekly schedule. With this C × T method, cytotoxic levels of MTX are maintained and lower peak CSF levels are realized. Although this method has been used to treat LM in instances of childhood leukemic meningitis, acquired immune deficiency syndrome–related lymphomatous meningitis, carcinomatous meningitis caused by breast cancer, and melanoma, no comparative trials exist demonstrating a treatment advantage with standard intermittent bolus therapy versus C × T intra-CSF drug administration.2,4,12–14 The second limitation of intraventricular chemotherapy, regardless of the drug or schedule used, is that few agents exist for treating patients with LM: only three agents are available for intra-CSF use, including MTX, ara-C, and thio-TEPA.6,7,9,23,35,38 Novel treatments such as the slow-release product DepoFoam ara-C are needed if significant improvements in treating these patients are to be realized.16

The final issue discussed here is that complications of intra-CSF drug therapy are not uncommon and may profoundly affect patients with LM and Ommaya systems.3,26,31–34,37 Complications of placing the Ommaya reservoir are well known and fortunately infrequent. Malpositioning of the catheter tip may be circumvented by obtaining postoperative plain skull x-ray films and performing radionuclide ventriculography. In our experience, clinically significant hemorrhage is essentially absent, which we believe reflects meticulous attention to preoperative coagulation parameters (prothrombin time, partial thromboplastin time, bleeding time, and platelet count). Infection is unfortunately a difficult problem arising from Ommaya placement or as a consequence of its use. In both circumstances, skin flora, primarily *S. epidermidis*, contaminates the system and results in an iatrogenic bacterial meningitis. Treatment of these infections has changed at our institution as we have become confident of our antibiotic strategy. In our initial experience, following bacteriological proof of CSF contamination, the Ommaya system was removed and bacteria-specific antibiotic drugs were initiated. Once bacteriological sterilization was achieved, a second Ommaya was inserted, permitting resumption of intra-CSF drug therapy. Our present policy is to treat with the Ommaya system in situ using intravenous, oral, and intra-Ommaya antibiotic drugs, which in our experience involves a combination of vancomycin and rifampin. For all recent infections regardless of relationship to surgery, we have been successful in preserving the Ommaya system and avoiding a repeated operation. Notwithstanding our favorable results, this approach will not be successful in all instances, and occasionally an Ommaya system will need to be removed. Other complications of Ommaya reservoir use relate primarily to the toxicity of drugs administered directly into the CNS. The majority of these complications are inflammatory and transient in nature and are easily managed with antipyretics, antiepileptics, and corticosteroids. Rarely, as seen in three of our 120 patients, direct neurotoxicity occurs that manifests either as a leukoencephalopathy or a myelopathy.29,31,33 These complications may be idiosyncratic or in some instances related to the total intra-CSF drug dosage and delayed drug clearance.

**Conclusions**

Ommaya systems are convenient and pharmacologically rational methods for administering chemotherapy. Overall, serious complications requiring surgery are infrequent (6% in our series) and most often secondary to catheter infections, Ommaya reservoir exposure, and initial catheter malpositioning. In the majority of instances of Ommaya system infection, the catheter may remain in place and the infection can be managed medically, as can the most common complication of intraventricular chemotherapy, the induction of an aseptic chemical meningitis.

**References**

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