

(10129)

(Formerly Tumor Treatment Fields Therapy for Glioblastoma)

Medical Benefit		Effective Date: 04/01/19	Next Review Date: 07/19
Preauthorization	Yes	Review Dates: 09/15, 05/16, 09/16, 09/17, 07/18, 01/19	

Preauthorization is required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> With newly diagnosed glioblastoma multiforme on maintenance therapy after initial treatment 	Interventions of interest are: <ul style="list-style-type: none"> Tumor treating fields therapy as an adjunct to standard maintenance therapy 	Comparators of interest are: <ul style="list-style-type: none"> Standard maintenance therapy alone 	Relevant outcomes include: <ul style="list-style-type: none"> Overall survival Disease-specific survival Quality of life Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> With progressive or recurrent glioblastoma multiforme 	Interventions of interest are: <ul style="list-style-type: none"> Tumor treating fields therapy as an adjunct or alternative to standard medical therapy 	Comparators of interest are: <ul style="list-style-type: none"> Standard medical therapy 	Relevant outcomes include: <ul style="list-style-type: none"> Overall survival Disease-specific survival Quality of life Treatment-related morbidity

DESCRIPTION

Glioblastoma multiforme (GBM) is the most common and deadly malignant brain tumor. It has a very poor prognosis and is associated with low quality of life during of treatment. Tumor treatment fields (TTF) therapy is a new, noninvasive technology intended to treat glioblastoma using alternating electric fields.

SUMMARY OF EVIDENCE

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). 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 (i.e., 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 EF14 trial. A high-quality, prospective RCT is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

POLICY

Tumor treating fields therapy to treat glioblastoma multiforme is considered **medically necessary** as an adjunct to standard maintenance therapy with temozolomide in patients with newly diagnosed glioblastoma multiforme following initial treatment with surgery, radiotherapy, and/or chemotherapy under the following conditions:

- Adult patients ≥ 22 years of age
- Supratentorial tumor
- Karnofsky Performance Status score $\geq 70\%$
- Patient understands device use, including the requirement for a shaved head, and is willing to comply with use criteria according to the Food and Drug Administration label (see Policy Guidelines).

Tumor treating fields therapy is considered **investigational** in all other conditions, including but not limited to the following situations:

- As an adjunct to standard medical therapy (e.g., bevacizumab, chemotherapy) for patients with progressive or recurrent glioblastoma multiforme
- As an alternative to standard medical therapy for patients with progressive or recurrent glioblastoma multiforme
- For brain metastases
- For cancer in areas other than the brain.

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 one or more new tumors in the brain that are diagnosed radiologically as glioblastoma multiforme).

The Food and Drug Administration label includes the following notices:

- Patients should use Optune for at least 18 hours a day to get the best response to treatment
- Patients should finish at least four full weeks of therapy to get the best response to treatment. Stopping treatment before four weeks lowers the chances of a response to treatment.

BACKGROUND

GLIOBLASTOMA MULTIFORME

Glioblastomas, also known as glioblastoma multiforme (GBM), are the most common form of malignant primary brain tumor in adults.¹ GBMs are grade IV astrocytomas, a rapidly progressing and deadly type of glial cell tumor that is often resistant to standard medical therapy (e.g., bevacizumab, chemotherapy). Together, anaplastic astrocytomas and glioblastomas comprise approximately 38% of all brain and central nervous system tumors.¹ 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; in one report, about a third of patients survived to one year, and the five-year survival rate was around 5%.²

Clinical Context and Therapy Purpose

The purpose of alternating electrical field therapy, more commonly known as TTF therapy, is to provide a treatment option that is better than existing therapies for GBM. TTF has been investigated as an adjunct to temozolomide for the treatment of newly diagnosed GBM and as an alternative or adjunct to medical therapy for progressive or recurrent GBM

Treatment of Newly Diagnosed GBM

The primary treatment for patients newly diagnosed with 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 (bis-chloroethylnitrosourea) impregnated wafer. Due to the poor efficacy of local treatment, postsurgical treatment with adjuvant radiotherapy, chemotherapy (typically temozolomide), or a combination of these two therapies is recommended. After adjuvant therapy, patients may undergo maintenance therapy with temozolomide. Maintenance temozolomide is given for five days of every 28-day cycle for six cycles. Response and overall survival rates with temozolomide are higher in patients who have O6-methylguanine-DNA methyltransferase (MGMT) gene promoter methylation.

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.³ 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 essentially all patients.

Treatment of Recurrent GBM

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 (e.g., 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 six months is less than 20%.⁴ 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.

The questions addressed in this protocol are:

- Does TTF, when used as an adjunct to maintenance medical therapy in patients with newly diagnosed GBM, improve the net health outcome?
- Does TTF, when used as an adjunct to medical therapy in patients with recurrent GBM, improve the net health outcome?
- Does TTF, when used as an alternative to medical therapy in patients with recurrent GBM, improve the net health outcome?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant populations of interest are patients who have newly diagnosed GBM with good performance status or patients with recurrent GBM with good performance status. Newly diagnosed patients would have undergone initial treatment with surgery, RT, and chemotherapy and be receiving maintenance chemotherapy.

Interventions

TTF therapy is a noninvasive technology intended to treat GBM on an outpatient basis and at home using electrical fields.^{4,5,6} TTF therapy exposes rapidly dividing cancer cells to electric fields of low intensity and intermediate frequency (200 kHz) that alternate in perpendicular orientation. TTF therapy is proposed to inhibit tumor growth by two mechanisms: the arrest of cell proliferation by causing microtubule misalignment in the mitotic spindle of rapidly dividing tumor cells and apoptosis due to movement of macromolecules and organelles during telophase.^{5,6} Preclinical studies have indicated that the electric fields may also make the cells more susceptible to chemotherapy.

Optune (formerly NovoTTF-100A System) is the only legally marketed TTF delivery system available in the United States. The portable, battery-powered device is carried in a backpack or shoulder pack while carrying out activities of daily living. For the treatment of glioblastoma, four disposable transducer arrays with insulated electrodes are applied to the patient's shaved head. The transducer array layout is typically determined using specialized software. The patient's scalp is re-shaved and the transducer arrays replaced twice a week by the patient, caregiver, or device technician. The device is worn for up to 24 hours a day for the duration of treatment, except for brief periods for personal hygiene and two to three days at the end of each month. The minimum daily treatment is 18 hours. The minimum duration of treatment is one month, with the continuation of treatment available until recurrence.

Comparators

The following practice is currently being used to make decisions about newly diagnosed GBM: maintenance chemotherapy with temozolomide alone.

The following practices are currently being used to make decisions about recurrent GBM: medical therapy.

TTF therapy might also be compared with palliative or supportive care, where survival rarely exceeds three to five months.⁴

Outcomes

The general outcomes of interest are whether TTF improves survival or quality of life during treatment and,

because most GBMs recur, the time to tumor recurrence. Measures of cognitive status and quality of life measures are also of interest to determine whether TTF alters the decline in cognition and quality of life that occur with GBM. Also, adverse events of treatment such as side effects of chemotherapy and the possibility of seizures need to be assessed.

Timing

Due to the rapid progression of GBM, the time of interest for both progression-free survival and overall survival is months.

Setting

The setting is outpatient care by an oncologist or neuro-oncologist.

REGULATORY STATUS

In April 2011, the NovoTTF-100A™ System (Novocure; assigned the generic name of TTF) was approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process.⁷ 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 Novocure’s request for a product name change from NovoTTF-110A System to Optune®.⁸

In October 2015, FDA expanded the indication for Optune® in combination with temozolomide to include newly diagnosed GBM.⁹ 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.”

FDA product code: NZK

RELATED PROTOCOLS

Intensity-Modulated Radiotherapy: Central Nervous System Tumors

Intracavitary Balloon Catheter Brain Brachytherapy for Malignant Gliomas or Metastasis to the Brain

Stereotactic Radiosurgery and Stereotactic Body Radiotherapy

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are

considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

REFERENCES

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

1. National Cancer Institute (NCI). Adult Central Nervous System Tumors Treatment (PDQ®)—Health Professional Version. 2018; https://www.cancer.gov/types/brain/hp/adult-brain-treatment-pdq#cit/section_1.1. Accessed April 28, 2018.
2. Chien LN, Gittleman H, Ostrom QT, et al. Comparative brain and central nervous system tumor incidence and survival between the United States and Taiwan Based on Population-Based Registry. *Front Public Health*. Jul 21 2016;4:151. PMID 27493936
3. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Central Nervous System Cancers. Version 1.2018. https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed April 28, 2018.
4. Stupp R, Wong ET, Kanner AA, et al. NovoTTF-100A versus physician’s choice chemotherapy in recurrent glioblastoma: a randomised phase III trial of a novel treatment modality. *Eur J Cancer*. Sep 2012;48(14): 2192-2202. PMID 22608262
5. Davies AM, Weinberg U, Palti Y. Tumor treating fields: a new frontier in cancer therapy. *Ann N Y Acad Sci*. Jul 2013;1291:86-95. PMID 23659608
6. Pless M, Weinberg U. Tumor treating fields: concept, evidence and future. *Expert Opin Investig Drugs*. Aug 2011;20(8):1099-1106. PMID 21548832
7. U.S. Food and Drug Administration (FDA). Tumor treatment fields. NovoTTF-10A System. Summary of safety and effectiveness data (SSED). Premarket Approval Application (PMA) No. P100034. 2011; http://www.accessdata.fda.gov/cdrh_docs/pdf10/P100034b.pdf. Accessed April 28, 2018.
8. U.S. Food and Drug Administration (FDA). Supplemental application for device name change. 2014; http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_template.cfm?id=p100034s010. Accessed April 28, 2018.
9. U.S. Food and Drug Administration (FDA). Summary of Safety and Effectiveness Data (SSED): Optune™ (formerly NovoTTF-100A™ System) 2015; https://www.accessdata.fda.gov/cdrh_docs/pdf10/P100034S013B.pdf. Accessed April 28, 2018.
10. Stupp R, Taillibert S, Kanner A, et al. Effect of tumor-treating fields plus maintenance temozolomide vs. maintenance temozolomide alone on survival in patients with glioblastoma: a randomized clinical trial. *JAMA*. Dec 19 2017;318(23):2306-2316. PMID 29260225
11. Stupp R, Taillibert S, Kanner AA, et al. Maintenance therapy with tumor-treating fields plus temozolomide vs. temozolomide alone for glioblastoma: a randomized clinical trial. *JAMA*. Dec 15 2015;314(23):2535-2543. PMID 26670971
12. Taphoorn MJB, Dirven L, Kanner AA, et al. Influence of treatment with tumor-treating fields on health-related quality of life of patients with newly diagnosed glioblastoma: a secondary analysis of a randomized clinical trial. *JAMA Oncol*. Apr 1 2018;4(4):495-504. PMID 29392280

13. Kesari S, Ram Z, Investigators EFT. Tumor-treating fields plus chemotherapy versus chemotherapy alone for glioblastoma at first recurrence: a post hoc analysis of the EF-14 trial. *CNS Oncol.* Jul 2017;6(3):185-193. PMID 28399638
14. Mrugala MM, Engelhard HH, Dinh Tran D, et al. Clinical practice experience with NovoTTF-100A system for glioblastoma: The Patient Registry Dataset (PRiDe). *Semin Oncol.* Oct 2014;41(Suppl 6):S4-S13. PMID 25213869
15. Wong ET, Lok E, Swanson KD, et al. Response assessment of NovoTTF-100A versus best physician's choice chemotherapy in recurrent glioblastoma. *Cancer Med.* Jun 2014;3(3):592-602. PMID 24574359
16. Kanner AA, Wong ET, Villano JL, et al. Post Hoc analyses of intention-to-treat population in phase III comparison of NovoTTF-100A system versus best physician's choice chemotherapy. *Semin Oncol.* Oct 2014;41(Suppl 6):S25-34. PMID 25213871