Kansas City

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Convection-Enhanced Delivery of Therapeutic Agents to the Brain

Policy Number: 8.01.504
Origination: 3/2007
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Next Review: 3/2015

Policy

Blue Cross and Blue Shield of Kansas City (Blue KC) will not provide coverage for convection-enhanced delivery of therapeutic agents to the brain. This is considered investigational.

When Policy Topic is covered

Not Applicable

When Policy Topic is not covered

Convection-enhanced delivery of therapeutic agents to the brain is considered **investigational**.

Description of Procedure or Service

Despite advances in diagnostic imaging and drug discovery, primary malignant brain tumors remain fatal. Median survival for patients with the most severe forms is rarely past eight months. Malignant gliomas have a characteristic ability to infiltrate healthy brain tissue and form satellite tumors. This capacity for migration makes them exceedingly difficult to treat. Even after resection, invasive cells can give rise to tumors within centimeters of the resection site. Untreated malignant tumors can eventually spread to the contralateral hemisphere.

Many forms of systemic chemotherapy are excluded from the central nervous system by the blood-brain barrier (BBB). The blood-brain barrier is the tight lining of the cerebral vessels that protects against damaging substances such as large molecular particles from entering the brain. Most chemotherapeutic agents are large in molecular weight and are not allowed through the blood-brain barrier to treat the brain tumor when administered intravenously. The failure of conventional systemic drug delivery for glioma has motivated more direct approaches to drug delivery. Direct intracranial drug delivery would eliminate the need for chemotherapeutic agent to cross the blood-brain barrier.

Convection-enhanced delivery of therapeutic agents to the brain is an attempt to deliver an increased concentration of the agent to the brain tumor. Research is being done utilizing the stereotactic method of placing catheter(s) into the brain through cranial burr holes. Therapeutic agents are delivered through the catheters using microinfusion pumps directly to the brain tumor bypassing the blood-brain barrier. This increases the drug-tumor contact time.

Convection-enhanced delivery is limited by its invasiveness and by the anatomical influences on drug distribution. It requires the insertion of a catheter several centimeters deep into the brain, which can cause tissue damage and may induce air bubbles. The anatomy of the brain affects the distribution of drugs. The unpredictable flow can lead to collection of drug either in the perivascular spaces, wound track, or under the scalp. This has caused incidences of edema and wound dehiscence.

There are ongoing clinical trials to better understand convection-enhanced delivery and its effect on health outcomes.

Rationale

Although blood brain barrier delivery (BBBD) techniques have been used for over 20 years, the efficacy of this technique has been questioned, as the long-term effects of BBBD chemotherapy are unknown, and no randomized controlled trials have established the superiority of BBBD chemotherapy over conventional chemotherapy. In addition, BBBD with chemotherapy is associated with a higher risk of complications than conventional chemotherapy. Complications associated with BBBD include seizures, obtundation, focal neurologic deficits, cerebral herniation, strokes, death, as well as the side-effects related to the chemotherapeutic agents themselves. CMS is opening a National Coverage Analysis to determine if BBBD chemotherapy is reasonable and necessary for Medicare beneficiaries.

Novel, targeted antineoplastics are in development for brain tumors. However, their administration has been hampered by the blood-brain barrier, which prevents passage of large molecules.

One such targeted antineoplastic that is administered by convection-enhanced delivery is cintredekin besudotox, a novel cytotoxin-based therapy that is being investigated for the treatment of recurrent glioblastoma multiforme. Cintredekin besudotox is a recombinant protein consisting of a single molecule composed of two parts: 1) interleukin-13 (IL13) which binds to receptors on tumor cells; and 2) Pseudomonas exotoxin (PE), a cytotoxin, which causes destruction of the tumor cell once the molecule is absorbed. IL13 receptors are present in substantial numbers on malignant glioma cells, but only a minimal amount on healthy brain cells. Hence, cintredekin besudotox has the potential to target tumor cells, with minimal impact on surrounding normal brain tissue.

Because of its large size, cintredekin besudotox cannot cross the blood brain barrier. In clinical studies, cintredekin besudotox has been administered by convection-enhanced delivery. Catheters are placed following tumor resection, in areas of microscopic tumor spread or at risk of tumor spread around the tumor resection cavity. Because of the need to achieve homogenous distribution of cintredekin besudotox throughout the tumor infiltrated tissue, the catheters cannot be placed in any previous resection cavity.

Once the patient is stable, approximately two weeks following craniotomy with tumor resection, the patient is admitted for catheter placement and antineoplastic infusion. Catheters are strategically placed by neurosurgeons, taking into account the location of residual non-resectable tumor, brain anatomy, and fluid dynamics. Anywhere from two to four catheters are placed during a surgical procedure lasting several hours. Cintredekin besudotox is then slowly infused through the catheter directly into the brain over 96 hours.

Available Phase I/II clinical studies of cintredekin besudotox suggest that this is a promising agent for treatment of recurrent glioblastoma multiforme. A phase III trial (PRECISE) is currently underway. Cintredekin besudotox has been granted fast track development designation and orphan drug designation by the U.S. Food and Drug Administration (FDA), and may be approved by the FDA as early as 2007.

At present, the pharmacokinetics of convection-enhanced delivery are poorly understood. More research is needed to determine the optimal catheter location to distribute a drug to target tumor cells within the tumor mass and in the infiltrated adjacent parenchyma. Optimal catheter design is being researched to minimize backflow, to maximize distribution in the brain, and to account for the need to maintain patient mobility.

Raghavan, et al. (2006) explain that, although convection-enhanced delivery has been under investigation since the early 1990's, "this technique remains experimental because of both the absence of approved drugs for intraparenchymal delivery and the difficulty of guaranteed delivery to delineated regions of the brain."

Sampson et al (2008) determined the maximum tolerated dose (MTD), dose-limiting toxicity (DLT), and intra-cerebral distribution of a recombinant toxin (TP-38) targeting the epidermal growth factor receptor in patients with recurrent malignant brain tumors using the intra-cerebral infusion technique of

convection-enhanced delivery (CED). A total of 20 patients were enrolled and stratified for dose escalation by the presence of residual tumor from 25 to 100 ng/ml in a 40-ml infusion volume. In the last 8 patients, co-infusion of (123)I-albumin was performed to monitor distribution within the brain. The MTD was not reached in this study. Dose escalation was stopped at 100 ng/ml due to inconsistent drug delivery as evidenced by imaging the co-infused (123)I-albumin. Two DLTs were seen, and both were neurological. Median survival after TP-38 was 28 weeks (95 % confidence interval: 26.5 to 102.8). Of the 15 patients treated with residual disease, 2 (13.3 %) demonstrated radiographical responses, including 1 patient with glioblastoma multiforme who had a nearly complete response and remains alive for over 260 weeks after therapy. Co-infusion of (123)I-albumin demonstrated that high concentrations of the infusate could be delivered over 4 cm from the catheter tip. However, only 3 of 16 (19 %) catheters produced intra-parenchymal infusate distribution, while the majority leaked infusate into the cerebrospinal fluid spaces. Intra-cerebral CED of TP-38 was well-tolerated and produced some durable radiographical responses at doses less than or equal to 100 ng/ml. The authors concluded that CED has significant potential for enhancing delivery of therapeutic macromolecules throughout the human brain. However, the potential efficacy of drugs delivered by this technique may be severely constrained by ineffective infusion in many patients.

Fiandaca and colleagues (2008) stated that CED of substances within the human brain is becoming a more frequent experimental treatment option in the management of brain tumors, and more recently in phase 1 trials for gene therapy in Parkinson's disease (PD). Benefits of this intracranial drug-transfer technology include a more efficient delivery of large volumes of therapeutic agent to the target region when compared with more standard delivery approaches (i.e., biopolymers, local infusion). These researchers developed a reflux-resistant infusion cannula that allows increased infusion rates to be used. They also described their efforts to visualize the CED process in vivo, using liposomal nanotechnology and real-time intra-operative MRI. In addition to carrying the MRI contrast agent, nanoliposomes also provide a standardized delivery vehicle for the convection of drugs to a specific brain-tissue volume. This technology provides an added level of assurance via visual confirmation of CED, allowing intra-operative alterations to the infusion if there is reflux or aberrant delivery. These investigators proposed that these specific modifications to the CED technology will improve efficacy by documenting and standardizing the treatment-volume delivery. Furthermore, they believe that this image-guided CED platform can be used in other translational neuroscience efforts, with eventual clinical application beyond neuro-oncology and PD.

In a review on novel drug delivery strategies in neuro-oncology, Bidros and Vogelbaum (2009) stated that an important impediment to finding effective treatments for malignant gliomas is the presence of the BBB, which serves to prevent delivery of potentially active therapeutic compounds. Multiple efforts are focused on developing strategies to effectively deliver active drugs to brain tumor cells. Convection-enhanced delivery and BBBD have emerged as leading investigational delivery techniques for the treatment of malignant brain tumors. Clinical trials using these methods have been completed, with mixed results, and several more are being initiated.

Bidros et al (2010) stated that CED has emerged as a leading investigational delivery technique for the treatment of brain tumors. Clinical trials utilizing these methods have been completed, with mixed results, and several more are being initiated. However, the potential effectiveness of drugs delivered by CED may be severely constrained by poor durg distribution.

Sampson et al (2010) retrospectively analyzed the expected drug distribution based on catheter positioning data available from the CED arm of the PRECISE trial. BrainLAB iPlan Flow software was used to estimate the expected drug distribution. Only 49.8 % of catheters met all positioning criteria. Still, catheter positioning score (hazard ratio 0.93, $p = 0.043$) and the number of optimally positioned catheters (hazard ratio 0.72, $p = 0.038$) had a significant effect on progression-free survival. Estimated coverage of relevant target volumes was low, however, with only 20.1 % of the 2-cm penumbra surrounding the resection cavity covered on average. Although tumor location and resection cavity volume had no effect on coverage volume, estimations of drug delivery to relevant target volumes did correlate well with catheter score ($p < 0.003$), and optimally positioned catheters had larger coverage

volumes ($p < 0.002$). Only overall survival ($p = 0.006$) was higher for investigators considered experienced after adjusting for patient age and Karnofsky Performance Scale score. The authors concluded that potential effectiveness of drugs delivered by CED may be limited by ineffective delivery in many patients.

Buonerba et al (2010) stated that glioblastoma multiforme (GBM) is the most frequent and aggressive malignant glioma (MG), with a median survival time of 12 to15 months, despite current best treatment based on surgery, radiotherapy and systemic chemotherapy. Many potentially active therapeutic agents are not effective by systemic administration, because they are unable to cross the BBB. As intra-cerebral administration bypasses the BBB, it increases the number of drugs that can be successfully delivered to the brain, with the possibility of minor systemic toxicity and better effectiveness. These researchers summarized the results of the extensive clinical research conducted on intra-cerebral therapy. Biodegradable drug carriers, implantable subcutaneous reservoirs and CED represent the main techniques for intra-cerebral delivery, while conventional chemotherapy agents, radiolabeled antibodies and receptor-targeted toxins are the main classes of drugs for intra-cerebral therapy. At the present time, biodegradable carmustine wafers, commercialized as Gliadel, are the only FDA-approved treatment for intra-cerebral chemotherapy of MG, but intra-cavitary delivery of mitoxantrone and radiolabeled anti-tenascin antibodies via implantable reservoirs has yielded promising results in uncontrolled trials. The pressure-driven flow generated by CED can potentially distribute convected drugs over large volumes of the brain, independently on their intrinsic diffusivity. Nevertheless, prominent technical problems, like back-flow, are yet to be properly addressed and contributed to the disappointing results of 2 phase III trials that investigated CED of cintredekin besudotox and TransMid in patients with recurrent GBM.

In a prospective, dose-escalation phase Ib study, Bruce et al (2011) examined the safety profile of topotecan via CED in the treatment of recurrent malignant gliomas and assessed radiographical response and survival. Significant anti-tumor activity as described by radiographical changes and prolonged overall survival with minimal drug-associated toxicity was demonstrated. A MTD was established for future phase II studies. The authors concluded that topotecan by CED has significant anti-tumor activity at concentrations that are non-toxic to normal brain. The potential for use of this therapy as a generally effective treatment option for malignant gliomas will be tested in subsequent phase II and phase III trials.

There continues to be a need for additional research into the use of convection-enhanced delivery of therapeutic agents to the brain to define effective agents and treatment parameters and to compare this treatment to standard medical and surgical care. There is insufficient evidence in the medical literature to demonstrate the safety and efficacy of this technique.

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Billing Coding/Physician Documentation Information

0169T	Stereotactic placement of infusion catheter(s) in the brain for delivery of therapeutic agent(s), including computerized stereotactic planning and burr hole(s)

Additional Policy Key Words

N/A

Policy Implementation/Update Information

3/1/07	New policy; considered investigational.
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3/1/13	No policy statement changes.
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