Comparison of intratumoral bolus injection and convection-enhanced delivery of radiolabeled antitenascin monoclonal antibodies

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Objectives. Convection-enhanced delivery (CED) is a novel technique used to deliver agents to the brain parenchyma for treatment of neoplastic, infectious, and degenerative conditions. The purpose of this study was to determine if CED would provide a larger volume of distribution ($V_d$) of a radiolabeled monoclonal antibody (mAb) than a bolus injection.

Methods. Patients harboring a recurrent glioblastoma multiforme that reacted with the antitenascin mAb 81C6 during immunohistochemical analysis were randomized to receive an intratumoral injection of the human--murine chimeric mAb Ch81C6, which had been labeled with the $^{131}$I tracer. The mAb was administered by either a bolus injection or CED via a stereotactically placed catheter; between 48 and 72 hours later the mAb was again administered using the other technique. Injections of escalating doses of a $^{131}$I-labeled therapeutic mAb were then delivered using the technique shown to produce the largest $V_d$ by single-photon emission computed tomography.

Conclusions. Convection-enhanced delivery has enormous potential for administering drugs to sites within the central nervous system. For the relatively small volumes injected in this study, however, CED did not provide a significant increase in the $V_d$ when compared with the bolus injection. Nevertheless, a clear cross-over effect was seen, which was probably related to the temporal proximity of the two infusions.

Key Words • brain neoplasm • convection-enhanced delivery • drug delivery system • glioblastoma multiforme • magnetic resonance imaging • single-photon emission computerized tomography

Malignant gliomas remain nearly uniformly fatal despite aggressive, computer-guided tumor resection, high doses of external beam radiation therapy or intracavitary brachytherapy, and multiple chemotherapy agents delivered at toxic doses. Although conventional forms of treatment sometimes result in positive responses on neuroimages, microscopic analyses of apparently normal brain tissue located some distance from the gross contrast-enhancing tumor show that the brain is diffusely infiltrated by frankly neoplastic cells at the time of diagnosis. This finding underscores the need for developing drug delivery systems capable of targeting neoplastic cells that may have migrated significant distances beyond the region of tumor visible on contrast-enhanced MR images. Although systemic drug delivery is theoretically capable of such broad coverage, available agents are severely limited by systemic dose-limiting toxicity, the tight junctions of the blood--brain barrier, and high intratumoral pressure. Similarly, surgery and radiation therapy cannot address these regions of likely tumor recurrence without inducing incapacitating tissue damage to the functional brain.

Convection-enhanced delivery is an innovative technique of administering drugs that promises to enhance the spatial distribution of therapeutic agents throughout the brain parenchyma. The tremendous potential of this simple approach has been clearly demonstrated in preclinical and early clinical studies conducted by our group and by others. To achieve concentration gradients of a drug within the interstitium of the brain, extremely high systemic doses are needed, which normally result in unacceptable toxicities. Traditional methods of local delivery of most therapeutic agents into the brain (by biodegradable polymers or direct intraventricular injection) has relied on diffusion, which is dependent on a concentration gradient, is inversely related to the size of the agent, and is usually slow with respect to tissue clearance. Thus, diffusion results in the nonhomogeneous distribution of most agents, which is restricted to a few millimeters from the source. In contrast to diffusion, CED uses a pressure gradient established at the tip of an infusion catheter.

Abbreviations used in this paper: CED = convection-enhanced delivery; CNS = central nervous system; CT = computerized tomography; mAb = monoclonal antibody; MR = magnetic resonance; SPECT = single-photon emission computerized tomography; $V_d$ = volume of distribution.
that creates bulk flow, which “pushes” the drug in the extracellular space). As a result, the drug is distributed more evenly, at higher concentrations, and over a larger area than in the absence of bulk flow (that is, when administered by diffusion alone).

For a given agent, the \( V_d \) depends on the structural properties of the tissue (hydraulic conductivity, vascular volume fraction, and extracellular fluid fraction) and the parameters of the infusion procedure (cannula placement, cannula design, and infusion rate). To maximize delivery and minimize reflux, the infusion procedure must be adjusted according to the tissue properties.

Although CED is being used clinically to treat human brain tumors, the pharmacokinetics of drug delivery using this system are very poorly understood, and the approach, which holds great promise, may fail unless the drug-delivery issues are well understood. In this paper we compare the \( V_d \) of a radiolabeled mAb delivered intratumorally using a traditional bolus injection with that of a radiolabeled mAb administered using CED.

### Clinical Material and Methods

**Radiolabeled 81C6.** The mAb 81C6 was originally produced to react to a human glioma cell line that expressed glial fibrillary acidic protein. It was subsequently found to react to the polymorphic extracellular glycoprotein tenascin. Tenascin is distinct from other extracellular matrix proteins and is composed of a radially arranged hexamer joined at the amino terminal central knob by disulfide bonds. Each arm contains a single subunit with a molecular weight in the range of 200 to 300 kD. The complete nucleotide sequence and the deduced amino acid sequence of the full-length complementary DNA for tenascin has been reported. For these studies, the human–murine chimeric mAb Ch81C6 was radiolabeled with iodine-123 or iodine-131 (MDS Nordion International, Vancouver, BC, Canada) by following a modified iodogen method.

**Patient Population and Clinical Protocol.** To qualify for the human study, patients had to harbor a recurrent glioblastoma multiforme visible on computerized tomography or MR imaging. The reactivity of neoplastic cells to the anti-tenascin mAb 81C6 was demonstrated by performing an immunohistological analysis. To be included in the study, patients had to have a midline brain shift of less than 0.5 cm and no evidence of any cerebral herniation syndrome.

Patients were randomized to receive a 3-ml injection of 1 mg of Ch81C6, which had been labeled with a \(^{123}\)I tracer (5 mCi). The Ch81C6 was administered by either a bolus injection (Technique A) or continuous bulk-flow microinfusion (Technique B), both of which were accomplished using a stereotactically placed pediatric silicone ventricular catheter.

Ten patients were enrolled in the study. Six were randomized to receive bolus injections first, three were randomized to receive microinfusion injections first, and one was treated on a compassionate plea basis with microinfusion alone.

For the bolus injection (Technique A), the radiolabeled antibody was injected by setting the rate of the infusion pump at 1000 µl/minute. For continuous bulk-flow microinfusion (Technique B), the infusion pump was initially set at a rate of 0.5 µl/minute and escalated hourly to rates of 1, 2, 4, and finally 6 µl/minute until the entire volume was delivered. If the initial injection was well tolerated, between 48 and 72 hours later the patients received a similar injection of \(^{121}\)I-Ch81C6 in which the other technique was used. The \( V_d \) produced by each technique was calculated based on images reconstructed by SPECT, which were obtained at the end of each injection. In group comparisons the \( V_d \)s are expressed as mean values ± standard deviations. Each patient also received a third injection that consisted of 10 mg of \(^{131}\)I-Ch81C6, which was administered using the technique that provided the largest \( V_d \). The dose of radioactivity used for the therapeutic portion of the study was escalated in a stratified fashion from 40 mCi in 20-mCi increments. In each case, SPECT scans were obtained immediately after the completion of the infusion.

**Single-Photon Emission Computerized Tomography.** The SPECT scans were obtained immediately following and 24 hours after the infusion of \(^{121}\)I-Ch81C6 into the human brain via CED. A three-head SPECT scanner fitted with two TRIAD LESR fanbeam collimators and a precise pinhole collimator (Trionix Research Labs, Twinsburg, OH) was used to obtain the scans. The \( V_d \) was subsequently determined using a threshold pixel method that has proved accurate at our institution for calculating the volumes of small spheres ranging in size from 1.3 to 5.3 cm³ in a brain phantom model. Isodose contours were calculated using a three-dimensional discrete Fourier transform convolution. Fiduciary markers were used to coregister these SPECT images with MR images with a spatial margin of error less than 0.1 mm.

### Results

The \( V_d \) could not be evaluated in two of the 10 patients: the one admitted on a compassionate plea basis received only a single injection and another patient did not receive the radiolabeled antibody for technical reasons and only received a therapeutic microinfusion.

Overall, the mean \( V_d \) for the bolus injections was 12.03 ± 10.82 cm³, whereas the mean \( V_d \) for the microinfusions was 12.47 ± 12.06 cm³. These two volumes are not significantly different. A clear cross-over effect was apparent, however, especially in patients who received the bolus injection second. In patients who received the bolus injection first, the mean \( V_d \) was 9.58 ± 11.03 cm³, whereas, in patients who received the bolus injection after microinfusion, the mean \( V_d \) of the bolus injections was 19.35 ± 8.27 cm³. Similarly, in five of eight patients (two patients could not be evaluated at this point) the microinfusion provided a larger \( V_d \) whereas in seven of eight patients the second modality of injection provided a larger \( V_d \) regardless of whether the mode of injection was by bolus or microinfusion.

During the third infusions, all three patients who received a bolus injection received the 40-mCi dose of therapeutic \(^{131}\)I-Ch81C6. Among the patients treated with microinfusion, three received the 40-mCi dose without adverse events and thereafter the dose was escalated to 60 mCi. Another three patients were treated without adverse event. The patient included on a compassionate plea basis was also treated with the 60-mCi dose. The median survival time for these heavily pretreated patients with recur-
recent glioblastomas multiforme was a favorable 30.3 weeks, which appears to be better than the natural course of the disease.

Discussion

The number of studies in humans in which CED has been used has naturally lagged behind that of studies in animals. The findings of the present human studies involving use of radiolabeled 81C6 have demonstrated that CED is as good or better than delivery of bolus injections, and that bolus injections would probably not be able to achieve the distributions predicted\(^\text{15,31}\) and more recently demonstrated\(^\text{7,8}\) for CED in the human brain. Also of interest is the significant cross-over effect seen in this study, which suggests that, as we infuse fluid into the brain, we would expect to see both neurological and physiological changes that may impact the subsequent course of the infusion anatomically and clinically.

Several questions about CED of therapeutic agents remain. For example, what is the optimal catheter location to distribute a drug to target tumor cells not only within the tumor mass but in the infiltrated adjacent parenchyma? It may be possible to exploit the increased interstitial pressures within a tumor that result in diffuse edema around the lesion to help distribute the drug farther throughout the brain by placing infusion catheters in or around the tumor. Based on the small number of tumors that have been resected postinfusion, however, there appears to be a heterogeneous distribution within the tumor. On the other hand, once the tumor has been removed, there may be a better chance to target the minimal residual disease represented by infiltrative tumor cells by using catheters located deep within the resection area, in areas suspected of tumor spread. The availability of selective molecule-targeted therapies makes them ideal for peritumoral therapy to target infiltrative cells without damaging the functional brain. Beyond selecting an appropriate drug, studies involving CED also need to address the appropriate form of drug delivery. Algorithms for predicting drug distribution based on catheter location may help improve drug distribution by CED. However, it will be critical to monitor actual drug distribution in patients to understand the cause of treatment failure better. Catheter design is also evolving to minimize backflow, to maximize distribution in the human brain, and to account for the need to maintain patient mobility.

Despite our enthusiasm for this approach, these data uncover some important potential limitations and opportunities for improvement that were not appreciated very well prior to these investigations. Further studies aimed at optimizing catheter design and infusion parameters should identify modifications capable of effectively addressing these issues now that the potential utility of this approach has been established in humans.

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