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Tumor-Treatment Fields Therapy for Glioblastoma

Policy # 00391

Original Effective Date: 11/20/2013

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Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers tumor-treatment fields (TTF) therapy to treat glioblastoma to be **investigational**.*

Background/Overview

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 (QOL) during the course of treatment. Tumor-treatment fields therapy is a new, noninvasive technology that is intended to treat glioblastoma using electrical fields.

Glioblastomas, also known as GBM, are the most common form of malignant primary brain tumor in adults, and they comprise approximately 15% of all brain and central nervous system tumors and more than 50% of all tumors that arise from glial cells. The peak incidence for GBM occurs between the ages of 45 and 70 years. Glioblastoma multiformes are grade IV astrocytomas, the most deadly type of glial cell tumor, and are 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."

The primary treatment for GBM is debulking surgery to remove as much of the tumor as possible. At that time, some patients may undergo implantation of the tumor cavity with a carmustine (bis-chloroethylnitrosourea [BCNU])-impregnated wafer. Depending on the patient's physical condition, adjuvant radiation therapy, chemotherapy (typically temozolomide), or a combination of the two are sometimes given. After adjuvant therapy, some patients may undergo maintenance therapy with temozolomide. In patients with disease that recurs after these initial therapies, additional debulking surgery may be used if recurrence is localized. Treatment options for recurrent disease include various forms of systemic medications such as bevacizumab, bevacizumab plus chemotherapy (e.g., irinotecan, BCNU/lomustine [CCNU], temozolomide), temozolomide, nitrosourea, PCV (procarbazine, CCNU, and vincristine), cyclophosphamide, and platinum-based agents. Response rates in recurrent disease are less than 10%, and progression-free survival (PFS) rates at 6 months are less than 20%.

Tumor-treatment fields therapy is a new, noninvasive technology that is intended to treat GBM on an outpatient basis using electrical fields. Tumor-treatment fields therapy exposes cancer cells to alternating electric fields of low intensity and intermediate frequency, which are purported to both selectively inhibit tumor growth and reduce tumor angiogenesis. Tumor-treatment fields are proposed to inhibit rapidly dividing tumor cells by two mechanisms, arrest of cell proliferation and destruction of cells while undergoing division.

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The NovoTTF-100A™[‡] System (Novocure Ltd., Haifa, Israel) has been approved by the U.S. Food and Drug Administration (FDA) to deliver TTF therapy. Tumor-treatment fields 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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration

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.”

Centers for Medicare and Medicaid Services (CMS)

No national coverage determination.

Rationale/Source

The literature on the efficacy of TTF therapy consists of small, single-arm studies and one randomized, controlled trial (RCT). Following is a summary of the key literature.

The use of TTF and the corresponding effects upon living tissue have been studied in clinical settings. Kirson and colleagues (2007), for example, reported the findings of a case study examining the effects of TTF therapy delivered by the NovoTTF-100A System in 10 patients with recurrent GBM. Median time to progression (TTP) in these patients was 26.1 weeks and median overall survival (OS) was 62.2 weeks. The authors noted that these TTP and OS values were more than double the reported medians of historical control patients. No device-related serious adverse events were seen after more than 70 months of cumulative treatment in all of the patients. The only device-related adverse event observed was a mild-to-moderate contact dermatitis beneath the field delivering electrodes. The primary limitation of this study was the use of historical controls, since the patients included may not be comparable on major clinical and prognostic features.

These preliminary findings served as a basis for a 2012 prospective Phase III multinational RCT by Stupp and colleagues, which was sponsored and funded by the manufacturer of the device (NovoCure). This study compared TTF therapy (delivered by the NovoTTF-100A System) to the best standard of care chemotherapy (active control). The FDA approval of the NovoTTF-100A System was based on the results of this RCT. Twenty-eight clinical centers (across 7 countries) enrolled 237 adult participants with relapsed or progressive GBM, despite conventional radiotherapy. Other prior treatments may have included surgery and/or chemotherapy. Patient characteristics were balanced in both groups, with median age of 54 years

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and median Karnofsky performance status (KPS) of 80%. More than 80% of participants had failed 2 or more prior chemotherapy regimens (\geq second recurrence), and 20% had failed bevacizumab prior to study enrollment.

Two-hundred and thirty-seven patients were randomized in a 1:1 ratio to receive TTF therapy only ($n = 120$) or active control ($n = 117$). The choice of chemotherapy regimens varied, reflecting local practice at each of the participating clinical centers. Chemotherapy agents considered as active control during the trial included platinum-based chemotherapy (i.e., carboplatin); nitrosureas; procarbazine; combination of procarbazine, lomustine and vincristine (PCV); temozolomide; and bevacizumab. For patients assigned to the TTF group, uninterrupted treatment was recommended, although patients were allowed to take treatment breaks of up to 1 hour, twice per day, for personal needs (e.g., shower). In addition, patients assigned to the TTF group were allowed to take 2–3 days off treatment at the end of each of 4-week period (which is the minimal required treatment duration for TTF therapy to reverse tumor growth). A period of 28 days of treatment with TTF was considered one full treatment course.

The primary study endpoint in this RCT was OS. Secondary endpoints included PFS at 6 months, TTP, one-year survival rate, QOL, and radiological response. Participants were seen in clinic monthly, and magnetic resonance imaging (MRI) was performed after 2, 4 and 6 months from initiation of treatment, with subsequent MRIs done according to local practice until disease progression. Medical follow-up continued for 2 months after disease progression. Monthly telephone interviews with the participants' caregivers were used to assess participant mortality rates.

Ninety-seven percent (116) of 120 participants in the TTF group started treatment and 93 participants (78%) completed one cycle (4 weeks) of therapy. Discontinuation of TTF therapy occurred in 27 participants (22%) due to noncompliance or the inability to handle the device. For each TTF treatment month, the median compliance was 86% (range 41-98%), which equaled a mean use of 20.6 hours per day. In the active control group, 113 (97%) of the 117 assigned participants received chemotherapy and all except one individual completed a full treatment course. 21 participants (18%) in the active control group did not return to the treating site and details on disease progression and toxicity were not available.

This RCT did not reach its primary endpoint of improved survival compared to active chemotherapy. With a median follow-up of 39 months, 220 participants (93%) had died. Median survival was 6.6 months in the TTF group compared to 6.0 months in the active control group (hazard ratio 0.86; 95% confidence interval [95% CI]: 0.66–1.12; $p = 0.27$). For both groups, one-year survival was 20%. The survival rates for 2- and 3-year survival were 8% and 4%, respectively, for the TTF group versus 5% and 1%, respectively, for the active control group. Progression-free survival rate at 6 months was 21.4% in the TTF group, compared to 15.1% in the active control group ($p = 0.13$). Objective radiological responses (partial and complete response) were noted in 14 participants in the TTF group and 7 in the active control group, with a calculated response rate of 14.0% (95% CI: 7.9–22.4%) compared to 9.6% (95% CI: 3.9–18.8%), respectively. Sixteen percent of the TTF participants had grade 1 and 2 contact dermatitis on the scalp, which resolved with topical corticosteroids. Active control participants experienced grade 2-4 events by organ system related to the pharmacologic activity of chemotherapy agents utilized; severe (grades 3 and 4) toxicity was observed in 3% of participants.

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Longitudinal QOL data were available in 63 participants (27%). There were no meaningful differences observed between the groups in the domains of global health and social functioning. However, cognitive, emotional, and rolefunctioning favored TTF therapy, whereas physical functioning favored chemotherapy. Symptom scale analysis was in accordance to treatment-associated toxicity; appetite loss, diarrhea, constipation, nausea and vomiting were directly related to the chemotherapy administration. Increased pain and fatigue was reported in the chemotherapy-treated patients and not in the TTF group. Post-hoc subgroup analyses of these trial data have been published in abstract form comparing outcomes of patients between both groups who had failed bevacizumab prior to study enrollment. Two very small case series have also been published of long-term survival (> 6 years) with TTF therapy.

In summary, this RCT failed to demonstrate the primary endpoint of improved survival with TTF therapy in comparison to chemotherapy. Limitations of the trial included a somewhat heterogeneous patient population, with participants included after progression of one or several lines of chemotherapy, as well as the use of different chemotherapy regimens in the control group. Another limitation is the absence of a placebo/supportive care arm. In the setting of advanced disease, the supportive care arm would have been useful to gauge the safety and efficacy of treatment for both groups of patients. Treatments used in the active control arm (best standard of care chemotherapy) in the recurrent disease setting have previously demonstrated limited efficacy, thus limiting the ability to determine the true treatment effect of TTF. Data from a trial of TTF versus placebo, or of TTF plus standard chemotherapy versus standard chemotherapy alone would therefore provide a better assessment of treatment efficacy. The latter study design is being used in an ongoing trial of TTF therapy in the treatment of patients with newly diagnosed GBM (see "Ongoing Clinical Trials").

A further limitation was high dropout rates in both groups. For example, over 20% of participants in the active control group were lost at follow-up, and this degree of dropouts may have underestimated the toxicity evaluation in this group. Similarly, over 20% of participants in the TTF arm discontinued treatment within a few days due to noncompliance or inability to handle the device. This implies that compliance might be an issue with TTF, as it requires the patient to continuously wear transducers on the shaved head and as a result. Finally, the number of patients who completed the QOL data was approximately one-quarter of total enrollment, and the self-reported QOL indicators may have been subject to bias due to the lack of blinding. Therefore, due to the numerous methodologic limitations, evidence from this trial is not sufficient to demonstrate that TTF therapy results in improved health outcomes for patients with recurrent GBM.

Ongoing Clinical Trials

Two manufacturer-sponsored studies on NovoTTF-100A System for treatment of GBM currently are listed at online site ClinicalTrials.gov.

Post-approval study of NovoTTF-100A in recurrent GBM patients (NCT01756729):

This study is a postmarket nonrandomized, concurrent control study, designed to confirm that the efficacy of the NovoTTF-100A System in patients with recurrent GBM treated in a real-life settings following FDA-approval is comparable to that of control chemotherapy patients. This trial has the estimated enrollment of 486 adult patients across two U.S. sites. The primary outcome measure is OS at 5 years of follow-up. This study is currently recruiting participants with the estimated completion date of January 2018.

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Effect of NovoTTF-100A together with temozolomide in newly diagnosed GBM (NCT00916409):

The study is a subsequent prospective multinational RCT designed to test the efficacy and safety of the NovoTTF-100A System, as an adjuvant to the best standard of care in the treatment of newly diagnosed GBM patients. This trial has the estimated enrollment of 700 adult patients across 79 sites. Trial participants randomized to the intervention arm will be treated continuously with the NovoTTF-100A device, in addition to temozolomide chemotherapy; patients in the control arm will be treated with temozolomide, as the best known standard of care for GBM patients. The primary outcome measure is progression-free survival at 5 years; the secondary outcome measure is OS at 5 years. This study is currently recruiting participants with the estimated completion date of April 2015.

Tumor-treatment fields therapy using the NovoTTF-100A System is also being studied as a treatment for other solid tumors including non-small cell lung cancer (NCT01755624).

Summary

Tumor-treatment fields therapy is a new noninvasive technology using electrical fields for treating recurrent glioblastoma. The available evidence consists of small case series and one randomized controlled superiority trial based on the FDA-approved device. This trial had numerous methodologic limitations and failed to demonstrate an improvement in OS or disease response. There were some differences reported in QOL, but these data were limited by a low response rate for QOL measures. In addition, the best standard chemotherapy protocols reported in the RCT may not reflect current practice, given the increased use of bevacizumab and temozolomide for treatment of patients with recurrent glioblastoma. No data were available to address a comparison to other third-line treatment modalities (i.e., radiation, surgery, combination therapy).

Further evidence from high-quality trials is needed to assess the long-term safety and efficacy of TTF. There are currently ongoing clinical trials of the TTF therapy including an ongoing post-marketing non-inferiority study that will provide additional data on outcomes of interest. Based on the small amount of evidence and lack of demonstrated treatment benefit to date, the use of TTF therapy for glioblastoma is considered investigational.

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Code Type	Code
CPT	No code
HCPCS	A9900, E1399
ICD-9 Diagnosis	All diagnoses
ICD-9 Procedure	No code

Policy History

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11/07/25013 Medical Policy Committee review

11/20/2013 Medical Policy Implementation Committee approval. New policy.

Next Scheduled Review Date: 11/2014

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- A. whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
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