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Intra-arterial Chemotherapy in the Treatment of Brain Tumors

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NEUROSCIENCE PROGRAM

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and
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This continuing medical education activity is authored by Virginia Stark-Vance, M.D., a board-certified medical oncologist in private practice, and Warren Whitlow, M.D., a board-certified neuroradiologist associated with Texas Neuroradiology. Both are members of the medical staff at Presbyterian Hospital of Dallas.

PURPOSE/CONTENT & TARGET AUDIENCE

This material will update internal medicine, primary care and specialty physicians' skills and knowledge of intra-arterial chemotherapy for malignant brain tumors including indications, toxicity, patient candidates and risks.

EDUCATIONAL OBJECTIVES

After studying these materials, participants should be able to:

- State and indicate the rationale for using intra-arterial chemotherapy in the treatment of primary brain tumors, including its benefits, risks and limitations;
- Discuss the toxicity of intra-arterial chemotherapy agents;
- Identify appropriate patient candidates for intra-arterial chemotherapy;
- And describe the advantages and disadvantages of treating malignant glioma with intra-arterial chemotherapy.

Intra-arterial Chemotherapy in the Treatment of Brain Tumors

Barry Foster, a 42-year-old businessman from Arlington, TX, presented to his ophthalmologist in May 1999, complaining of blurred vision. He had experienced headaches for several months, which he thought were exacerbated by stress. However, his ophthalmologist noted mild papilledema and referred him for a MRI.*

The MRI revealed a 7 x 6 x 5 cm mass with its epicenter in the right thalamus. No enhancement was noted. A stereotactic brain biopsy revealed anaplastic astrocytoma. Mr. Foster was referred to a radiation oncologist and a medical oncologist and received 3-D conformal radiation therapy and concurrent nitrosourea (BCNU) chemotherapy. A follow-up MRI in September 1999 showed a ring of enhancement in the right thalamus; a positron emission tomography (PET) scan showed radionuclide uptake consistent with residual tumor.

Mr. Foster was given a five-day course of temozolomide (Temodar®), an oral chemotherapy agent. The subsequent MRI scan showed no evidence of disease progression, but Mr. Foster tolerated Temodar poorly and experienced severe thrombocytopenia. He then received two cycles of irinotecan (Camptosar®), which he also tolerated poorly.

He was evaluated for Gamma Knife radiosurgery and received a stereotactic boost of 3000 cGy to the residual tumor. Despite these interventions, a follow-up MRI scan in January 2000 showed evidence of tumor progression.

Mr. Foster's MRI scans were reviewed by a neuroradiologist, who felt that he would be a good candidate for intra-arterial chemotherapy with carboplatin. Mr. Foster was admitted for his first cycle of treatment January 13, 2000, and he received a total dose of 600 mg into the right internal carotid artery and the right posterior cerebral artery.

Examining diagnostic angiograms

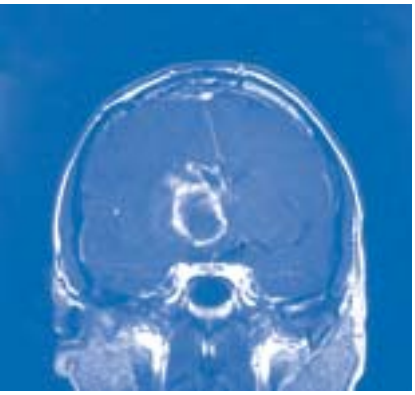
He tolerated the procedure well and was observed overnight in the intensive care unit. He was followed as an outpatient by his medical oncologist and his blood counts and neurological examination remained stable.

Over the next year, he received a total of eight courses of carboplatin. His tumor remained stable over that period of time, and he remained free of toxicity between courses of intra-arterial chemotherapy.

** The patient's name has been changed to protect his privacy.*

RATIONALE AND HISTORICAL BASIS OF INTRA-ARTERIAL CHEMOTHERAPY

The treatment of primary cerebral neoplasms is limited by multiple factors common to other types of systemic neoplasms and by the unique sensitivity of the brain to debilitating injury. Primary brain tumors cause permanent injury and death despite tumor volumes of only a few cubic centimeters. Most patients succumb to local recurrence of the tumor; rarely do primary brain tumors metastasize outside the central nervous system. Because of the need for multiple types of interventions to achieve tumor control, the treatment of primary central nervous system tumors involve multiple disciplines, including neurosurgery, radiation oncology, medical oncology, neurology and increasingly, neuroradiology.



MRI, Jan. 2000

Chemotherapy in the treatment of primary tumors is limited by the physiochemical properties of the drugs, since many drugs that appear to be effective against brain tumor cell lines in vitro appear to have little to no penetration across the intact blood-brain barrier.[1]

It is well recognized that many tumors disrupt the blood-brain barrier, and the brain-adjacent-to-tumor also exhibits increased permeability. Nevertheless, achieving cytotoxic levels of a systemically administered chemotherapeutic agent almost invariably leads to other end-organ effects. In patients receiving treatment with nitrosoureas, for example, both myelosuppression and pulmonary toxicity can be lethal.[2]

Many primary brain tumors—malignant glioma being the most common example—tend to recur within a few centimeters of the original site following surgery and radiation therapy.[3] Therefore, the delivery of cytotoxic agents via the arterial supply of the tumor should, at least in theory, provide a higher concentration of the agent to the tumor and the adjacent brain at risk. Studies using intra-arterial (IA) radio labeled chemotherapy agents such as BCNU and cisplatin have demonstrated a consistent advantage in the concentration of drug within the brain, in some studies up to 50-fold over IV infusion.[4, 5]

Successful treatment with intra-arterial chemotherapy also depends upon the characteristics of the drug to be administered. Ideal candidates for intra-arterial agents include highly lipid soluble drugs, drugs that have a rapid metabolism or excretion and drugs that have demonstrated efficacy against the tumor.[6] Germ cell tumors, lymphomas and oligodendrogliomas are sensitive to a large number of chemotherapeutic agents, while malignant gliomas respond to relatively few.[7]

EARLY STUDIES AND RANDOMIZED TRIALS

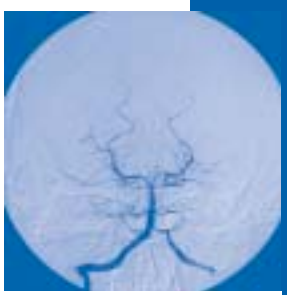
BCNU (carmustine), cisplatin, VP-16 (etoposide), AZQ (diazequone), ACNU (nimustine), carboplatin and multiple other agents have been studied in clinical trials of intra-arterial chemotherapy, usually in malignant glioma.[8] Many of the early Phase I or Phase II studies of BCNU in recurrent malignant gliomas reported high response rates and median survivals of 23-50 weeks after the initiation of IA therapy.[9, 10, 11, 12] Studies using cisplatin also demonstrated high response rates with median survivals of 25-38 weeks.[13, 14] Most studies of IA chemotherapy administered before or after radiation therapy in newly diagnosed patients with malignant glioma have shown an improvement in overall survival from historical controls of radiation therapy alone.[15]

However, only two randomized clinical trials in the U.S. have studied intra-arterial chemotherapy in one of the arms. The first study, initiated in 1983 and sponsored by the Brain Tumor Cooperative Group, randomized patients with high-grade glioma to receive intravenous or intra-arterial BCNU with or without intravenous 5-fluorouracil. In the trial, 167 patients received intra-arterial BCNU and 148 received intravenous BCNU. The authors concluded that there was no difference in survival and that intra-arterial BCNU was more toxic.[16] A second study by the Brain Tumor Cooperative Group randomized patients with recurrent malignant gliomas to intravenous PCNU (a nitrosourea) or intra-arterial cisplatin. Patients in this study receiving IA cisplatin had a slightly shorter overall median survival.[17] The toxicity of intra-arterial administered BCNU and cisplatin in these studies included leukoencephalopathy, visual loss, neurological deterioration, seizures and hearing loss.[18, 19] Despite intra-arterial drug doses often exceeding the usual intravenous doses of the same drug, myelosuppression was usually not seen.

INTRA-ARTERIAL CHEMOTHERAPY TODAY

Advances in neuro-imaging and interventional neuroradiology have been substantial since the first patients treated with intra-carotid chemotherapy 20 years ago. MRI has allowed more precise definition of tumor volumes in three planes, but it has also identified patients who are poor candidates for intra-arterial chemotherapy because of other lesions too small to be seen on CT. Modern microcatheters are tapered and slightly curved at the tip to allow placement above the ophthalmic artery in the anterior circulation and above the anterior inferior cerebellar artery in the posterior circulation, avoiding ocular and otologic toxicity. The radio-opaque catheter tip is visible during the procedure, allowing precise guidance by the neuro-radiologist.

The presence of significant amounts of tumor distant from the index lesion, tumor in the posterior fossa or tumor crossing the midline, are relative contraindications for intra-arterial chemotherapy.



Diagnostic angiography

In recent years, carboplatin has been more frequently studied in centers using intra-arterial administration. Carboplatin has the advantage over cisplatin, because it causes less neurotoxicity and ototoxicity; myelosuppression, while dose limiting, is transient. Leukoencephalopathy, more commonly reported with IA BCNU, appears to be less common with IA carboplatin.[20]

IA carboplatin has not yet been studied in a randomized clinical trial. However, a number of investigators have reported radiographic responses, improved overall survival and a more favorable toxicity profile than previous studies with cisplatin. Median survivals in patients with recurrent malignant glioma have been reported from 36-62 weeks from the initiation of therapy.[21, 22, 23]

A unique complication of intra-arterial chemotherapy is stroke, either related to embolic phenomena from the catheter tip or from carotid plaques. This risk is related to both the technique of the procedure itself and to the intrinsic stroke risk of the population. However, in most centers performing intra-arterial chemo-therapy regularly, the incidence of cerebral vascular accidents is less than 5%. The reported complication rate relating to arterial puncture or hemorrhage is very low.[24]

Radiologist administers carboplatin in angiogram suite.

PATIENT SELECTION FOR INTRA-ARTERIAL CHEMOTHERAPY

Patient selection for intra-arterial chemotherapy at most centers may be dictated by a local treatment protocol, but in general, it includes patients with a single supratentorial malignant brain neoplasm (limited to one cerebral hemisphere), good performance status, normal hepatic and renal function, and the ability to give informed consent.

Patients who have had previous chemotherapy may not have normal bone marrow reserve; however, because myelosuppression is usually not dose-limiting, patients who cannot tolerate systemic chemotherapy may be able to tolerate intra-arterial carboplatin.

THE TECHNIQUE OF INTRA-ARTERIAL CHEMOTHERAPY

Patients who are suitable candidates for intra-arterial chemotherapy are identified by a medical oncologist and a neuro-radiologist. They review the MRI scans of the patient—particularly the arterial blood supply of the tumor—and decide on the initial dose of chemotherapy and, if divided among arterial branches, how it will be divided.

The patient is scheduled for the procedure by the neuroradiologist. On the day of the procedure, the patient is admitted to the hospital and taken to the angiography suite. General anesthesia is administered by an anesthesiologist. The patient is premedicated with phenobarbital, an anticonvulsant and an antiemetic, such as ondansetron (Zofran®).

Following insertion of the catheter in the femoral artery, the patient is fully anticoagulated with heparin. An initial cerebral angiogram determines the anatomy of the normal brain and vessels supplying the tumor. A microcatheter is inserted into the artery and contrast is injected to verify its position.

The chemotherapy dose to be administered will be divided among the arterial supply to the tumor, but the distribution is weighted according to the usual blood flow to the normal cerebral hemisphere: 60% middle cerebral, 20% anterior cerebral, 15% posterior cerebral and 5% perforating arteries.[25]

Following the procedure, anticoagulation is reversed and the femoral catheter is removed. The patient is awakened from anesthesia and brought to the recovery room. Hemostasis at the femoral puncture site is monitored frequently, and the patient continues on anticonvulsant and antiemetic support throughout the evening. Most patients are monitored overnight in the intensive care unit and discharged home the following morning after the procedure.

PATIENTS EXPERIENCE AT PRESBYTERIAN HOSPITAL OF DALLAS

Intra-arterial chemotherapy has been performed since 1999 by physicians on the medical staff at Presbyterian Hospital of Dallas (PHD). The 20 patients treated have had primary or metastatic brain tumors refractory to standard therapy and/or unresectable lesions. The majority of patients treated by medical staff physicians at PHD have had recurrent malignant glioma, but other subtypes have included malignant ependymoma, primitive neuro-ectodermal tumor, pleomorphic xanthroastrocytoma and oligodendroglioma. One patient who had failed multiple prior treatments for a solitary metastasis of lung cancer to the central nervous system has also been treated.

The majority of patients treated have had reassessment of their tumor by MRI after the second cycle (two administrations, four weeks apart) of treatment. Patients who have had response to treatment or stabilization have completed at least four cycles of treatment. Patients with significant residual tumor after four cycles, as determined by MRI or PET, are given the option of further treatment cycles until disease response or progression.

Treatment related toxicities have been limited to focal seizures (one patient); cerebral vascular accident (one patient); ocular toxicity (one patient); transient neurological worsening (two patients). The majority of patients experience fatigue and nausea in the days following chemotherapy, but most characterize it as mild.

All patients have failed other forms of therapy, and many are not candidates for other types of salvage therapy; therefore, the impact of the procedure on expected survival is difficult to ascertain. Three patients with malignant glioma who had stabilization or response to the tumor treated with intra-arterial chemotherapy had progression of glioma distant from the treated tumor. Among the 20 patients treated at PHD, three died of complications unrelated to the tumor, and ten died of disease progression. Seven patients remain alive between 6-30 months after initial treatment.

Mr. Foster, our case-study patient, remained neurologically stable for several months following the completion of eight courses of intra-arterial carboplatin chemotherapy. He eventually developed disease progression and died, ten months after the completion of his IA chemotherapy.

CONCLUSION

Intra-arterial chemotherapy is a generally well tolerated treatment for brain neoplasms refractory to other forms of therapy. The relative lack of myelosuppression associated with intra-arterial chemotherapy makes it one of the few treatment alternatives available to heavily pre-treated patients. In patients with recurrent but localized tumors, the administration of carboplatin into the tumor's arterial supply may allow prolonged stabilization and control without the neurotoxicity or ototoxicity associated with cisplatin.

Good candidates for the procedure have a single localized lesion on MRI, good performance status, and no other serious co-morbid medical problems. Patients should be informed of the potential risks and toxicities of the procedure, including the risk of general anesthesia and arteriography. For more information regarding intra-arterial chemotherapy call 1-800-4-Presby.

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1. True or False: Malignant primary brain tumors often spread throughout the body.

2. True or False: Because of the blood brain barrier, drug therapy is ineffective in the treatment of brain tumors.

3. True or False: The early trials of chemotherapy administered intra-arterially used the drugs BCNU (carmustine) and cisplatin.

4. True or False: Patients with several metastases scattered throughout the cerebral hemispheres are good candidates for intra-arterial chemotherapy.

5. True or False: Neuroradiologists choose patients for intra-arterial chemotherapy based on a localized arterial supply of a well-defined malignant tumor.

6. True or False: Medical oncologists can choose from a variety of drugs, all equally effective in the treatment of malignant glioma.

7. True or False: Patients who have a tumor mass on CT or MRI but have never undergone biopsy are good candidates for intra-arterial chemotherapy.

8. True or False: Intra-arterially administered carboplatin appears to have less neurotoxicity than IA BCNU and IA cisplatin.

FACULTY DISCLOSURE

The intent of this disclosure is not to prevent a faculty member with commercial affiliations from presenting, but rather to provide participants with information from which they may make their own judgements.

Dr. Warren D. Whitlow's presentation includes discussions of investigational or unlabeled uses of Intra-arterial chemotherapy for brain tumors.

Dr. Virginia I. Stark-Vance's presentation includes discussions of investigational or unlabeled uses of Intra-arterial chemotherapy of carboplatin.

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