


MEDICAL POLICY	Blood Brain Barrier Disruption and Bypass (All Lines of Business Except Medicare)
Effective Date: 7/1/2022	Medical Policy Number 147
	Technology Assessment Committee Approved Date: 11/10; 11/12
Medical Officer	Medical Policy Committee Approved Date: 6/02; 7/03; 7/04; 7/06; 11/08; 9/13; 8/14; 9/15; 2/16; 5/17; 6/18; 8/19; 04/2020; 5/2021; 6/2022
Date	

See Policy CPT/HCPCS CODE section below for any prior authorization requirements

SCOPE:

Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as “Company” and collectively as “Companies”).

APPLIES TO:

All lines of business except Medicare (*unless otherwise directed by a Medicare medical policy. Note that investigational services are considered “not medically necessary” for Medicare members.*)

BENEFIT APPLICATION

Medicaid Members

Oregon: Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

POLICY CRITERIA

- I. Blood brain barrier disruption (BBBD) is considered **investigational and is not covered** as a method of treatment for any condition.
- II. Convection-enhanced delivery (CED) of therapeutic agents to the brain is considered **investigational and is not covered** as a method of treatment for any condition.

Link to [Policy Summary](#)

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CPT/HCPCS CODES

All Lines of Business Except Medicare	
Prior-authorization Required	
36215	Selective catheter placement, arterial system; each first order thoracic or brachiocephalic branch, within a vascular family
36216	Selective catheter placement, arterial system; initial second order thoracic or brachiocephalic branch, within a vascular family
36217	Selective catheter placement, arterial system; initial third order or more selective thoracic or brachiocephalic branch, within a vascular family
36218	Selective catheter placement, arterial system; additional second order, third order, and beyond, thoracic or brachiocephalic branch, within a vascular family (List in addition to code for initial second or third order vessel as appropriate)
Unlisted Codes	
All unlisted codes will be reviewed for medical necessity, correct coding, and pricing. If an unlisted code is billed related to services addressed in this policy then it will be denied as not covered .	
64999	Unlisted procedure, nervous system
96549	Unlisted chemotherapy procedure

DESCRIPTION

Primary and metastatic brain tumors are a heterogeneous group of neoplasms currently affecting almost 700,000 people in the United States.¹ These neoplasms have varied outcomes and management strategies depending on whether the malignancy is surgically curable or responsive to radiation and/or chemotherapy. Traditional chemotherapy is considered to be of marginal benefit for many types of brain tumors primarily due to its inability to reach the tumor in effective concentrations. The blood-brain barrier (BBB) prevents uptake of most traditional chemotherapeutic agents into the brain, thereby limiting the efficacy of treatment. However, new treatments have been developed in an effort improve drug delivery to brain tumors and lead to prolonged survival, including:

- Blood-brain barrier disruption (BBBD): A technique also referred to as “barrier modification” therapy that typically utilizes a hyperosmotic solution such as mannitol to increase the permeability of the blood-brain barrier (BBB). The osmotic agent is purported to temporarily shrink the brain’s protective barrier of tightly knit cells, to allow for transport of drugs to the brain.
- Convection-enhanced delivery (CED): CED facilitates drug infusion directly into the tumor or resection cavity through surgically implanted catheters. CED has the potential to optimize the delivery of drugs to the affected area through positive-pressure via a microinfusion pump to control drug distribution.

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In addition to enhancing delivery of therapeutic agents for brain tumors, BBBD and CED have been proposed as potential delivery methods for drugs to treat neurological disorders such as epilepsy and Alzheimer’s.

REVIEW OF EVIDENCE

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the use of blood-brain barrier disruption and convection-enhanced delivery as treatments for any condition. Below is a summary of the available evidence identified through April 2022.

Blood-Brain Barrier Disruption

Systematic Reviews

In 2021, Arba and colleagues conducted a systematic review and meta-analysis reviewing blood-brain barrier disruption and hemorrhagic transformation (HT) in acute ischemic stroke.² Investigators systematically searched the literature through March 2020, identified eligible studies, assessed study quality, extracted data and pooled results. The outcome of interest was HT at follow-up imaging evaluation (within 48 h from symptom onset). We pooled data from available univariate odds ratios (ORs) in random-effects models with DerSimonian-Laird weights and extracted cumulative odds ratios. In total, 30 eligible studies were included for review, assessing 2,609 patients, with 88% and 70% of patients included in computed tomography (CT) and magnetic resonance (MR) studies treated with acute stroke therapy, respectively. The majority of studies were retrospective and had high or unclear risk of bias. BBB disruption was measured with consistent methodology in CT studies, whereas in MR studies, there was more variability. All CT studies provided a BBB disruption cutoff predictive of HT. Four CT and 10 MR studies were included in the quantitative analysis. Authors reported that BBB disruption was associated with HT with both CT and MR. Authors concluded that BBB disruption is associated with HT in both CT and MR studies. Compared with MR, CT has been more uniformly applied in the literature and has resulted in more consistent results. Additional studies with standardized protocols and methodology for implementation of BBB disruption were determined to be necessary.

Randomized Controlled Trials (RCTs)

No randomized controlled trials were identified comparing blood-brain barrier disruption to standard delivery methods for chemotherapeutic agents for any type of brain tumor.

Nonrandomized Studies

In 1991, Neuwelt et al. reported on a case series of 30 consecutive patients with primary CNS lymphoma who were treated with barrier-dependent chemotherapy using intra-arterial mannitol to disrupt blood-brain barrier (BBB).³ Seventeen patients received initial BBB disruption chemotherapy with subsequent radiation only for tumor progression or recurrence. A complete response was observed in seven

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patients, six of which maintained preservation of cognitive function for between one to seven years. The authors concluded that this treatment may lead to increase in patient survival without the neuropsychologic sequelae associated with cranial radiation. However, the study is limited by a lack of randomized design and small sample size which preclude conclusions regarding the use of mannitol to disrupt the BBB.

In 2008, Jahnke et al. evaluated the use of intra-arterial chemotherapy (either carboplatin or methotrexate) and osmotic blood-brain barrier disruption (IA/BBBD) to treat 54 patients with embryonal and certain germ cell tumors of the central nervous system (CNS).⁴ The median overall survival (OS) was 2.8 years for all patients, 2.5 years for supratentorial and disseminated primitive neuroectodermal tumors (PNETs, n = 29), 1.7 years for medulloblastomas (n = 12), and 5.4 years for germ cell tumors (n = 13). OS and time to progression (TTP) were reported as being significantly better when IA/BBBD as used as first-line treatment compared to salvage treatment in all patients (p=0.0059 and 0.029, respectively). In PNETs, OS was higher with pineal location (p=0.045) and IA/BBBD as first-line treatment (p= 0.0036), and TTP was improved with radiotherapy before IA/BBBD (p=0.036) and IA/BBBD as first-line treatment (p=0.0079). The authors concluded that the results of their study were promising and that a plateau in survival curves suggests a cure for some patients and long-term survival (4-18 years) may be achieved, but future studies were needed.

In 2009, Angelov et al. reported on a multi-institutional case series of 149 newly diagnosed patients with primary CNS lymphoma (PCNSL) treated with osmotic BBBD and intra-arterial (IA) methotrexate.⁵ The overall response rate was 81.9% (57.8% complete; 24.2% partial). Median overall survival (OS) was 3.1 years and median progression-free survival (PFS) was 1.8 years, with 5-year PFS of 31% and 7-year PFS of 25%. A total of 697 treatment-related complications occurred, with the most frequent being periprocedural focal seizures, occurring in 50 patients (33.6%; 9.2% of procedures). The overall rate of procedural morbidity was reported as 327 events (15.7% of procedures). Clinical strokes occurred in 11 patients (7.4%); and four patients were left with permanent neurologic deficits.

In 2010, Boockvar et al. prospectively assessed the safety of intra-arterial cerebral infusion of bevacizumab after osmotic disruption of the BBB with mannitol in 30 patients with recurrent malignant glioma.⁶ The results reported from the completed Phase I portion of a Phase I/II study design. Two groups of patients were studied; those without prior bevacizumab exposure (naïve patients; Group I) and those who had received previous intravenous bevacizumab (exposed patients; Group II). At one month post-procedure group I patients, showed a median reduction in the area of tumor enhancement of 34.7% and a median reduction in the volume of tumor enhancement of 46.9%. Conversely, group II patients showed a median reduction in the area of tumor enhancement of 15.2% and a median volume reduction of 8.3%. The authors conclude that further examination of this treatment modality is required.

Several additional small case series, typically including less than 20 patients have also been published, on the efficacy, toxicity and adverse event associated with this treatment for various brain cancers.⁷⁻¹⁰

Summary

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The evidence regarding the safety and efficacy of blood-brain barrier disruption using hyperosmotic compounds to shuttle chemotherapeutic agents into the brain to treat brain tumors mainly consists of small to moderately sized case series for a number of different neoplasms. The largest case series published to date (n=149) reported promising response and overall survival rates, but also reported concerning rates of moderate to severe adverse events. Overall, the current evidence indicated this treatment has led to a significant increase in neurotoxicity compared with standard chemotherapeutic administration and has not demonstrated overall survival benefit at this time. Further studies reporting long-term outcomes for specific brain neoplasms are needed to determine the safety and efficacy of the treatment modality.

In addition, no clinical studies in humans have been published that address the use of BBBD for the treatment of Alzheimer’s disease, Parkinson’s disease, epilepsy, or any other neurological disorder.

Convection-enhanced Delivery (CED)

Systematic Reviews

No systematic reviews were identified evaluating convection-enhanced delivery of therapeutic agents to the brain.

Randomized Controlled Trials (RCTs)

In 2010, Kunwar et al. reported results of phase 3 of the PRECISE trial; a multicenter study of 296 adult patients with glioblastoma multiforme (GBM) randomized to either postoperative cintredekin besudotox (CB) or gliadel wafer (GW) to treat first recurrence.¹¹ Patients were enrolled at 52 centers between March 2004 and December 2005. CB was administered using convection-enhanced delivery (CED), over 96 hours via 2-4 intraparenchymal catheters placed after tumor resection at a flow rate 0.75 mL/h. GW (carmustine wafers) were placed immediately after tumor resection. Median survival was not significantly different between groups (9.1 months for CB versus 8.8 months for GW). There was no significant difference in the primary endpoint of overall survival (OS) between groups. The adverse-events profile was similar in both treatment groups; however, pulmonary embolism was significantly higher in the CB group (8% versus 1%, p=0.014), which was thought to be due to the prolonged hospital stayed required for the CED infusion procedure. The authors stated that drug distribution, which is crucial in evaluating whether the agent is distributed to the targeted region in sufficient concentrations to have a therapeutic effect, was not assessed in this study.

In 2011, Bogdahn et al. reported on an RCT that evaluated the efficacy and safety of trabedersen administered intratumorally by CED compared with standard chemotherapy in 145 patients with recurrent/refractory GBM or anaplastic astrocytoma (AA).¹² Patients were either treated with trabedersen at doses of 10 or 80 µM using CED, or with standard chemotherapy. Six-month tumor control rates were analyzed in 134 patients (a composite outcome consisting of complete response, partial response, and stable disease) at six-month follow-up were not significantly different between treatment groups. At 14-month follow-up, the group treated with 10 µM trabedersen had a significantly

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better tumor control rate compared to the chemotherapy group (p= 0.0032). Median survival rates and two-year survival rates were not significantly different between treatment groups. In GBM patients alone, response and survival results were comparable among the three treatments. Similar results were seen when AA patients were analyzed separately. The authors reported that adverse events (AEs) leading to permanent discontinuation of treatment were more common in the trabedersen groups than with standard chemotherapy, but the frequency of drug-related adverse events was higher with standard chemotherapy than with either trabedersen treatment. However, it is unclear if these differences were significant, as no p-values were reported. Of note, procedure-related serious AEs were reported in between 31-34% of patients receiving trabedersen via CED, including application site infection and complications associated with catheter placement.

Nonrandomized Studies

In 2006, Kunwar et al. reported on the use of CED for the delivery of cintredekin besudotox (CB) in 51 individuals with malignant gliomas, 46 of which were GBM.¹³ Patients fell into three treatment groups: (1) tumor resection followed immediately by intraoperative placement of CED catheters, (2) tumor resection followed by delayed placement of catheters (one to three days), and (3) catheter placement and infusion preceding tumor resection. Adverse events were reported in all three groups, with the most common being headaches, sensory disturbances and aphasia. The majority of these AEs (77%) resolved, except hemiparesis, which was considered a serious AE, observed in 12% of patients.

In 2010, Sampson et al. reported a retrospective analysis of catheter positioning and drug distribution on 174 patients from the CED arm of the PRECISE trial, described above.^{11,14} Only 49.8% of the catheters placed met all criteria for positioning. However, catheter positioning score and the number of optimally positioned catheters had a significant effect on progression-free survival. The authors concluded that potential effectiveness CED to deliver drugs may be ineffective in many patients, but additional trials were necessary to determine optimized CED catheter placement; verification of drug delivery and distribution.

In 2010, Carpentier et al. published the results from a phase to study evaluating CED-based delivery of CpG oligonucleotides for treatment of recurrent GBM, including 34 patients enrolled at two centers from November 2004 and March 2006.¹⁵ For the 31 patients who received treatment, progression-free survival (PFS) at six months was 19%. The median overall survival was 28 weeks. At one- and two-year follow up, eight patients (24%) and 5 patients (15%) were alive, respectively. The most common adverse events reported were lymphopenia, mild fever, seizures, and transient neurological decline. The authors concluded that this treatment only showed modest efficacy in this patient population.

In 2012, Shahar et al. reported a retrospective analysis of adverse events associated with CED catheter placement for treatment of recurrent GBM at a single institution including 25 patients who underwent placement of a total of 64 CED catheters.¹⁵ Participants were treated with one to three catheters, and the timing and number of surgeries varied within the patients. Complications included increased edema (31%), infection (6.9%), bleeding (6.9%) and seizures (13.8%). Significant neurological deterioration occurred in 4 patients (13.8%). The authors concluded that CED procedures for high-grade gliomas may

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be associated with surgical morbidity and that further studies are needed to determine the risks and benefits of CED for GBM treatment.

Several additional small to moderately-sized case series (n=18-51) have been published on the efficacy, toxicity and adverse event associated with CED-based treatment for various brain cancers. The majority of these studies included patients with GBM and/or anaplastic astrocytomas, treat with different antitumor drugs, have heterogeneous treatment protocols a variable follow-up times.¹⁶⁻¹⁹

Summary

The evidence regarding the safety and efficacy of convection-enhanced delivery chemotherapeutic agents to the brain to treat brain tumors consists of two large randomized controlled trials and several small to moderately sized case series. The majority of studies focused on patients with glioblastoma and/or anaplastic astrocytoma, but all were administering different antitumor agents, using heterogeneous delivery protocols. The largest RCT published to date (n=296), and the only phase 3 study, reported that there were no significant differences in median or overall survival in patients treated with CED-administered drugs compared to those treated with gliadel wafers placed after resection. Further studies reporting longer-term follow-up and more standardized treatment protocols are needed to determine the safety and efficacy of CED-administered antitumor agents.

CLINICAL PRACTICE GUIDELINES

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for central nervous system cancers (v.2.2021) do not address blood brain barrier disruption or convection-enhanced delivery of antitumor drugs for any brain cancer.²⁰

POLICY SUMMARY

Blood-Brain Barrier Disruption

There is insufficient evidence to support the use of blood-brain barrier disruption for the treatment of glioma or any indication. The evidence regarding the safety and efficacy of blood-brain barrier disruption consists of small to moderately sized case series. Overall, the current evidence indicated this treatment has led to a significant increase in neurotoxicity compared with standard chemotherapeutic administration and has not demonstrated overall survival benefit at this time. Further studies reporting long-term outcomes for specific brain neoplasms are needed to determine the safety and efficacy of the treatment modality. In addition, no clinical studies in humans have been published that address the use of BBBD for the treatment of Alzheimer’s disease, Parkinson’s disease, epilepsy, or any other neurological disorder. Therefore, the use of BBBD is considered investigational as a treatment for any indication.

Convection-Enhanced Delivery

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There is insufficient evidence to support convection-enhanced delivery of chemotherapeutic agents to the brain for any indication. The evidence regarding the safety and efficacy of convection-enhanced delivery consists of two large randomized controlled trials and several small to moderately sized case series. The majority of studies focused on patients with glioblastoma and/or anaplastic astrocytoma, but all were administering different antitumor agents, using heterogeneous delivery protocols. The largest RCT published to date (n=296), and the only phase 3 study, reported that there were no significant differences in median or overall survival in patients treated with CED-administered drugs compared to those treated with gliadel wafers placed after resection. Further studies reporting longer-term follow-up and more standardized treatment protocols are needed to determine the safety and efficacy of CED-administered antitumor agents. Therefore, convection-enhanced delivery of chemotherapeutic agents to the brain is considered investigational for any indication.

INSTRUCTIONS FOR USE

Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Companies reserve the right to determine the application of Medical Policies and make revisions to Medical Policies at any time. Providers will be given at least 60-days notice of policy changes that are restrictive in nature.

The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement.

REGULATORY STATUS

Mental Health Parity Statement

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case. In cases where medical necessity is not established by policy for specific treatment modalities, evidence not previously considered regarding the efficacy of the modality that is presented shall be given consideration to determine if the policy represents current standards of care.

REFERENCES

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