Corporate Medical Policy

Tumor-Treatment Fields Therapy

File Name: tumor_treatment_fields_therapy
Origination: 9/2013
Last Review: 8/2023

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. Glioblastomas have the lowest survival rate of any central nervous system tumor; the 5-year survival rate and average length of survival is estimated at 6.8 % and 12 to 18 months, respectively.

Treatment of Newly Diagnosed Glioblastoma Multiforme

The primary treatment for newly diagnosed GBM is resection of 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. The response and overall survival rates with temozolomide are higher in patients who have O^6-methylguanine-DNA methyltransferase (*MGMT*) gene promoter methylation (see 2.04.113 on *MGMT* promotor methylation for malignant gliomas).

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. Hypo-fractionated RT is indicated for patients with poor performance status because it is better tolerated, and more patients can 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

In April 2011, The NovoTTF-100A™ System (Novacure, assigned the generic name of (TTF) tumor-treatment fields) was approved by the FDA through the premarket approval process. The FDA-approved label reads as follows: "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 to include newly diagnosed glioblastoma. The device was granted priority review status in May 2015 because there was no legally marketed alternative device available for the treatment of newly diagnosed GBM, a life-threatening condition. In July 2016, a smaller, lighter version of the Optune device, called the Optune System (NovoTTF-200A System), received FDA approval.

The FDA-approved label for newly diagnosed GBM reads as follows: "This device is indicated as treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM). Optune with temozolomide is indicated for the treatment of adult patients with newly

diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy."

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."

In September 2021, the FDA granted breakthrough designation to the NovoTTF-200T System for use together with atezolizumab and bevacizumab for the first-line treatment of patients with unresectable or metastatic liver cancer.

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:
Molecular Analysis for Gliomas AHS-M2139

******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 individual has completed initial treatment with surgery, radiation therapy and concomitant chemotherapy; **AND**
- The individual 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 individuals 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 who receive TTF therapy as an adjunct to standard maintenance therapy, the evidence includes a randomized controlled trial (RCT) and a systematic review. Relevant outcomes include overall survival (OS), 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 (PFS) and an increase of 4.9 months in OS 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, PFS was assessed by blinded evaluators, and the placebo effects on the objective measure of OS are expected to be minimal. In a systematic review that included the EF-14 trial along with other observational studies, the pooled median OS and PFS in newly diagnosed patients who received TTF therapy was 21.7 months and 7.2 months, respectively. 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 an 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, nonrandomized comparative studies, and a systematic review of these data. Relevant outcomes are OS, 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 (OS) 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. In a systematic review

that included the RCT and post hoc analysis of the EF-14 trial, along with other observational studies, the pooled median OS and PFS in patients with recurrent GBM who received TTF therapy was 10.3 months and 5.7 months, respectively. A high-quality, prospective RCT is needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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 and a retrospective study of 5 US 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 retrospective study is the first publication of real-world implementation of TTF for MPM. 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

Medical Director review 8/2022

Specialty Matched Consultant Advisory Panel- 8/2022

National Cancer Institute (NCI). Adult Central Nervous System Tumors Treatment (PDQ)Health Professional Version. Updated January 18, 2022; https://www.cancer.gov/types/brain/hp/adult-brain-treatment-pdq#cit/section_1.1. Accessed May 28, 2022.

National Brain Tumor Society. Glioblastoma Facts & Figures. https://braintumor.org/take-action/about-gbm/. Accessed May 24, 2022.

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Central Nervous System Cancers. Version 2.2021. https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed May 24, 2022.

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Malignant Pleural Mesothelioma. Version 1.2022. https://www.nccn.org/professionals/physician_gls/pdf/mpm.pdf. Accessed May 24, 2022.

U.S. Food and Drug Administration (FDA). Summary of Safety and Effectiveness Data (SSED): OptuneTM (formerly NovoTTF-100ATM System) 2015; https://www.accessdata.fda.gov/cdrh_docs/pdf10/P100034S013B.pdf. Accessed May 23, 2022.

U.S. Food and Drug Administration (FDA). NovoTTF 100L System: Summary of Safety and Probable Benefit. May 23, 2019. Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf18/H180002B.pdf. Accessed May 20, 2022.

Specialty Matched Consultant Advisory Panel review 8/2023

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)

9/13/22 Specialty Matched Consultant Advisory Panel review 8/24/22. No change to policy statement. (lpr)

9/30/22 Under related policies section: changed title of related policy AHS-M2139 to Molecular Analysis for Gliomas from Analysis of MGMT Promotor Methylation in Malignant Gliomas. No change to policy statement. (lpr)

8/29/23 Specialty Matched Consultant Advisory Panel review 8/16/2023. Updated description policy guidelines and references. No change to policy statement. (lpr)