Corporate Medical Policy

Tumor-Treatment Fields Therapy

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Origination:	9/2013
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Description of Procedure or Service

Tumor-treatment fields therapy is a noninvasive technology that uses alternating electrical fields. It is used to treat glioblastoma multiforme and has been proposed for use in other tumor types.

Glioblastoma, also known as glioblastoma multiforme (GBM), is the most common form of malignant primary brain tumor in adults, comprising approximately 38% of all brain and central nervous system tumors. The peak incidence for GBM occurs between the ages of 45 and 70 years, with a median age at diagnosis of 64 years. GBMs are grade IV astrocytomas, a rapidly progressing and deadly type of glial cell tumor, which is often resistant to standard chemotherapy. According to the National Comprehensive Cancer Network (NCCN), GBM is the "deadliest brain tumor with only a third of patients surviving for one year and less than 5% living beyond 5 years."

Treatment of Newly Diagnosed Glioblastoma Multiforme

The primary treatment for newly diagnosed GBM is to resect the tumor to confirm a diagnosis while debulking the tumor to relieve symptoms of increased intracranial pressure or compression. If total resection is not feasible, subtotal resection and open biopsy are options. During surgery, some patients may undergo implantation of the tumor cavity with a carmustine (BCNU) - impregnated wafer. Due to the poor efficacy of local treatment, postsurgical treatment with adjuvant radiotherapy, chemotherapy (typically temozolomide), or a combination of these 2 therapies is recommended. After adjuvant therapy, some patients may undergo maintenance therapy with temozolomide. Maintenance temozolomide is given for 5 days of every 28-day cycle for 6 cycles.

Prognostic factors for therapy success are age, histology, performance status or physical condition of the patient, and extent of resection. National Comprehensive Cancer Network recommendations include patient age and Karnofsky Performance Status score as important determinants of postsurgical treatment choice.

For patients with good performance status, the most aggressive treatment (standard radiotherapy [RT] plus temozolomide) is recommended. For patients with poor performance status, only single treatment cycles or even palliative or supportive care are recommended. Hypofractionated RT is indicated for patients with poor performance status because it is better tolerated, and more patients are able to complete RT.

Treatment of GBM is rarely curative, and tumors will recur in essentially all patients.

Treatment of Recurrent Glioblastoma Multiforme

When disease recurs, additional debulking surgery may be used if the recurrence is localized. Due to radiation tolerances, re-radiation options for patients with recurrent GBM who have previously received initial external-beam radiotherapy are limited. There is no standard adjunctive treatment for recurrent GBM. Treatment options for recurrent disease include various forms of systemic medications such as the antivascular endothelial growth factor drug bevacizumab, alkylating agents such as nitrosoureas (eg, lomustine, carmustine), or retreatment with temozolomide. Medical therapy is associated with side effects that include hematologic toxicity, headache, loss of appetite, nausea, vomiting, and fatigue. Response rates in recurrent disease are less than 10%, and the progression-free survival rate at 6 months is less than 20%. There is a need for new treatments that can improve survival in patients with recurrent GBM or reduce the side effects of treatment while retaining survival benefits.

Malignant Pleural Mesothelioma

Malignant pleural mesothelioma (MPM) is an aggressive tumor that is associated with significant morbidity and mortality. It is associated with asbestos exposure and has a latency period of about 40 years after asbestos exposure. Recommendations for treatment are mainly chemotherapy as first line with pemetrexed plus platinum. Surgical cytoreduction is also recommended in selected patients with early-stage disease. Adjuvant radiation can be offered for patients who have resection of intervention tracts found to be histologically positive or for palliation of symptomatic patients.

The NovoTTF-100A™ System (Novocure Ltd., Haifa, Israel) has been approved by the U.S. Food and Drug Administration (FDA) to deliver TTF therapy. TTF therapy via the NovoTTF-100A™ System is delivered by a battery-powered, portable device that generates the fields via disposable electrodes that are noninvasively attached to the patient's shaved scalp over the site of the tumor. The device is used by the patient at home on a continuous basis (20–24 hours per day) for the duration of treatment, which can last for several months. Patients can carry the device in a backpack or shoulder pack while carrying out activities of daily living.

Regulatory Status
The NovoTTF-100A™ System (assigned the generic name of tumor-treatment fields) was approved by the FDA in April 2011 through the premarket approval process. The FDA-approved indication for use is: "The NovoTTF-100A System is intended as a treatment for adult patients (22 years of age or older) with confirmed GBM, following confirmed recurrence in an upper region of the brain (supratentorial) after receiving chemotherapy. The device is intended to be used as a stand-alone treatment and is intended as an alternative to standard medical therapy for recurrent GBM after surgical and radiation options have been exhausted."

In September 2014, FDA approved a request for Novocure to change its products name from Novo-TTF-110A System to Optune™.

In October 2015, FDA expanded the indication for Novocure's use of Optune in combination with temozolomide for newly diagnosed glioblastoma.

In May 2019, FDA approved a modified version of the Optune System (NovoTTF-100A System), which is now called the Optune Lua™ System (NovoTTF™-100L System), for "treatment of adult patients with unresectable, locally advanced or metastatic, malignant pleural mesothelioma (MPM) to be used concurrently with pemetrexed and platinum-based chemotherapy. The indication was modified from that granted for the Humanitarian Device Exemption designation to more clearly identify the patient population the device is intended to treat and in which the safety and probable benefit of the device is supported by the available clinical data."

To date, all the existing tumor treating fields products fall under the brand name Optune®. In March 2020, the manufacturer of Optune products announced a plan to include a suffix after the brand name for newly approved indications to further delineate specific indications for individual products (eg, Optune Lua)

Related Policies:
Analysis of MGMT Promoter Methylation in Malignant Gliomas

Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

BCBSNC will provide coverage for tumor treatment fields therapy when it is determined to be medically necessary because the medical criteria shown below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Tumor-Treatment Fields Therapy is covered

Tumor treatment fields (TTF) therapy is considered **medically necessary** for the treatment of newly diagnosed, supratentorial glioblastoma multiforme, as an adjunct to standard maintenance therapy with temozolomide when **ALL** of the following conditions are met:

- The patient has completed initial treatment with surgery, radiation therapy and concomitant chemotherapy; **AND**
- The patient is ≥18 years of age; **AND**
- Has a Karnofsky Performance Status score ≥70%; **AND**
- There is documentation of lack of tumor progression following radiation and chemotherapy (see Policy Guidelines); **AND**
- The individual is willing and capable of wearing the device for at least 18 hours a day.

Initial authorization should be approved for no longer than 3 months.

Continuation of therapy requires documentation of lack of tumor progression while using TTF, with a brain MRI every 3 months.

When Tumor-Treatment Fields Therapy is not covered

Tumor treatment fields therapy (TTF) is considered **investigational**, including, but not limited to, the following situations:

- As an alternative or an adjunct to standard medical therapy (eg bevacizumab, chemotherapy) for patients with progressive or recurrent glioblastoma multiforme.

- In the treatment of other types of malignant tumors, including but not limited to, pancreatic adenocarcinoma, lung cancer and brain metastases.

Policy Guidelines

Progression was defined in the EF-14 trial (Stupp et al [2015, 2017]), according to the MacDonald criteria (tumor growth >25% compared with the smallest tumor area measured in the patient during the trial or appearance of 1 or more new tumors in the brain that are diagnosed radiologically as glioblastoma multiforme).

For individuals who have newly diagnosed GBM on maintenance therapy after initial treatment with surgery, radiotherapy, and/or chemotherapy who receive TTF therapy as an adjunct to standard maintenance therapy, the evidence includes an RCT. Relevant outcomes include overall survival, disease-specific survival, symptoms, functional outcomes, quality of life, and treatment-related morbidity. The EF-14 trial found a significant increase of 2.7 months in progression-free survival and an increase of 4.9 months in overall survival with the addition of TTF therapy to standard maintenance therapy (ie, temozolomide) in patients with newly diagnosed GBM. Although patients were not blinded to treatment assignment, progression-free survival was assessed by blinded evaluators, and the placebo effects on the objective measure of overall survival are expected to be minimal. This technology represents a clinically significant option in the treatment of patients with GBM, for whom options are limited. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have progressive or recurrent GBM who receive TTF therapy as an adjunct or alternative to standard medical therapy, the evidence includes an RCT and nonrandomized comparative studies. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related morbidity. The single RCT evaluating TTF therapy for recurrent GBM did not show superiority of TTF therapy for the primary outcome (overall survival) compared with physicians' choice chemotherapy. Because no serious adverse effects have been identified with TTF therapy, this raises the possibility that treatment with TTF might reduce the toxicity associated with treatment for recurrent GBM. A reduction in chemotherapy-associated toxicity without loss of efficacy would be considered a net health benefit. However, this RCT is not sufficient to permit conclusions on the efficacy of the device. Because the trial was not designed as a noninferiority trial, no inferences of noninferiority compared with chemotherapy can be made. Also, quality of life assessment was measured in an insufficient number of patients to reach firm conclusions on differences in quality of life between TTF therapy and medical treatment. The highest quality study of TTF combined with medical treatment for recurrent GBM is a post hoc analysis of the EF-14 trial. A high-quality, prospective RCT is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have unresectable, locally advanced or metastatic, malignant pleural mesothelioma who receive TTF therapy as an adjunct to standard maintenance therapy, the evidence includes 1 single-arm observational study conducted in 80 patients. Relevant outcomes include overall survival, disease-specific survival, symptoms, functional outcomes, quality of life, and treatment-related morbidity. In patients who received TTF therapy in combination with pemetrexed and cisplatin or carboplatin, median overall survival was 18.2 months (95% CI 12.1 to 25.8 months). Because there was no comparison group, it is not possible to make conclusions about the effectiveness of the intervention compared to medical therapy alone. The evidence is insufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: *A4555, E0766*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

BCBSA Medical Policy Reference Manual [Electronic Version], 1.01.29, 8/8/2013

Specialty Matched Consultant – 9/2013

Senior Medical Director – 9/2013

Specialty Matched Consultant Advisory Panel – 11/2013

BCBSA Medical Policy Reference Manual [Electronic Version], 1.01.29, 8/14/14

Specialty Matched Consultant Advisory Panel – 11/2014

BCBSA Medical Policy Reference Manual [Electronic Version], 1.01.29, 8/13/15

Specialty Matched Consultant Advisory Panel- 11/2015

BCBSA Medical Policy Reference Manual [Electronic Version], 1.01.29, 8/11/16

Specialty Matched Consultant Advisory Panel- 11/2016

BCBSA Medical Policy Reference Manual [Electronic Version], 1.01.29, 7/13/17

Specialty Matched Consultant Advisory Panel- 11/2017

BCBSA Medical Policy Reference Manual [Electronic Version], 1.01.29, 6/14/18

Medical Director review 6/18/18

Specialty Matched Consultant Advisory Panel- 11/2018

Medical Director review 1/2019

BCBSA Medical Policy Reference Manual [Electronic Version], 1.01.29, 7/11/19

Specialty Matched Consultant Advisory Panel- 11/2019

Medical Director review 11/2019

BCBSA Medical Policy Reference Manual [Electronic Version], 1.01.29, 7/16/20

Specialty Matched Consultant Advisory Panel- 11/2020

Medical Director review 11/2020

Specialty Matched Consultant Advisory Panel- 8/2021

Policy Implementation/Update Information

For Policy Titled: Tumor-Treatment Fields Therapy for Glioblastoma

10/1/13 New policy. Tumor treatment fields therapy to treat glioblastoma is considered investigational. Senior Medical Director review 8/30/2013. Specialty Matched Consultant review 9/18/2013. (btw)

12/10/13 Specialty Matched Consultant Advisory Panel review 11/20/2013. No change to policy statement. (btw)

12/31/13 Added new HCPCS codes, A4555 and E0766, to the Billing/Coding section. Removed the following statement from the Billing/Coding section; "Providers will most likely use E1399 and A9900 for claim submission." (btw)

12/9/14 Specialty Matched Consultant Advisory Panel review 11/24/2014. No change to policy intent. Reference added. (lpr)

12/30/15 Updated Policy Guidelines. Specialty Matched Consultant Advisory Panel review 11/18/2015. Reference added. No change to policy statement. (lpr)

12/30/16 Updated Policy Guidelines, Description and Regulatory status. Clarified non-covered indications. Reference added. Medical Director review 9/2016. Specialty Matched Consultant Advisory Panel review 11/30/2016. No change to policy intent. (lpr)

8/11/17 Updated Policy Guidelines section. Clarified policy statement: 1) as an alternative to standard chemotherapy for patients with progressive or recurrent glioblastoma multiforme after initial or repeat treatment with surgery, radiotherapy, and/or chemotherapy; 2) as an adjunct to standard maintenance therapy in patients with newly diagnosed glioblastoma multiforme following initial treatment with surgery, radiotherapy and/or chemotherapy. No change to policy intent and the service remains investigational. Reference added. (lpr)

8/25/17 Under "When Not Covered" section: clarified investigational indications. No change to policy intent. (lpr)

12/15/17 Specialty Matched Consultant Advisory Panel review 11/29/2017. No change to policy statement. (lpr)

For Policy Titled: Tumor-Treatment Fields Therapy

06/29/18 Updated Description and Policy Guidelines sections. Under "When Covered section, revised policy statement to reflect medical necessity coverage for the treatment of newly diagnosed, supratentorial glioblastoma multiforme, as an adjunct to standard maintenance therapy with temozolomide when **ALL** of the following conditions are met: The patient has completed initial treatment with surgery, radiation therapy, and concomitant chemotherapy; **AND**; The patient is ≥18 years of age; **AND;** Has a Karnofsky Performance Status score ≥70%; **AND;** There is documentation of lack of tumor progression following radiation and chemotherapy (see Policy Guidelines); **AND; t**he individual is willing and capable of wearing the device for at least 18 hours a day. **Title changed from "Tumor-Treatment Fields Therapy for Glioblastoma" to "Tumor-Treatment Fields Therapy.** Reference added. Medical Director review 6/18/18. (lpr)

12/14/18 Specialty Matched Consultant Advisory Panel review 11/28/2018. No change to policy statement. (lpr)

2/12/19 Under "When Covered" section: added continuation therapy criteria. Medical Director review. Notification 2/12/19 for effective date 4/16/19. (lpr)

12/31/19 Specialty Matched Consultant Advisory Panel review 11/20/2019. Reference added. No change to policy statement. (lpr).

12/8/20 Updated Policy Guidelines and Regulatory section. Reference added. Specialty Matched Consultant Advisory Panel review 11/18/2020. No change to policy statement. (lpr)

9/7/21 Specialty Matched Consultant Advisory Panel review 8/18/2021. Updated Description and Policy Guidelines. No change to policy statement. (lpr)