Convection-enhanced delivery of paclitaxel for the treatment of recurrent malignant glioma: a Phase I/II clinical study

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Object. A minority of patients with recurrent glioblastomas multiforme (GBMs) responds to systemic chemotherapy. The authors investigated the safety and efficacy of intratumoral convection-enhanced delivery (CED) of paclitaxel in patients harboring histologically confirmed recurrent GBMs and anaplastic astrocytomas.

Methods. Fifteen patients received a total of 20 cycles of intratumoral CED of paclitaxel. The patients were observed daily by performing diffusion-weighted (DW) magnetic resonance (MR) imaging to assess the convective process and routine diagnostic MR imaging to identify the tumor response. Effective convection was determined by the progression of the hyperintense signal within the tumor on DW MR images, which corresponded to a subsequent lytic tumor response displayed on conventional MR images. Of the 15 patients, five complete responses and six partial responses were observed, giving a response rate of 73%. The antitumor effect was confirmed by one biopsy and three en bloc resections of tumors, which showed a complete response, and by one tumor resection, which demonstrated a partial response. Lack of convection and a poor tumor response was associated with leakage of the convected drug into the subarachnoid space, ventricles, and cavities formed by previous resections, and was seen in tumors containing widespread necrosis. Complications included transient chemical meningitis in six patients, infectious complications in three patients, and transient neurological deterioration in four patients (presumably due to increased peritumoral edema).

Conclusions. On the basis of our data we suggest that CED of paclitaxel in patients with recurrent malignant gliomas is associated with a high antitumor response rate, although it is associated with a significant incidence of treatment-associated complications. Diffusion-weighted MR images may be used to predict a response by demonstrating the extent of convection during treatment. Optimization of this therapeutic approach to enhance its efficacy and reduce its toxicity should be explored further.

Key Words • brain neoplasm • convection-enhanced delivery • paclitaxel • diffusion-weighted imaging

Malignant gliomas are invariably fatal; they display a well-established lack of response to chemotherapy, which is mainly due to the poor penetration of chemotherapeutic drugs across the BBB into the tumor. Although the BBB is somewhat disrupted at the core of a tumor, it is largely intact at the tumor margins, where cells actively engaged in invasion and proliferation are located. In an attempt to bypass the BBB, intratumoral chemotherapy has been applied using various methods including direct injection, intracavitary topical application, chronic low-flow microinfusion, and controlled-release polymer implants. The efficacy of intratumoral drug administration, however, is greatly restricted by the poor diffusion of drugs throughout the tumor and brain interstitium, resulting in the presence of therapeutic drug levels in a relatively small volume of tissue surrounding the drug source. Poor drug delivery to the CNS therefore limits the use of many potentially effective antitumor drugs.

Fluid convection, or bulk flow, which occurs in brain interstitial fluid under normal conditions, with vasogenic edema, and after infusion of solutions directly into brain parenchyma, is a promising new method for the distribution of drugs into brain and tumor tissue. Recently, it has been shown that fluid convection, established by maintaining a pressure gradient during interstitial infusion, can supplement simple diffusion to enhance the distribution of large and small molecules in brain or tumor tissue while achieving in situ drug concentrations that are several orders of magnitude greater than those achieved by systemic administration. The predicted concentration profile is relatively flat until it declines precipitously at the flow front, providing control over undesired toxicity.

Convection-enhanced delivery of various drugs and molecules is currently under investigation for the treatment of malignant brain tumors. These studies include the delivery of immunotoxins, such as cytotoxic proteins and Pseudomonas toxins conjugated to a targeting construct, to increase specificity and enhance the safety of the approach.

Paclitaxel (Taxol) is an antineoplastic agent with proven antimitosis and antitumor activity against advanced ovarian, breast, lung, and head and neck cancers. Paclitaxel acts by promoting the assembly of microtubules into a meta-

Abbreviations used in this paper: BBB = blood–brain barrier; CED = convection-enhanced delivery; CR = complete response; CSF = cerebrospinal fluid; CT = computerized tomography; DW = diffusion-weighted; GBM = glioblastoma multiforme; MR = magnetic resonance; PR = partial response.
stable structure that the cell cannot disassemble.\textsuperscript{11} The efficacy of paclitaxel against malignant brain tumors has recently been examined. In vitro and in vivo animal studies have shown it to be an effective drug against gliomas;\textsuperscript{22,23} however, pharmacokinetic evidence from clinical trials indicates that paclitaxel penetrates the intact BBB poorly and, thus, cannot be delivered by routine systemic administration.\textsuperscript{5,9}

Diffusion-weighted MR imaging enables the physician to form a noninvasive characterization of biological tissues based on their water diffusion characteristics.\textsuperscript{1} We have recently shown that DW MR imaging may serve as a surrogate marker in assessing the propagation of the convective wave of paclitaxel in brain tumors and in the prediction of a tumor response in tumor volumes covered with convection.\textsuperscript{14}

We evaluated the intratumoral CED of paclitaxel in 15 patients with histologically confirmed recurrent malignant glioma. The goals of the study were to assess the safety of the approach as well as the neuroimaging and clinical responses of patients to this therapeutic approach.

Clinical Material and Methods

Study Design

This study was an open-label, prospective, Phase I/II clinical trial of intratumoral paclitaxel administration by enhanced convection. The primary objective was to evaluate the safety of CED of paclitaxel in patients with recurrent malignant gliomas; secondary objectives included evaluations of neuroimaging and clinical responses to the drug.

Characteristics of Patients and Tumors

Approval was obtained from the local institutional review board and the Ministry of Health before initiation of the study. Fifteen adult patients with recurrent malignant gliomas (13 GBMs and two anaplastic astrocytomas), who had previously undergone radical resection, radiotherapy, and, in five patients, chemotherapy for their initial tumors, were included in the study. Tumor volumes ranged between 6 and 148 cm\textsuperscript{3}. All patients had a Karnofsky Performance Scale score of at least 70 and harbored a tumor that was measurable, progressive, and enhancing on MR images. The patients were fully coherent and had signed an informed consent form. Patients were excluded from the study if they had received radiotherapy or any chemotherapy within 8 weeks before enrollment or if they had ever received paclitaxel. Additional exclusion criteria were elevated liver enzymes (> three times the upper limit of normal), serum creatinine (> 3 mg/dl), neutrophil count (< 1500/\mu l), platelet count (< 100,000/\mu l), and hemoglobin (< 8 g/dl). Before initiation of therapy, the tumor was histologically confirmed by a stereotactic biopsy at the time of catheter placement. The presence of multifocal lesions or brainstem and/or cerebellar involvement served as exclusion criteria. The characteristics of the patients are summarized in Table 1.

Operative Technique

Surgical Procedures. On the day of surgery, at the patient’s bedside a stereotactic head frame (CRW frame; Radionics, Inc., Burlington, MA) was applied to the patient’s head in a routine fashion. Contrast-enhanced CT scanning was performed with the aid of a stereotactic localizer. The brain was scanned using 5-mm contiguous slices. The coordinates for the biopsy site and catheter placement were selected and documented. Initially, the catheters were placed empirically within the center of the enhancing tumor mass. Subsequently, the catheters were placed within the enhanc-

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex, Time to Current No. of Previous Tumor Resections</th>
<th>No. of Previous Tumor Resections</th>
<th>Previous Chemo</th>
<th>KPS Score</th>
<th>Tumor Location</th>
<th>Histological Grade†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>78, F 12</td>
<td>1</td>
<td>no</td>
<td>90</td>
<td>rt frontal</td>
<td>IV</td>
</tr>
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<td>4</td>
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<td>80</td>
<td>rt frontal</td>
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</tr>
<tr>
<td>3</td>
<td>46, M 6</td>
<td>1</td>
<td>PCV</td>
<td>70</td>
<td>rt parietal</td>
<td>IV</td>
</tr>
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<td>4</td>
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<td>1</td>
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<td>100</td>
<td>lt frontal</td>
<td>IV</td>
</tr>
<tr>
<td>5</td>
<td>61, M 7</td>
<td>1</td>
<td>no</td>
<td>80</td>
<td>rt temporoparietal</td>
<td>IV</td>
</tr>
<tr>
<td>6</td>
<td>55, F 6 — 1st‡</td>
<td>2</td>
<td>Gliadel wafer during initial surgery</td>
<td>90</td>
<td>rt frontal</td>
<td>IV</td>
</tr>
<tr>
<td>7</td>
<td>30, M 10</td>
<td>1</td>
<td>no</td>
<td>80</td>
<td>lt parietal</td>
<td>IV</td>
</tr>
<tr>
<td>8</td>
<td>70, M 6</td>
<td>1</td>
<td>no</td>
<td>70</td>
<td>rt temporal</td>
<td>IV</td>
</tr>
<tr>
<td>9</td>
<td>56, F 24</td>
<td>1</td>
<td>no</td>
<td>100</td>
<td>rt frontal</td>
<td>IV</td>
</tr>
<tr>
<td>10</td>
<td>51, M 6</td>
<td>1</td>
<td>no</td>
<td>70</td>
<td>lt frontal</td>
<td>IV</td>
</tr>
<tr>
<td>11</td>
<td>64, M 11</td>
<td>1</td>
<td>no</td>
<td>90</td>
<td>rt parietal</td>
<td>IV</td>
</tr>
<tr>
<td>12</td>
<td>51, M 31</td>
<td>1</td>
<td>Gliadel wafer during initial surgery; PCV</td>
<td>90</td>
<td>lt frontoparietal</td>
<td>III (mixed astro-o)</td>
</tr>
<tr>
<td>13</td>
<td>35, M 4</td>
<td>1</td>
<td>no</td>
<td>100</td>
<td>lt frontoparietal</td>
<td>IV</td>
</tr>
<tr>
<td>14</td>
<td>65, M 4</td>
<td>1</td>
<td>temozolomide</td>
<td>90</td>
<td>lt parietooccipital</td>
<td>IV</td>
</tr>
<tr>
<td>15</td>
<td>59, M 6</td>
<td>2</td>
<td>Gliadel wafer implanted after 1st recurrence</td>
<td>90</td>
<td>rt temporal</td>
<td>IV</td>
</tr>
</tbody>
</table>

* All patients had received previous radiotherapy. Abbreviations: astro-oligo = astrocytoma–oligodendroglioma; chemo = chemotherapy; KPS = Karnofsky Performance Scale; PCV = procarbazine, lomustine, and vincristine.
† Grades based on the World Health Organization classification.
‡ This patient was treated two times for the second recurrence.
ing tumor, as distant as possible from cystic or necrotic cavities and from the ventricular system. A single intravenous dose of an antibiotic agent (1 g of cefazolin) was given preoperatively. The patient was taken to the operating room and given a local anesthetic agent; one or two burr holes were then placed and a biopsy was obtained and submitted for frozen-section examination. On confirmation of the diagnosis of recurrent malignant glioma, the distal portion of a silicone catheter that is used for a ventriculoperitoneal shunt (Medtronic Neurosurgery, Goleta, CA) was cut to obtain a single opening at the tip and was placed in the selected target by using coordinates obtained during the CT planning. The catheters were tunneled subcutaneously and secured to the scalp. After completion of the procedure, the patients underwent MR imaging to ensure the appropriate location of the catheter within the tumor. Following this, the patients were transferred to the neurosurgical department, where initiation of infusion took place.

Dose and Infusion Parameters

The first three patients received 7.2 mg of paclitaxel per day, which had been diluted in 6 ml of normal saline. Infusion took place over a 24-hour period for 5 days. All other patients received 3.6 mg of paclitaxel per day, which had been diluted in 6.6 ml of normal saline in a similar fashion. The infusion rate in all patients was 0.3 ml/hour.

The infusion was performed using a syringe pump (model 2010; Medfusion Systems, Norcross, GA). Non–polyvinyl chloride tubing connected the pump to the distal portion of the catheter. The syringe and the paclitaxel were replaced every 12 hours to prevent precipitation or crystallization of the paclitaxel.

Patients were eligible to receive up to two additional cycles of therapy if an initial response was observed.

Patient Care

Patients were admitted to the neurosurgical department following the operation and were monitored for hemodynamic and neurological statuses. All patients received dexamethasone (32 mg/day) and valproate (1200 mg/day) for seizure prevention. Phenytoin therapy was discontinued in all patients before CED of paclitaxel because of reports of increased seizure activity in patients who had received concomitant systemic paclitaxel and phenytoin. The steroid dosage was tapered in all patients immediately after completion of the treatment period.

Imaging Studies

Equipment and Software. Data were acquired using a 0.5-tesla interventional MR imaging machine (Signa SP; General Electric Medical Systems, Milwaukee, WI) with a standard birdcage head-coil (General Electric) at the Chaim Sheba Medical Center. Image analysis was performed with the aid of a Pentium III personal computer by using a software package (Interactive Data Language [version 3.6.1]; Research Systems, Inc., Boulder, CO).

Imaging. Line scan DW MR images, 10 Gd-enhanced T1-weighted MR images, and T2-weighted MR images were obtained to monitor the patients before, during (daily), and periodically (monthly) following treatment. The images were acquired using 5-mm slices, two signal averages, and a 22 × 16-cm field of view. The following parameters were used for image acquisition: for T2-weighted MR images, a 256 × 128 matrix, TR 3000 msec, and TE 95 msec; for T1-weighted MR images a 256 × 128 matrix, TR 500 msec, and TE 14.5 msec; and for DW MR images, a 128 × 64 matrix, b factor 1000 seconds/mm², 6 value 31 msec, Δ value 51 msec, TR 2907 msec, and TE 105.2 msec.

The neuroimaging tumor response was defined as one of the following: 1) resolution of the enhancing mass (CR); 2) reduction by more than 50% of the enhancing mass (PR); or 3) no response.

Results

Safety of the Procedure

In 11 treatment cycles CED of the drug was given for 5
full days. In two treatment cycles CED of the drug was given for 4 days, in one cycle for 3 days, and in six cycles for 2 days. Treatment was discontinued prematurely because of the development of complications (six patients), identification of fluid penetration into a cyst with disappearance of the convective effect on DW MR images (two patients), and the accidental removal of the catheter (one patient). Overall, in 11 of 20 treatment cycles no or only mild toxicity was observed.

In two of the first three patients who had received the higher paclitaxel dose (7.2 mg/day), chemical meningitis with pleocytosis developed in the CSF, but there was no growth of microorganisms. This was associated with a mild state of somnolence and ventriculomegaly (Case 1) and was attributed to a presumed leakage of paclitaxel into the subarachnoid space. Symptoms resolved within days after discontinuation of therapy with CSF values returning to normal. The patient in Case 1 subsequently required endoscopic shunt placement and died of a complication related to the shunt procedure 25 days after completing CED of the drug. Accordingly, the dose of paclitaxel was reduced to 3.6 mg/day in all subsequent treatments (Cases 4–15). Chemical meningitis remained the most frequent side effect among the patients treated subsequently, occurring in four of 12 patients treated with the low-dose protocol (Cases 4–15). Infectious complications occurred in three patients. In one patient bacterial meningitis developed during infusion and was treated successfully with antibiotic agents. Two patients experienced subdural empyema 2 to 3 weeks after treatment and required surgical evacuation of the empyema and long-term antibiotic therapy. Neurological deterioration with new deficits persisted in one patient and resolved in the other. Two patients experienced poor wound healing and required revised treatment of the local wound. Three patients experienced neurological deterioration due to increased peritumoral edema and required resection of necrotic tumor; there was a gradual resolution of deficits in all three patients. After discharge from the hospital, one patient died of a massive pulmonary embolism from a known deep vein thrombosis, despite adequate anticoagulant therapy.

**Neuroimaging and Clinical Evaluation**

Conventional and DW MR images were obtained before and during the course of CED of paclitaxel and at regular intervals during the follow-up period. Changes in signal intensity (appearance of an enlarging hyperintense signal around the tip of the catheter) were observed as early as 24 hours after initiation of therapy. These early changes seen on the DW MR images are believed to represent tissue changes associated with the convective process, and the volumes of signal intensity appeared to correlate with tumor volumes by displaying a lytic effect on subsequent contrast-enhanced T₁-weighted images (Fig. 1). No changes were observed on T₁- and T₂-weighted images obtained at the same time. When no changes were observed on DW MR images, no significant antitumor response was ever detected on the other MR images. Convection (as seen on DW MR images) appeared to stop when the convective wave reached a cystic cavity such as the ventricular system or a tumor cyst. This was often associated with the development of symptoms and CSF characteristics of chemical meningitis, presumably due to a leakage of paclitaxel into the CSF.
Similarly, encroachment on cystic or necrotic regions within the tumor led to the arrest of convection and the absence of a subsequent tumor response.

Fifteen patients received a total of 20 cycles of paclitaxel treatment. Neuroimaging evidence of a tumor response was observed in 11 of the 15 patients (five CRs and six PRs, giving an overall 73% response rate) or 14 of 20 treatment cycles (five CRs and nine PRs) (Fig. 2). A response was observed as a regression of the enhanced tumor mass with transformation of the solid tumor into a cystlike cavity. A residual thin rim of enhancement usually persisted in all responders (Figs. 1 and 3), but was found to represent nontumoral changes in pathological specimens.

The added effect of simple diffusion, after CED of paclitaxel had been discontinued, appeared to be significant in some patients. Although simple diffusion can usually penetrate for a limited distance from its source, the starting point after convection (that is, the circumference of the treated volume) is much larger than a point source. Accordingly, even a small expansion of paclitaxel due to diffusion may add significantly to the volume of distribution achieved by convection alone (Fig. 3). In some patients, an early tumor response was also associated with the resolution of peritumoral edema while the patients were receiving a decreasing dosage of steroid medication.

Thirteen of 15 patients have died, with a median survival of 7.5 months (range 1–14 months; excluding the patient who died of a massive pulmonary embolus). Two patients are still living 12 and 24 months after therapy, respectively.

**Histological Evaluation**

Tissue specimens were obtained from five patients between 2 and 10 weeks after treatment. Three of the resected tumors displayed a CR on neuroimaging studies and two exhibited a significant PR. The residual cystic lesions remaining after paclitaxel treatment were resected en bloc in these patients and cut into serial sections for histopathological evaluation. One patient in whom a CR was demonstrated on neuroimaging studies underwent a stereotactic biopsy from the treated site.

Widespread necrosis was identified in all lesions; macroscopically, this resembled infarcted, avascular brain tissue. A histological evaluation revealed necrotic or fibrotic tissue...
### TABLE 2

Effect of paclitaxel treatment for recurrent malignant glioma*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs)</th>
<th>Tumor Type†</th>
<th>Prior Therapy</th>
<th>Cycle</th>
<th>Timing of Repeated Therapy (mos)</th>
<th>Duration of Therapy (days)</th>
<th>Response to Therapy/ Survival (mos)</th>
<th>Histological Confirmation of Response</th>
<th>Complication(s)</th>
<th>Outcome &amp; Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>78</td>
<td>GBM</td>
<td>S, RT</td>
<td>1</td>
<td>—</td>
<td>5</td>
<td>CR/1 (see comment)</td>
<td>—</td>
<td>chemical meningitis, seizures, hydrocephalus</td>
<td>dead 25 days post-Tx due to complications of endoscopic procedure for hydrocephalus</td>
</tr>
<tr>
<td>2</td>
<td>43</td>
<td>GBM</td>
<td>S × 2, RT</td>
<td>1</td>
<td>5</td>
<td>PR/2</td>
<td>biopsy showed no tumor</td>
<td>no complications</td>
<td>bacterial meningitis, wound dehiscence, lowered KPS score that gradually improved over 12 mos</td>
<td>alive 24 mos post-Tx</td>
</tr>
<tr>
<td>3</td>
<td>46</td>
<td>GBM</td>
<td>S, RT</td>
<td>1</td>
<td>2</td>
<td>PR/1</td>
<td>biopsy showed no tumor</td>
<td>no complications</td>
<td>no complications</td>
<td>dead 1 mo post-Tx</td>
</tr>
<tr>
<td>4</td>
<td>58</td>
<td>GBM</td>
<td>S, RT</td>
<td>1</td>
<td>3</td>
<td>PR/1</td>
<td>biopsy showed no tumor</td>
<td>no complications</td>
<td>late wound dehiscence requiring local reconstructive surgery</td>
<td>dead 14 mos after 2nd therapy; KPS score 100%; no evidence of tumor progression on MIR 1 mo before death</td>
</tr>
<tr>
<td>5</td>
<td>61</td>
<td>GBM</td>
<td>S, RT</td>
<td>1</td>
<td>5</td>
<td>CR/7 (see comment)</td>
<td>complete resection of tumor site; no viable tumor</td>
<td>no complications</td>
<td>30 days post-Tx due to tumoral necrosis; excision of necrotizing tumor w/ development of brain abscess 2 wks later</td>
<td>dead 7 mos post-Tx because of Escherichia coli sepsis; at time of death no evidence of tumor on enhanced CT scan</td>
</tr>
<tr>
<td>6</td>
<td>55</td>
<td>GBM</td>
<td>S × 2, RT, chemo</td>
<td>1</td>
<td>5</td>
<td>PR/3</td>
<td>biopsy showed diffuse necrosis w/ residual tumor</td>
<td>no complications</td>
<td>worsening of hemiparesis &amp; seizures; increased edema &amp; mass effect; marked clinical improvement postop</td>
<td>2 catheters placed during 2nd therapy; dead 4 mos after 1st therapy because of rapid tumor progression outside Tx site</td>
</tr>
<tr>
<td>7</td>
<td>30</td>
<td>GBM</td>
<td>RT</td>
<td>1</td>
<td>5</td>
<td>PR/4</td>
<td>biopsy showed no tumor</td>
<td>no complications</td>
<td>mild chemical meningitis</td>
<td>refused 2nd therapy; dead 5 mos later of local tumor progression because of local tumor progression</td>
</tr>
<tr>
<td>8</td>
<td>70</td>
<td>GBM</td>
<td>RT</td>
<td>1</td>
<td>5</td>
<td>NR</td>
<td>biopsy showed no tumor</td>
<td>no complications</td>
<td>mild chemical meningitis on 2nd day post-Tx</td>
<td>dead 6 mos post-Tx because of local tumor recurrence</td>
</tr>
<tr>
<td>9</td>
<td>56</td>
<td>Grade III</td>
<td>RT</td>
<td>1</td>
<td>2</td>
<td>PR/5</td>
<td>biopsy showed no tumor</td>
<td>no complications</td>
<td>mild chemical meningitis on 2nd day post-Tx</td>
<td>dead 1 wk after discharge</td>
</tr>
<tr>
<td>10</td>
<td>51</td>
<td>GBM</td>
<td>S, RT</td>
<td>1</td>
<td>4</td>
<td>PR/(see comment)</td>
<td>biopsy showed no tumor</td>
<td>no complications</td>
<td>massive pulmonary embolism due to a known deep vein thrombosis</td>
<td>rapid tumor progression; dead 6 wks post-Tx</td>
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<tr>
<td>11</td>
<td>64</td>
<td>GBM</td>
<td>S, RT</td>
<td>1</td>
<td>5</td>
<td>NR</td>
<td>biopsy showed no tumor</td>
<td>no complications</td>
<td>subdural empyema 2 wks post-Tx</td>
<td>dead 5 mos post-Tx; tumor recurrence outside Tx site</td>
</tr>
<tr>
<td>12</td>
<td>51</td>
<td>mixed astro-</td>
<td>S, chemo, RT</td>
<td>1</td>
<td>2</td>
<td>CR/4</td>
<td>biopsy showed no tumor</td>
<td>no complications</td>
<td>subdural empyema 3 wks post-Tx</td>
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</table>

(continued on next page)
with surrounding early gliotic changes (Fig. 4A). No tumor cells were found in three lesions and small islands of viable tumor cells were found in the others. At some distance from the center of the lesion, crystals of foreign material were identified and interpreted as possible paclitaxel crystals (Fig. 4B).

The treatment results and complications are summarized in Table 2.

**Discussion**

Intratumoral CED of paclitaxel appeared to induce a significant antitumor response in recurrent malignant gliomas. A marked antitumor effect was noted in 11 of 15 patients (14 of 20 treatment cycles), as assessed by complete or partial regression of the enhancing tumor on contrast-enhanced MR images. The neuroimaging response (appearance of an enlarging hyperintense signal around the tip of the catheter on DW MR images and subsidence of enhancement on Gd-enhanced T1 MR images) became evident as early as 24 hours after initiation of therapy, with early changes manifested on the DW MR images and later on the contrast-enhanced T1-weighted images. These changes were accompanied in some cases by resolution of peritumoral edema, from which we could infer that the biological behavior of the tumor had been modified and, perhaps, that the tumor-infiltrated brain adjacent to the visible tumor mass had been targeted as well by paclitaxel. These neuroimaging changes in response correlated with the histological appearance of necrotic or fibrotic tissue with surrounding early gliotic changes in lesions that had been resected at various time points after treatment. Although in most patients the disease subsequently progressed and led to death, one patient is currently alive 24 months after completing treatment with no residual enhancing tumor on a recent MR image. An additional patient remains alive 12 months after therapy with no evidence of progressing tumor and two other patients died 7 and 14 months after treatment from apparently unrelated causes with no evidence of tumor on MR images, which had been obtained only days prior to death. Although the 73% response rate of tumors observed in our study seems high, the overall impact on survival still remains to be determined in larger scale, controlled studies.

The biochemical basis for the paclitaxel selectivity to tumor tissue depends on its ability to interfere with cell division by assembly of microtubules. Thus, normal postmitotic brain cells are less susceptible to the effect of paclitaxel. In some cases paclitaxel appeared to have reached beyond the boundaries of the enhancing tumor mass into regions that presumably were infiltrated by tumor. This effect may have been augmented by the late concentration-dependent diffusion effect from the peripheral convective wave of paclitaxel.

The antitumor activity was associated with a significant rate of treatment-related toxicity and complications. Paclitaxel appears to be a strong irritant of the leptomeninges, causing chemical meningitis as soon as it reaches the subarachnoid space and the CSF. This effect seems to be dose dependent because it was more pronounced in patients who had received a higher dose of paclitaxel. After a dose reduction and recognition of this potential complication, an early cessation of drug administration in response to the first symptoms suggestive of chemical meningitis led to a rap-

**Table 2 (continued)**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs)</th>
<th>Tumor Type†</th>
<th>Prior Therapy</th>
<th>Timing of Therapy (mos)</th>
<th>Repeated Therapy Cycle (days)</th>
<th>Duration of Therapy (mos)</th>
<th>Histological Confirmation of Response</th>
<th>Neuroimaging Response</th>
<th>Neuroimaging Complications</th>
<th>Outcome &amp; Comments</th>
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<td>35</td>
<td>GBM</td>
<td>S, RT</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>PR/8</td>
<td>no complications</td>
<td>no complications</td>
<td>alive with no residual tumor mass effect; clinical progression on MRI improvement postop</td>
</tr>
<tr>
<td>14</td>
<td>65</td>
<td>GBM</td>
<td>S, RT</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>NR</td>
<td>no complications</td>
<td>no complications</td>
<td>minor local response; infarct development; clinical improvement postop</td>
</tr>
<tr>
<td>15</td>
<td>59</td>
<td>GBM</td>
<td>S</td>
<td>2 (Gliadel wafer), RT</td>
<td>1</td>
<td>2</td>
<td>NR</td>
<td>no complications</td>
<td>no complications</td>
<td>rapid tumor progression after 2 mos; dead 3 mos post-Tx; slow tumor progression; alive 2 mos post-Tx</td>
</tr>
<tr>
<td>21</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>rapid tumor progression after 2 mos; dead 3 mos post-Tx; slow tumor progression; alive 2 mos post-Tx</td>
</tr>
</tbody>
</table>

† Based on World Health Organization classification.

NR = no response; RT = radiotherapy; S = surgery; Tx = treatment; –– = not available.
id resolution of these symptoms, usually within 24 hours. Cremophor, which is used as the vehicle in commercially available preparations of paclitaxel may be responsible for this unique toxicity. Other treatment-related complications included wound dehiscence, presumably due to a subcutaneous leakage of paclitaxel, which interferes with wound healing. This direct toxic effect became less of a problem when skin incisions for tunneling the catheter were placed on previous surgical scars after debriding the scar edges to facilitate wound healing. Problems associated with wound healing were probably the cause of infectious complications that occurred in three patients. Rapid tumor necrosis with an associated edema and a mass effect caused neurological deterioration, despite high-dose steroid therapy in two patients. In both patients surgical debulking of the necrotic tissue was required and resulted in resolution of the symptoms.

Conclusions

The CED of paclitaxel into recurrent malignant brain tumors was associated with high neuroimaging and histological response rates. The data obtained using DW MR imaging indicate that the convective process can be visualized and may be used to predict subsequent changes on contrast-enhanced T1-weighted MR images that correspond to an antitumor response.

Convection appeared to have very little effect on the normal brain. Some of the antitumor activity may be due to the additive effect of diffusion, which supplemented the effect of convection in delivering paclitaxel to the tumor mass.

The high incidence of complications observed in our patients is a cause for concern. Modifications of this therapeutic modality may be considered, such as a dose adjustment, use of a Cremophor-free paclitaxel preparation, and optimization of catheter placement within the tumor to avoid leakage into the CSF. An effort to develop computerized simulation software to allow pretreatment planning of catheter placement and prediction of the direction and extent of convection is currently under way.

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Disclaimer

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References