Direct Intracerebral Delivery of Cintredekin Besudotox (IL13-PE38QQR) in Recurrent Malignant Glioma: A Report by the Cintredekin Besudotox Intraparenchymal Study Group


ABSTRACT

Purpose
Glioblastoma multiforme (GBM) is a devastating brain tumor with a median survival of 6 months after recurrence. Cintredekin besudotox (CB) is a recombinant protein consisting of interleukin-13 (IL-13) and a truncated form of Pseudomonas exotoxin (PE38QQR). Convection-enhanced delivery (CED) is a locoregional-administration method leading to high-tissue concentrations with large volume of distributions. We assessed the use of intracerebral CED to deliver CB in patients with recurrent malignant glioma (MG).

Patients and Methods
Three phase I clinical studies evaluated intracerebral CED of CB along with tumor resection. The main objectives were to assess the tolerability of various concentrations and infusion durations; tissue distribution; and methods for optimizing delivery. All patients underwent tumor resection followed by a single intraparenchymal infusion (in addition to the intraparenchymal one following resection), with a portion of patients who had a preresection intratumoral infusion.

Results
A total of 51 patients with MG were treated including 46 patients with GBM. The maximum tolerated intraparenchymal concentration was 0.5 μg/mL and tumor necrosis was observed at this concentration. Infusion durations of up to 6 days were well tolerated. Postoperative catheter placement appears to be important for optimal drug distribution. CB- and procedure-related adverse events were primarily limited to the CNS. Overall median survival for GBM patients is 42.7 weeks and 55.6 weeks for patients with optimally positioned catheters with patient follow-up extending beyond 5 years.

Conclusion
CB appears to have a favorable risk-benefit profile. CED is a complex delivery method requiring catheter placement via a second procedure to achieve accurate catheter positioning, better drug distribution, and better outcome.

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INTRODUCTION

Malignant glioma (MG) is the most common type of primary brain tumor in adults. According to the Central Brain Tumor Registry of the US, it is estimated that each year there are approximately 10,000 new cases. Despite treatment with surgery, radiation therapy, and chemotherapy, the prognosis remains poor particularly for glioblastoma multiforme (GBM) with a median survival of 1 year with best available therapy at initial diagnosis and approximately 6 months after recurrence or progression.1 Even at initial presentation, infiltrating tumor cells extend at least 2 cm away from the radiographic enhancing mass.2,3 The infiltrating tumor component in functional tissue has limited the efficacy of surgery and radiation therapy. Systemic agents are generally ineffective in part because of limited drug delivery. Recent advances in alkylator therapy, either systemic4,6 or intracavitary,7,8 have had some impact, but new avenues of treatment are clearly needed, including new delivery methods.

The vast majority of MG cell lines and explants overexpress a high number of interleukin-13 receptors (IL-13R).9,10 Furthermore, detection of mRNA and protein for the IL-13Rα2 chain indicates MG...
specificity and a much higher expression than in low-grade glioma or non-neoplastic glia.\textsuperscript{11,12} This differential expression provides a specific target for MG therapy.

Cintredex besudotox (CB; Diosynth; Morrisville, NC) is a recombinant cytotoxin composed of human IL-13 and a truncated form of \textit{Pseudomonas aeruginosa} Exotoxin A (PE38QQR).\textsuperscript{9,13} IL-13-PE38QQR mediates cytotoxicity by enzymatic inhibition of protein synthesis and apoptosis leading to cell death.\textsuperscript{14,15} It is highly cytotoxic in vitro and in vivo to IL-13R expressing cells with a 50% inhibitory concentration (IC\textsubscript{50}) of 0.1 to 30 ng/mL.\textsuperscript{5,16}

Tissue distribution of macromolecules into brain parenchyma interstitial space can be facilitated by convection-enhanced delivery (CED), a regional delivery technique with catheters placed directly in target tissue, using a continuous pressure gradient over periods of hours to days circumventing the blood-brain barrier. CED advantages reside in its capability of distributing therapeutic compounds over large volumes of tissue as suggested by preclinical studies showing clinically significant (in the order of cm), reproducible, and homogeneous distribution of molecules of various sizes.\textsuperscript{17-22} CED of therapeutic agents in MG has shown promise in preclinical studies and early clinical development.\textsuperscript{23-29}

\section*{Patients and Methods}

\subsection*{CB}

The full sequence encoding CB was developed by Dr Raj K. Puri (Tumor Vaccines and Biotechnology Branch, Division of Cellular and Gene Therapies, Center for Biologics Evaluation and Research, US Food and Drug Administration, Bethesda, MD) and incorporated into a plasmid at Advanced Bioscience Laboratories (Kensington, MD) and later at Diosynth (Morrisville, NC). \textit{E. coli} cells were transformed with the plasmid-containing CB gene sequence and Master Cell Bank and Working Cell Bank (Diosynth, Morrisville, NC) were prepared. The protein expressed after induction was purified from inclusion bodies under current good manufacturing practice conditions.

\subsection*{Patients}

The clinical studies were open to adults with histologically confirmed recurrent/progressive resectable supratentorial MG (WHO grade 3/4) including GBM, anaplastic astrocytoma, and mixed anaplastic oligoastrocytoma. A Karnofsky performance score (KPS) \(\geq 70\) was required. Patients completed external-beam radiation therapy \(\geq 4\) weeks before study entry and recovered from toxicities from prior systemic therapies. Patients had adequate baseline organ function as assessed by laboratory studies. Patients were excluded if they had signs of impending herniation, multifocal disease, or subependymal or leptomeningeal spread. Patients signed an institutional review board-approved written informed consent before enrollment. Studies were approved by the institutional review boards of all participating centers. Patients were enrolled between December 2001 and June 2004. Study IL13PEI-002 was conducted in four sites, and studies IL13PEI-103 and IL13PEI-105 were each conducted in one site.

\section*{Study Design and Treatment}

Given overlapping objectives, end points, and designs across the three phase I studies (IL13PEI-002, IL13PEI-103, and IL13PEI-105), an aggregate summary of individual studies along with results is presented in Table 1. All patients had tumor resection followed by intraparenchymal placement of one to three silicone barium-impregnated catheters in areas at risk for residual infiltrating tumor, such as regions displaying hyperintense signal abnormality on T2-weighted or fluid-attenuated inversion recovery (FLAIR) images or any residual contrast-enhancing nodule. Immediate catheter placement occurred intraoperatorily after tumor resection using the navigation magnetic resonance imaging (MRI) for image guidance placement while deferred catheter placement occurred 1 to 3 days after tumor resection using the postoperative MRI for stereotactic placement planning. CB was then administered by CED for 96 hours at a fixed total infusion rate of 0.750 mL/h divided by the number of catheters. To control potential mass effect caused by the volume of infusate, patients were maintained on high-dose dexamethasone during and after the infusion. An intratumoral CB infusion preceding tumor resection was also performed in 18 of 51 patients for nontherapeutic exploratory purposes including drug distribution assessments.

A standard dose escalation scheme was used where the maximum-tolerated infusate concentration (MTIC) was defined as the dose-level below that causing dose-limiting toxicity (DLT) in two or more and up to six patients. Each cohort was observed for at least 30 days after completion of administration of study drug to capture unacceptable toxicity before the next cohort was enrolled.

\section*{Patient Assessments}

All patients underwent screening evaluations within 14 days before study entry including medical history, concomitant medications, complete physical and neurologic examinations, KPS, Mini-Mental Status Examination, and

\begin{table}[h]
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\begin{tabular}{|c|c|c|c|c|c|}
\hline
\textbf{Study No.} & \textbf{Patient No.} & \textbf{Objectives} & \textbf{Radiographic and clinical} & \textbf{Study Design} & \textbf{Patient Disposition by CED Parameters} & \textbf{Results} \\
\hline
IL13PEI-002 & 42 & Determine the intraparenchymal MTIC of CB; assess tolerability of longer infusion durations; assess method for catheter positioning optimization & 96-hr intraparenchymal infusion with concentration escalation from 0.25 to 1.0 \(\mu\)g/mL; escalation of duration of infusion at MTIC from 4 to 6 d; immediate or deferred (1-3 d after tumor resection) intraparenchymal catheter placement & 0.25 \(\mu\)g/mL, 2; 0.5 \(\mu\)g/mL, 18; 1.0 \(\mu\)g/mL, 3; 4 d, 36; 5 d, 3; 6 d, 3; immediate placement, 30; deferred placement, 12 & 0.5 \(\mu\)g/mL defined as intraparenchymal MTIC; Infusions up to 6 d well tolerated; deferred stereotactic catheter placement improved positioning and compliance with study guidelines \\
\hline
IL13PEI-105 & 6 & Assess tissue distribution of \(^{123}\text{I}-\text{HSA}\) co-infused with CB & 96-hr intraparenchymal infusion at concentration of 0.5 \(\mu\)g/mL with \(^{123}\text{I}-\text{HSA}\); SPECT and MR imaging at 6 hr, 24 hr, and 48 hr & 0.5 \(\mu\)g/mL, 6 & Intraparenchymal distribution of imaging tracer showed variability based on catheter positioning, with adequate distribution in 10/19 catheters \\
\hline
IL13PEI-103 & 3 & Assess method for catheter positioning optimization & 96-hr intraparenchymal infusion with concentration of 0.5 \(\mu\)g/mL; deferred (1-3 d after tumor resection) intraparenchymal catheter placement & 0.5 \(\mu\)g/mL, 3; deferred placement, 3 & Deferred stereotactic catheter placement improved positioning and compliance with study guidelines \\
\hline
\end{tabular}
\caption{Clinical Study Summary: Patient Disposition, Objectives, and Results}
\end{table}

Abbreviations: CED, convection-enhanced delivery; MTIC, maximum-tolerated infusate concentration; CB, cintredex besudotox; DLT, dose-limiting toxicity; hr, hour; d, day; \(^{123}\text{I}-\text{HSA}\), human serum albumin radiolabeled with \(^{123}\text{I}\); SPECT, single photon emission computed tomography.
laboratory assessments. MRI was obtained at screening, preoperation, within 48 hours after resection, 4 weeks and 8 weeks postoperation, and then every 8 weeks until recurrent or progressive disease. Additional ancillary imaging techniques were used as needed when imaging changes were suggestive of treatment effect. Adverse events were graded according to National Cancer Institutes Common Toxicity Criteria, version 2.0. MRI changes related to CB were evaluated using a 3-point grading system previously published by Parney et al (Appendix Table A1, online only). 50

Catheter Placement and Positioning Evaluation
All catheters were placed with image guidance. Catheter positioning was evaluated with computed tomography or MRI within 24 hours of placement before initiating infusion. Any catheter tip positioned in the CSF compartment on imaging or catheters with any CSF return regardless of imaging appearance were removed. Retrospective catheter positioning evaluation was performed with an objective scoring system based on depth \( \geq 25 \) mm from brain surface, sulcus, or resection cavity; tip distance \( \geq 10 \) mm from ependymal/pial surfaces; and tip distance \( \geq 5 \) mm from resection cavity walls: score 2 = optimal positioning fulfilling all criteria; score 1 = fair positioning fulfilling criteria A and either B or C; score 0 = poor positioning with criteria A not fulfilled. Optimally positioned catheters were defined as score 2.

Drug Distribution Imaging Assessments
Highly purified human serum albumin (HSA; Plasbumin-25, Bayer Corporation, Elkhart, IN) was radiolabeled with \(^{123}\)I (MDS Nordion International, Vancouver, BC, Canada) using a modified iodogen method with a specific activity of 80 mCi/10 mg. A final concentration of \(^{123}\)I-HSA of 0.2% in the infusate was used. Single photon emission computed tomography scans were obtained 6 hours, 24 hours, and 48 hours after infusion initiation and overlaid on MRI scans to evaluate isotope distribution. No additional time points were obtained because of the isotope limited half-life.

Statistical Analyses
Overall survival was estimated by the Kaplan-Meier method. Stratification by drug concentration and catheter positioning was performed. Patients with other histopathology than GBM were excluded from the analysis to insure that the statistical inferences are relevant to the intended patient population and dosage regimens. Log-rank test was used to assess the statistical significance of catheter positioning effect on GBM patient survival. Because most patients had two or three intraparenchymal catheters placed, two catheters optimally positioned was the categorical cut off for outcome analysis by catheter positioning.

To explore survival determinants, a Cox regression model was used to assess the effect of age, sex, performance status, number of prior resections, catheter positioning, and drug concentration. The Cox regression model was a proportional hazards general linear model permitting case-mix adjustment for covariate effects on survival time. Site stratification allowed adjustment for site-specific effects and removal of potential confounds (by site) from the overall treatment effect of interest. Models with and without site stratification were used to provide a sensitivity analysis on potential site differences that could possibly provide a biased estimate of the overall treatment effect.

Patient Demographics
Fifty-three patients were enrolled and had a catheter placed at six study sites in the United States and Israel. Fifty-one patients received intraparenchymal CB. Forty-seven of 51 treated patients received \( \geq 90 \% \) of the intended dose. Demographics are summarized in Table 2.

Safety and Toxicity
Intraparenchymal concentrations of 0.25 \( \mu \)g/mL and 0.5 \( \mu \)g/mL were well tolerated with no patients experiencing any DLT. However, two of three patients treated at 1.0 \( \mu \)g/mL developed DLTs with symptomatic imaging changes consistent radiographically and histopathologically with a necrotic and inflammatory process. The first patient improved with high-dose corticosteroids, while the other patient ultimately required a craniotomy for debulking. Based on those findings, 1.0 \( \mu \)g/mL was determined to be the intraparenchymal dose limiting concentration and 0.5 \( \mu \)g/mL the MTIC. Durations of infusion of 5 and 6 days at the MTIC were well tolerated.

Adverse Events
From the first procedure (stereotactic biopsy or craniotomy) to a minimum of 30 days after completion of drug infusion, adverse events were reported for all patients. Most of the reported adverse events originated from the CNS. Approximately 60% of all
adverse events and 85% of study drug-related adverse events were neurologic or psychiatric. The most common adverse events related to CB were outlined in Table 3. Seventy-seven percent of these events resolved except for hemiparesis where most events were not resolved at the time of data cut off. There was no relationship between drug concentration and severity of adverse events. No specific adverse events were observed with suboptimally positioned catheters associated with leakage in the CSF compartment (for example, chemical meningitis) as observed in CB distribution by imaging. No patients were lost to follow-up. The majority of patients died from tumor progression while three patients died from other causes, and two patients had an unknown cause of death. One patient died of neurologic decline possibly related to CB. No clinical or laboratory abnormalities were suggestive of drug effect on organ functions.

CB-Related Imaging Changes

The profile of MRI changes related to CB was described by Parney et al. Grade IV changes were only seen in patients receiving the dose limiting intraparenchymal concentration (1.0 mg/mL). Grade III changes were observed predominantly in patients receiving intraparenchymal concentrations 0.5 mg/mL, but also at 0.25 mg/mL. For patients receiving intraparenchymal concentrations ≤ 0.5 mg/mL, imaging changes reached their maximum grade by 4 weeks to 8 weeks post-treatment, then stabilized or slowly resolved over several weeks. Patients who received 1.0 mg/mL had a more protracted time course.

Catheter Positioning Evaluation

Timing of catheter placement revealed that 56% and 83% of patients had two or more catheter(s) with score 2 with immediate placement and deferred placement, respectively.

CB Distribution Assessment by Imaging

Descriptive imaging assessment of drug distribution using 123I-HSA as imaging tracer surrogate for CB was based on 17 intraparenchymal catheters placed in six patients. Ten catheters resulted in clinically significant distribution defined as distribution of the majority of the imaging tracer into brain parenchyma with no or minimal leakage in the CSF compartment while seven catheters did not because of leakage in the CSF compartment primarily related to presence of deep sulci crossing the distal catheter trajectory (in general within 20 mm from the tip) and less commonly because of catheter tip violating pial or ependymal surfaces. Single photon emission computed tomography imaging demonstrated, for infusion without complete leakage in the CSF compartment, that the volume of distribution increased progressively over 48 hours and the mean volume of distribution at 48 hours for the 50% isodose level was 17.9 cm³ ± 12.5 cm³ (mean ± standard deviation). Deeply positioned catheters, in general greater than 20 mm from any surfaces (including deep sulci), provided some of the best volumes of distribution catheters. Catheters perforating pial or ependymal surfaces consistently led to complete CSF compartment leakage of the imaging tracer. Examples of poor and clinically significant drug distribution are displayed in Appendix Figures A1 and A2, and suboptimal catheter positioning in Appendix Figure A3 (all online only).

Survival

Four of 51 patients are alive, all GBM. An overall median survival after treatment of 45.9 weeks (95% CI, 37.4 to 59.3) was observed for the entire group (N = 51). There was no significant survival difference across drug concentrations. Median survival after treatment for GBM patients was 42.7 weeks (95% CI, 35.6 to 55.6) including 1-year and 2-year survival of 39.1% and 13%, respectively (n = 46). Considering catheter positioning, the median survival was 55.6 weeks (95% CI, 36.1 to 74.3) for GBM patients with two or more catheters that met the guidelines (n = 24) and 37.4 weeks (95% CI, 21.0 to 45.9) for GBM patients with fewer than two catheters optimally positioned (n = 19) statistically significant by log-rank test (P = .0520) and significant by Cox regression (P = .0013; Fig 1). Nine patients (17.6%) and seven patients (13.7%), all with GBM except one, had a prolonged progression-free survival beyond 1 and 2 years, respectively. Follow-up continues for all patients who are alive.

Survival Determinants

A total of 41 patients with histopathologically confirmed GBM treated at concentrations of 0.25 and 0.5 mg/mL were examined. One patient was excluded because of missing baseline KPS and one patient was excluded because of change in histopathology to GBM after the analyses were performed. Without site stratification the number of

| Table 3. Summary of the Most Frequently Reported Adverse Events Related to Cintredekin Besudotox | Patients |
| --- | --- | --- | --- |
| Patients | Events of Any Grade | Grade 3 or 4 Events | |
| Adverse Event | No. | % | No. | % |
| Headache | 21 | 41 | 1 | 2 |
| Sensory disturbance | 13 | 25 | 0 | 0 |
| Aphasia/speech disorder | 9 | 18 | 1 | 2 |
| Asthenia | 8 | 16 | 0 | 0 |
| Convulsion | 7 | 14 | 1 | 2 |
| Hemiparesis | 7 | 14 | 6 | 12 |
| Facial paresis | 6 | 12 | 0 | 0 |
| Gait disorder | 6 | 12 | 0 | 0 |
| Upper motor neuron lesion | 5 | 10 | 0 | 0 |
| Nausea | 4 | 8 | 0 | 0 |
| Pyrexia | 4 | 8 | 0 | 0 |
| Memory impairment | 4 | 8 | 0 | 0 |

Fig 1. Overall survival for glioblastoma multiforme (GBM) treated with intraparenchymal cintredekin besudotox at 0.25 μg/mL, 0.5 μg/mL, or 1.0 μg/mL by catheter positioning.
optimally positioned catheters and PS appeared to have a significant inverse relationship with time to death while site stratification revealed even more pronounced hazard ratios for the same variables and significance for sex favoring female (Table 4).

### DISCUSSION

The early phase results presented suggest that CB has a favorable risk-benefit profile. All concentrations used in the studies presented were considered equivalent in terms of efficacy based on in vitro data and as shown in the survival determinants analysis. However, 1.0 μg/mL appears dose limiting and consequently 0.5 μg/mL the MTIC. Most adverse events observed originated from the CNS, particularly those related to CB and catheter placement, and the majority of the latter was reversible. The nonresolution of most CB-related hemiparesis could be related to other factors that may have been difficult to differentiate from CB in the patient population including underlying disease and surgical procedures. CB and procedure-related adverse events were often worsening of pre-existing neurologic deficits. Those adverse events were also typical of events that are expected in a population of patients with brain tumors undergoing surgical procedures. No significant systemic toxicity was noted consistent with locoregional delivery and minimal systemic exposure.

Imaging changes related to CB observed appear concentration dependent with grade IV changes only observed at the dose-limiting concentration (1.0 μg/mL). While grade III and IV imaging changes are regarded as a necrotic and inflammatory process involving tumor-infiltrated and normal brain parenchyma, grade I and II, which were always asymptomatic even in eloquent brain region, are probably expected changes if the drug is successfully distributed. While the exact mechanism underlying those grades III and IV imaging changes is unclear, nonspecific internalization of CB appears conceivable above certain concentrations through cell surface saturation and random uptake. In addition, in vitro observations suggest that concentrations higher than 0.7 μg/mL result in cytotoxicity in astrocyte cultures (Puri et al, unpublished data). An immune-mediated mechanism is also conceivable given the delayed onset and the response to corticosteroids. Diagnosis and management of these changes have been previously published.

Timing of catheter placement appears to influence positioning accuracy based on postplacement imaging. Immediate placement after tumor resection is based on the preoperative navigation MRI, which becomes less accurate as brain shift and re-expansion develop during resection. In addition, postoperative edema may result in catheter displacement. Based on these observations, deferred placement using a postoperative navigation imaging for planning and an additional stereotactic procedure appears justified. Meticulous catheter placement planning using the guidelines outlined in the scoring system is critical in optimizing drug distribution as shown by imaging tracer coinfusion with CB with catheter depth as the most critical factor, survival results stratified by number of optimally positioned catheters, and survival determinants analysis. The importance of depth is related to the fact that deep sulcus may often intersect the catheter trajectory if placement is not planned properly and this may in turn lead to a path of least resistance for the infusate to leak into the CSF compartment as preclinical modeling studies have shown an average backflow of infusate of 20 mm along the catheter with the catheter configuration and diameter as well as flow rates used in these studies. The significant correlation of catheter score and survival (Table 4) suggests that drug delivery strongly influences overall outcome as optimal catheter positioning improves drug distribution into the surrounding tissue while suboptimal catheter positioning results in partial or total distribution into the CSF compartment. Example cases of local disease control in relation to catheter positioning are shown in Figure 2. Implementation of those measures in turn will help provide a better assessment of drug safety and efficacy.

Pooling of the three phase I studies without compromising the interpretability of overall findings is supported by the absence of effect attenuation with stratification by site in the Cox regression
model. Survival observations, especially GBM patients with two or more optimally positioned catheters at 55.6 weeks, compare favorably with the literature data for bis-chloroethyl nitrosourea wafers (BCNU; Gliadel Wafer; Guilford Pharmaceuticals; Baltimore, MD) in GBM with a median survival of 28 weeks and an estimated 1-year and 2-year survival of $\approx 15\%$ and $\approx 10\%$, respectively. Particularly compelling is the fact that several recurrent GBM patients had a prolonged progression-free survival more than 1 to 2 years—most of them without any additional antitumor treatment after ILQQR CB administration.

In conclusion, CB appears to have a favorable risk-benefit profile at clinically tolerated concentrations. Direct interstitial delivery of a targeted recombinant cytotoxin, such as CB into tumor-infiltrated brain, can lead to preservation of neuronal function and local tumor control. Survival results from those early phase studies are very encouraging and warrant further evaluation of CB.
Phase III Randomized Evaluation of Convection Enhanced Delivery
of IL13-PE38QQR Compared to Gliadel Wafer with Survival Endpoint in Glioblastoma Multiforme Patients at First Recurrence (PRECISE) study comparing CB to Gliadel Wafer are expected in early 2007. Establishing methodologies, such as catheter positioning guidelines, to consistently achieve optimal drug distribution is critical for safety and efficacy assessment of putative therapeutic agents administered by CED such as CB.

**AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest.

No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO’s conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Appendix
The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).