Neuroradiographic changes following convection-enhanced delivery of the recombinant cytotoxin interleukin 13–PE38QQR for recurrent malignant glioma

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Object. Convection-enhanced delivery (CED) is a novel method for delivering therapeutic agents to infiltrative brain tumor cells. For agents administered by CED, changes on magnetic resonance (MR) imaging directly resulting from catheter placement, infusion, and the therapeutic compound may confound any interpretation of tumor progression. As part of an ongoing multiinstitutional Phase I study, 14 patients with recurrent malignant glioma underwent CED of interleukin (IL) 13–PE38QQR, a recombinant cytotoxin consisting of human IL-13 conjugated with a truncated Pseudomonas exotoxin. Serial neuroradiographic changes were assessed in this cohort of patients.

Methods. Patients were treated in two groups: Group 1 patients received IL13–PE38QQR before and after tumor resection; Group 2 patients received infusion only after tumor resection. Preoperative and postinfusion MR images were obtained prospectively at specified regular intervals. Changes were noted along catheter tracks on postresection MR images obtained in all patients. A simple grading system was developed to describe these changes. When MR imaging changes appeared to be related to IL13–PE38QQR, patients were followed up without instituting new antitumor therapy.

Conclusions. As CED of therapeutic agents becomes more common, clinicians and investigators must become aware of associated neuroimaging changes that should be incorporated into toxicity assessment. We have developed a simple grading system to facilitate communication about these changes among investigators. Biological imaging modalities that could possibly distinguish these changes from recurrent tumor should be evaluated. In this study the authors demonstrate the challenges in determining efficacy when surrogate end points such as time to tumor progression as defined by new or progressive contrast enhancement on MR imaging are used with this treatment modality.

Key Words • glioma • convection-enhanced delivery • interleukin-13 • Pseudomonas exotoxin • magnetic resonance imaging

Convection-enhanced delivery has shown promise as a drug delivery method in several preclinical and clinical models.13,14,17,38 Phase I clinical trial data demonstrating the safety of conjugated IL4–Pseudomonas exotoxin (IL4[38-37]–PE38KDEL) infusion by CED in patients with recurrent malignant glioma have been reported.39 More recently, a recombinant protein with fusion of IL-13 and the functional subunits of Pseudomonas exotoxin (IL13–PE38QQR) has been developed for CED.4 This strategy takes advantage of the high expression of the IL-13 receptor on the surface of glioma cells and has shown promise in animal studies.49,19 Several Phase I clinical trials in which authors delivered IL13–PE38QQR by CED to treat patients with recurrent malignant glioma have been initiated.

For agents administered through CED, changes on MR images resulting directly from catheter placement, infusion, or the therapeutic compound itself may confound any interpretation of tumor progression. In this paper we reviewed MR imaging findings in 14 patients enrolled at the UCSF in a multiinstitutional study and reported treatment-related

Abbreviations used in this paper: CED = convection-enhanced delivery; CSF = cerebrospinal fluid; FDG-PET = fluorodeoxyglucose positron emission tomography; IL = interleukin; KPS = Karnofsky Performance Scale; MR = magnetic resonance; UCSF = University of California at San Francisco.
MR imaging changes distinct from tumor recurrence that could be seen following CED of IL13–PE38QQR.

Clinical Material and Methods

Entry Criteria and Enrollment

The study was open to patients 18 years of age or older who had recurrent or progressive resectable supratentorial malignant glioma (Grade III or IV) including glioblastoma, anaplastic astrocytoma, and mixed anaplastic oligoastrocytoma. A KPS score of at least 70 was required for enrollment. Patients must have completed external beam radiotherapy at least 4 weeks prior to study entry and must have recovered from any toxicities caused by prior cytotoxic (6 weeks for nitrosourea and 4 weeks for nonnitrosourea), investigational (4 weeks), or cytostatic (2 weeks) therapies. Patients were excluded if they demonstrated signs of impending herniation, multifocal tumor, or subependymal or leptomeningeal spread or if they had other significant, uncontrolled medical illness. Patients were recruited by their neurosurgeon and/or neurooncologist and informed consent was obtained from all who participated. The study protocol was reviewed and approved by the UCSF Committee on Human Research.

Treatment Outline

Patients were assigned to a treatment group in stages as they were enrolled in the trial. Group 1 patients underwent intratumoral placement of a single infusion catheter after stereotactic biopsy. Thirty-six milliliters of escalating concentrations of IL13–PE38QQR (0.25–2 μg/ml) were infused over 48 hours (three patients received 0.25 μg/ml, two received 0.5 μg/ml, one received 1 μg/ml, and one received 2 μg/ml). The catheter was then removed. Patients underwent craniotomy and resection of tumors 1 week after the start of the preoperative infusion, and two to three infusion catheters were placed in the brain parenchyma surrounding the resection cavity; three catheters were required according to the protocol, but two were acceptable if technical difficulties precluded the placement of all three. Seventy-two milliliters of IL13–PE38QQR at a fixed concentration of 0.25 μg/ml were then infused over 96 hours. Group 2 patients underwent craniotomy and tumor resection without prior intratumoral IL13–PE38QQR infusion, and two to three infusion catheters were placed in the brain parenchyma surrounding the resection cavity. Seventy-two milliliters of escalating concentrations of IL13–PEQQR (0.5–1 μg/ml) were infused over 96 hours (four patients received 0.5 μg/ml and three received 1 μg/ml). The total dose of IL13–PE38QQR in this dose-escalation study bore no relation to tumor size. These two treatment groups are summarized schematically in Fig. 1.

Several strategies were used to avoid inadvertent infusion of the cytotoxin into the ventricles or subarachnoid spaces. Catheters situated around the resection cavity were placed through small separate corticostomy (not through the cavity itself) to reduce the chance of backflow into the cavity. All catheters were placed using image guidance to avoid entering sulci or ventricles. Placement was confirmed on MR imaging on postoperative Day 1. Any catheter that traversed sulci or entered the ventricles was removed prior to commencing infusion, as was any catheter with the free flow of CSF when opened (regardless of its appearance on MR images).

Magnetic Resonance Imaging

All patients underwent preresection MR imaging (with and without intravenous contrast agent) within 14 days of enrolling in the study. Each received a stable dose of dexamethasone (no changes for > 5 days) before pretreatment MR imaging was performed. Follow-up MR images (with...

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Fig. 1. Schematic diagram outlining treatment plans for Groups 1 and 2. Note that infusion catheters were placed during procedures for biopsy (Group 1) and resection (Groups 1 and 2). AR1 = after resection Day 1; BR1 = before resection Day 1.
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<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>age (yrs)</td>
<td>46</td>
</tr>
<tr>
<td>range</td>
<td>24–62</td>
</tr>
<tr>
<td>sex</td>
<td>male 7 (50)</td>
</tr>
<tr>
<td></td>
<td>female 7 (50)</td>
</tr>
<tr>
<td>median KPS score</td>
<td>90</td>
</tr>
<tr>
<td>Group 1</td>
<td>7 (50)</td>
</tr>
<tr>
<td>Group 2</td>
<td>7 (50)</td>
</tr>
<tr>
<td>no. w/ 3 catheters</td>
<td>12 (86)</td>
</tr>
<tr>
<td>no. w/ GTR</td>
<td>11 (78)</td>
</tr>
</tbody>
</table>

* GTR = gross-total resection.

and without intravenous contrast agent) were obtained within 48 hours of resection, at 4 and 8 weeks postresection, and every 8 weeks thereafter until tumor progression.

Based on MR imaging results, progression is usually defined as new or enlarging contrast enhancement; during the study, however, some patients demonstrated contrast enhancement that appeared to be related solely to catheter track and region of infusion. To differentiate these findings from recurrence, some patients whose imaging changes were likely related to treatment underwent further biological imaging with MR spectroscopy, MR cerebral blood volume studies, or FDG-PET.

**Results**

The median age among the 14 patients enrolled in this study was 46 years (range 24–62 years), 50% were male, and the median KPS score was 90. Seven patients were enrolled in Group 1 and seven were enrolled in Group 2. Twelve patients (86%) underwent placement of three catheters postresection. Eleven patients (78%) underwent gross-total resection. Patient demographics and treatment parameters are summarized in Table 1.

Changes observed on MR images were deemed to be caused by treatment when they occurred along catheter tracks (determined by comparison to postoperative MR images with catheters in place) and there was no associated change elsewhere on the image. Findings were graded on a five-point scale (Table 2). Representative MR images for Grades I to IV changes are featured in Fig. 2. In most cases (71%), some form of biological imaging was performed (MR spectroscopy, MR perfusion imaging, and/or PET scanning), although this was not required by the study protocol and not all patients underwent the same tests. Four patients with nonprogressive asymptomatic Grade II lesions did not undergo any biological imaging. In most cases in which it was performed, MR spectroscopy findings were equivocal (heterogeneous areas of low metabolites and nonspecific, increased cellularity). Cerebral blood volume on MR perfusion images was generally increased, and FDG-PET scans often demonstrated increased glucose uptake. Three patients underwent subsequent biopsy/resection: in two cases, results confirmed the diagnosis of recurrent tumor indicated on biological imaging: in one case (Fig. 2D), results of biological imaging were conflicting, but results of two subsequent biopsies confirmed treatment-related changes (necrosis/inflammation without recurrent tumor). Biological imaging findings and biopsy results are summarized in Table 3. Representative MR spectroscopy, MR perfusion, and PET images for a patient with Grade IV changes are featured in Fig. 3. Note that this is the same patient whose MR images are shown in Fig. 2D.

The MR imaging–demonstrated changes along different catheter tracks were variable in individual patients. Note, however, that the 4-week postresection MR images obtained in all 14 patients revealed at least Grade I changes along at least one catheter track. Images obtained in all patients eventually demonstrated at least some degree of enhancement along at least one catheter track (Grade II or greater). Grade IV changes occurred in two of three patients who had received the highest postresection IL13–PE38QQR concentrations (1 μg/ml, from Group 2) but not in patients who had received lower postresection concentrations. Maximal imaging-grade changes related to different infusion concentrations are summarized in Table 4. These changes were dynamic over several time points. For patients receiving 0.5 μg/ml or less of IL13–PE38QQR postresection, imaging changes reached the maximal grade by 4 to 8 weeks postresection, then reached a plateau or slowly resolved during several months. Imaging findings for the three patients who had received the maximal postresection concentration (1 μg/ml) had a more protracted time course. One patient demonstrated the maximal imaging grade in approximately 12 weeks. Another patient showed late progression of treatment-associated MR imaging changes 4 to 6 months after initial IL13–PE38QQR therapy and after resection of a treatment-associated contrast-enhancing mass. The time courses for these changes for different postresection infusion concentrations are shown in Fig. 4.

No patient received new antitumor therapy as a result of these MR imaging changes. Patients with new treatment-associated neurological symptoms were given corticosteroid agents. Such symptoms were more common as the imaging change–grade increased (0% for Grade II changes, 25% for Grade III changes, and 100% for Grade IV changes). Neurological symptoms were progressive and included features of raised intracranial pressure in one patient with Grade IV changes, which prompted another craniotomy and resection of the contrast-enhancing mass situated along the catheter track. Results of histopathological examination of this specimen revealed features of inflammation and necrosis...
FIG. 2. Representative Grade I (A), II (B), III (C), and IV (D) imaging changes. All images are T₁-weighted postcontrast sequences except for the fluid-attenuated inversion-recovery (FLAIR) images in A. Normal postoperative changes are seen on all postoperative Day 1 images, but no residual postoperative enhancement was noted in any of these cases (not shown). Contrast-enhancing changes (Grades II–IV) had associated FLAIR abnormalities (not shown). Black arrows indicate infusion catheters on postoperative Day 1 images. White arrows indicate treatment-related changes. The distinction among Grades II through IV is based purely on the maximal diameter of enhancement, as these lesions are otherwise quite similar. Note that the anterior treatment-related ring-enhancing mass seen at 2 months in D has been subjected to an interval subtotal resection at 6 months (necrosis/inflammation but no tumor), but there is new progression of treatment-related changes posteriorly. A biopsy specimen was subsequently obtained from this region as well, confirming necrotic/inflammatory changes in the absence of recurrent tumor. Gad = gadolinium.
without evidence of active tumor. Both craniotomy and resection improved the MR imaging appearance temporarily (Fig. 2D), but progressive contrast enhancement recurred at the infusion sites. This consequence prompted another biopsy, which again showed inflammation and necrosis without active tumor.

All patients were considered on study until clear evidence for tumor progression was observed. Increasing contrast en-
hancement at the resection cavity and/or at areas distant from the infusion catheters combined with biological imaging results indicative of tumor was taken as adequate evidence of recurrence. In three ambiguous cases, biopsy and/or further debulking was performed. Figure 5 features representative MR images, MR spectroscopy scans, and histopathological findings demonstrating tumor recurrence distinct from changes associated with IL13–PE38QQR.

Discussion

Convection-enhanced delivery is a novel method for delivering agents locally to brain tumors and surrounding brain parenchyma. It reliably achieves large and clinically significant volumes of distribution rather than relying on diffusion and is well tolerated in preclinical models. Early results also indicate that the method generally is well tolerated clinically and shows some promise for the delivery of several agents, including IL13–PE38QQR.12 Data in this report reveal a potential difficulty in the interpretation of treatment-related changes on MR images, however, which has not been reported in detail previously. These treatment-related imaging changes can confound attempts to determine disease progression or recurrence.

Magnetic resonance imaging is the standard evaluation method in patients with malignant glioma. Along with clinical evaluation, MR imaging is used both to assess response to treatment and to determine tumor progression (usually defined as new or enlarging contrast enhancement).16 Distinguishing recurrent tumor from treatment effect can sometimes be difficult, as has been shown for high-dose focal radiation therapies such as radiosurgery and brachytherapy.8 As a result, the practice of relying solely on MR imaging data to determine glioma progression has been increasingly questioned.20 During this clinical trial, we primarily used criteria such as relationship to catheter tracks and resection bed, linearity, nodularity, time course, and symptoms to determine whether changes were treatment related, although these measures are essentially subjective and can be ambiguous. Repeated biopsy for tissue diagnosis remains the gold standard for differentiating treatment-related changes from recurrent/progressive tumor. This procedure was performed only in a minority of the patients (21%) in our study given their reluctance to undergo unnecessary neurosurgical interventions. Although we believe that such a procedure was in the best interests of our patients, the fact that it was not performed in more patients is clearly a weakness of this study. Note, however, that this weakness is mitigated somewhat

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TABLE 4

Maximal imaging changes related to infusion concentrations*

<table>
<thead>
<tr>
<th>Group</th>
<th>Intratumoral Concentration (µg/ml)</th>
<th>Peritumoral Concentration (µg/ml)</th>
<th>Max MR Imaging Grade per Patient, Respectively</th>
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<tr>
<td>0.25</td>
<td>0.25</td>
<td>3 II, III, III</td>
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<tr>
<td>0.50</td>
<td>0.25</td>
<td>2 II, II</td>
<td></td>
</tr>
<tr>
<td>1.00</td>
<td>0.25</td>
<td>1 II</td>
<td></td>
</tr>
<tr>
<td>2.00</td>
<td>0.25</td>
<td>1 II</td>
<td></td>
</tr>
<tr>
<td>NA</td>
<td>0.50</td>
<td>4 II, II, III, II</td>
<td></td>
</tr>
<tr>
<td>NA</td>
<td>1.00</td>
<td>3 IV, IV, III</td>
<td></td>
</tr>
</tbody>
</table>

*NA = not available.

Fig. 4. Time course of maximal imaging changes in patients who received 0.25 µg/ml (Group 1, upper), 0.5 µg/ml (Group 2, center), or 1 µg/ml (Group 2, lower) IL13–PE38QQR postoperatively. Letters A through N represent individual patients. Note the trend to increased change grade as the IL13–PE38QQR concentration increases (Grade IV changes occurred exclusively in patients who received 1-µg/ml infusions). Most patients (93%) reached their maximal imaging grade by 2 months posttreatment, and all but one reached it by 3 months posttreatment. For patients with Grade III or lower, changes stabilized or slowly resolved during the next 1 to 10 months; however, no resolution (and some progression) occurred in the two patients with Grade IV changes.
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by the use of biological imaging to evaluate most of the patients (71%). Biological imaging modalities such as MR spectroscopy, MR perfusion studies, single-photon emission computerized tomography, and PET are assuming more importance in determining tumor progression. Results of FDG-PET studies generally demonstrated increased metabolic activity, and those of MR perfusion studies tended to reveal increased blood flow. In contrast, MR spectroscopy findings tended to be equivocal, with no clear evidence of recurrent tumor. These studies were not mandated by protocol, however, and were obtained solely at the discretion of the participating clinicians. Not all patients underwent the same biological imaging modalities, and four patients with nonprogressive asymptomatic Grade II lesions underwent no biological imaging at all. Further rigorous prospective evaluation is needed to clarify the role of these modalities in assessing imaging changes related to CED of IL13–PE38QQR and other agents.

All patients enrolled in this trial at UCSF demonstrated imaging changes on MR imaging that were attributed to IL13–PE38QQR infusion. To facilitate interpretation in future studies and to simplify communication among investigators about these changes, we developed a simple five-point grading scale (Table 2). Although this is an empirical grading scale, it encompasses the spectrum of changes seen and demonstrated a concentration-dependent effect for IL13–PE38QQR in this study. Furthermore, it helped to identify the time course for these changes (early increase followed by plateau or slow resolution at lower infusion concentrations and potential for a more protracted course at higher concentrations; Fig. 4). This is a key finding, as it helps to differentiate between treatment-related changes (usually apparent by 4 weeks posttherapy and maximal by 8 weeks posttherapy) and tumor recurrence, which usually occurs at a later date.

In most patients (78%), changes related to IL13–PE38QQR and demonstrated on images were asymptomatic and required no further treatment. Among these individuals, the MR imaging changes were significant only in that they had to be taken into account when determining disease progression. At the highest postresection IL13–PE38QQR concentration (1 μg/ml), imaging changes associated with cytoxin infusion were significant and predictive of progressive neurological symptoms. The changes in these patients represented important clinical complications requiring medical and surgical intervention. Increasing the corticosteroid dose was the most common intervention and required an increased frequency in clinical evaluation and neuroimaging to monitor these patients closely. Some patients required resection to relieve mass effect. A full report on this multiinstitutional Phase I trial will be published subsequently; note, however, that the imaging findings and associated symptoms reported here represent the dose-limiting toxicity for this agent at the 1 μg/ml concentration level. If traditional end points for disease progression such as simple contrast enhancement on MR imaging were used, these treatment-related toxicities might be declared as tumor progression or recurrence. This factor underscores the importance of distinguishing treatment-related imaging changes when conducting trials of agents delivered by CED.

Recognizing imaging changes and possible associated neurologic sequelae associated with CED of this agent has important implications for clinicians treating patients who have undergone this therapy. New enhancement on MR images alone cannot be used as an indicator of tumor progression and mandate changing or adding antitumor therapy. In addition, symptomatic cases may require therapy (such as corticosteroids or, in severe cases, craniotomy and resection) directed at the treatment-related changes themselves to reduce swelling and mass effect. Furthermore, recognizing the potential for treatment-related changes on images has been important in the design and conduction of subsequent studies focused on this therapy. The grading scale described in this paper has been incorporated into the ongoing clinical trials of CED of this agent. The assessment of clinical features associated with the imaging changes as well as new treatment guidelines (for example, increased use of corticosteroids and more frequent clinical assessment of and neuroimaging in patients) has also been developed. A description of the nature and time course of these changes must be communicated to investigators participating in CED of cytotoxic agents, and this description...
must be part of the guidelines provided to clinicians participating in these trials.

The origin of our findings is not immediately clear. Glioma cells are reported to overexpress the IL-13 receptor on their surface, whereas normal brain cells do not express this molecule. The IL13–PE38QQR therapy is molecularly targeted to glioma cells through the IL-13 receptor in addition to being physically targeted by CED. Data from preclinical studies did not reveal significant cytotoxin-mediated injury to normal brain parenchyma at lower IL13–PE38QQR doses delivered by CED, but acute brain necrosis occurred in rats receiving doses greater than 500 µg/ml when administered through CED (1 µl/minute). The highest dose level administered into surrounding brain parenchyma in the present trial (1 µg/ml) is two orders of magnitude less than the minimal dose required to induce acute brain necrosis in preclinical studies. Therefore, the concentration-dependent effect on relatively normal brain in this study is somewhat surprising. Only two of 14 patients underwent placement of two instead of three catheters, and therefore the effect of flow rate on treatment changes could not be evaluated. Differences in receptor structure and expression between species, and differences in the timing of toxicity assessment may explain differences between preclinical toxicological and clinical studies; however, similar (albeit less marked) changes have been seen with other tumor-directed therapies including HSVtk/ganciclovir gene therapy, IL-4 (38–37)–PE38KDEL administered by CED, and direct intracerebral immunotherapy with tumor-infiltrating lymphocytes and IL-2. Relatively uniform treatment-related MR imaging changes from these disparate, tumor-specific therapies indicate that this result may reflect a ubiquitous normal brain response to treatment rather than direct therapy-related damage. Interestingly, all of these tumor-targeted therapies have some potential to stimulate antitumor immune responses (by design or otherwise). In the present study, four of five patients with Grade III or IV MR imaging–demonstrated changes caused by treatment are also long-term survivors (> 12 months after recurrence of glioblastoma multiforme). Pathological specimens collected from one of these patients at various time points after IL13–PE38QQR infusion have consistently demonstrated necrosis and inflammatory cell infiltrates without evidence of active tumor. It is tempting to speculate that these changes may represent a robust immune response, but the topic will require further study to delineate.

Conclusions

Convection-enhanced delivery is a novel method for delivering therapeutic agents to brain tumors and surrounding parenchyma. The procedure can be associated with treatment-related changes on MR images. We reported on such changes in a small group of patients with recurrent malignant glioma who had been seen at a single institution as part of a multicenter study of IL13–PE38QQR administration by CED. A simple five-point grading scale was developed to classify the imaging changes, which can confound efforts to determine tumor progression or recurrence. Biological imaging such as MR spectroscopy, MR perfusion imaging, and PET scanning may be helpful in differentiating treatment-related changes from recurrent tumor, but further study of these imaging modalities is needed. Until noninvasive methods of evaluation are reliable, stereotactic biopsy and histopathological evaluation will remain the standards. Treatment-associated MR imaging–demonstrated changes are usually asymptomatic but at higher grades can be associated with symptoms. The cause of these changes is unclear, but such changes may reflect injury from a brain response to therapy rather than direct treatment-related brain damage. Clinicians and investigators must be aware of these potential complications as tumor-targeted therapies become more common and CED is increasingly used. Incorporation of our five-point grading scale for treatment-related imaging changes, if validated in larger studies, may be helpful in future clinical trials of tumor-targeted therapy administered through CED.

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References

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