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Medical Policy Manual Durable Medical Equipment, Policy No. 85

Tumor Treating Fields Therapy

Effective: May 1, 2019

Next Review: February 2020
Last Review: April 2019

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Tumor treating fields therapy is a noninvasive technology that is intended to treat glioblastoma using alternating electric fields.

MEDICAL POLICY CRITERIA

I. Tumor treating fields (TTF), including the use of mapping software for optimizing TTF therapy, may be considered **medically necessary** when all of the following (A.- F.) are met:

A. To treat newly diagnosed glioblastoma; and

B. Patient is 18 years of age or older; and

C. Location of the tumor is in the supratentorial region of the brain; and

D. Tumor is a histologically-confirmed glioblastoma. (Note: Glioblastoma includes grade IV astrocytoma and grade IV glioma, and glioblastoma subtypes are gliosarcoma and giant cell glioblastoma); and

E. Following radiation and chemotherapy; and

F. Concurrent treatment with temozolomide (TMZ), unless TMZ has been ineffective, not tolerated, or is contraindicated.

II. The use of TTF and/or TTF-associated mapping software is considered **investigational** for all other indications and conditions, including but not limited to recurrent glioblastoma.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and Physical/Chart Notes
- Documentation of histologically-confirmed glioblastoma demonstrating tumor is in the supratentorial region of the brain
- Radiation and chemotherapy history
- Documentation of Temozolomide (TMZ) maintenance treatment and response

CROSS REFERENCES

None

BACKGROUND

Glioblastomas (also referred to as glioblastoma multiforme [GBM) are the most common and deadly malignant brain tumor. Glioblastomas 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).[1] The peak incidence for glioblastomas 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 1 year, and the 5-year survival rate was around 5%.[2]

The primary treatment for glioblastoma 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.[3] Depending on the patient's physical condition, adjuvant radiation therapy, chemotherapy (typically temozolomide [TMZ]), or a combination of the two are sometimes given. After adjuvant therapy, some patients may undergo maintenance therapy with TMZ.

Nearly all high-grade gliomas recur. In patients with disease that recurs after 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/chloroethylnitrosourea (CCNU), TMZ), TMZ, nitrosourea, PCV (procarbazine, CCNU, and vincristine), cyclophosphamide, and platinum-based agents.[3] Response rates in recurrent disease are less than 10%, and progression-free survival rates at 6 months are less than 20%.[3,4]

TUMOR TREATING FIELDS THERAPY

Tumor Treating fields (TTF) therapy is a noninvasive technology that is intended to treat glioblastomas on an outpatient basis using electrical fields.[4-6] TTF 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. TTF are proposed to inhibit rapidly dividing tumor cells by 2 mechanisms, arrest of cell proliferation and destruction of cells while undergoing division.[5,6]

The Optune™, formerly known as NovoTTF-100A™ System, (Novocure Inc.) has been approved by the U.S. Food and Drug Administration (FDA) to deliver TTF therapy. TTF therapy via the Optune™ 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.[4,5] 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.[4,5]

NOVOTAL™ SYSTEM

The NovoTAL™ (Transducer Array Layout) System (Novocure Inc.) is a proprietary software tool that produces a custom transducer array layout to optimize Optune therapy for each patient. The software accomplishes this by maximizing the intensity of Tumor Treating Fields (TTFields) based on MRI measurements of the head, tumor size and location(s) and optimizing TTFields distribution.

REGULATORY STATUS

Optune™, (assigned the generic name of TTF) was approved by Food & Drug Administration (FDA) in April 2011 through the premarket approval (PMA) process.[7] FDA-approved indication for use are:

"Optune™ is intended as a treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM).

Optune™ with temozolomide (TMZ), 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 PMA approval granted in October 2015)

For the treatment of recurrent GBM, Optune™ is indicated following histologically- or radiologically-confirmed recurrence in the supratentorial region of the brain after receiving chemotherapy. The device is intended to be used as a monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted."[8]

The NovoTAL™ System, was approved by the FDA in November 2013 through a PMA supplement for the Optune™ System. It is the software approved for use by physicians certified to prescribe the Optune™ System.

FDA product code: NZK.

EVIDENCE SUMMARY

PRIMARY GLIOBLASTOMA

In 2015, Stupp published interim results of the EF-14 study, a randomized controlled trial (RCT) regarding the safety and efficacy of TTF used in combination with temozolomide maintenance treatment after chemoradiation therapy for patients with GBM.[9] Patients were randomized in a 2:1 fashion to receive maintenance treatment with TTF and TMZ (n=466) or TMZ only (n=229). Study eligibility required patients to be 18 years or older, have a histologically confirmed supratentorial glioblastoma, be progression-free after having undergone maximal safe debulking surgery when feasible or biopsy, and have completed standard concomitant chemoradiotherapy with TMZ. The median time from diagnosis to randomization was 3.8 months in both groups and patients were not blinded due to ethical concerns. TTF was delivered continuously (> 18 hours/day) via 4 transducers placed on the shaved scalp and TMZ (150-200 mg/m2/d) was given for 5 days of each 28-day cycle. Transducer array layouts were determined using the NovoTAL™ mapping software system for TTFields to optimize field intensity within the treated tumor. A planned interim analysis was to be conducted on the first 315 patients at 18 months follow-up. The primary study endpoint was progression-free survival (PFS) in the intent-to-treat populations (with a significance threshold of .01) with overall survival (OS) in the per-protocol population (n = 280) as a powered secondary end point (significance threshold of .006). A total of 695 patients were enrolled across 83 centers; however, the trial was terminated as it met its efficacy endpoints at interim analysis (median 38 months, 315 patients).

The interim analysis included the planned 315 subjects, with 210 in the TTF/TMZ group and 105 in the TMZ only group. The analysis was conducted at a median 38 months follow-up (range, 18-60 months). Prespecified per-protocol median PFS in the TTF/TMZ group was 7.1 months (95% CI, 5.9-8.2 months) compared to 4 months (95% CI, 3.3-5.2 months) in the TMZ only group (hazard ratio [HR], 0.62 [98.7% CI, 0.43-0.89]; P = .001). The median OS in the per-protocol population was statistically improved in the TTF/TMZ group (20.5 months; 95% CI, 16.7-25.0 months) compared to the TMZ only group (15.6 months; 95% CI, 13.3-19.1 months; HR, 0.64 [99.4% CI, 0.42-0.98]; P = .004). An additional analysis of the intention-to-treat population demonstrated and OS of 19.6 months (95% CI, 16.6-24.4 months) in the TTF/TMZ group compared to 16.6 months (95%CI, 13.6-19.2months) in the TMZ only group (HR,0.74 [95% CI,0.56-0.98]; stratified log-rank p = .03). Forty-three percent of patients in the TTF/TMZ group were alive at 2-year follow-up, compared to 29% in the TMZ only group (p = .006).

These interim results demonstrate an approximate three-month improvement of PFS and five-month improvement of OS when TTF therapy is used concurrently with TMZ in patients with newly diagnosed GBM.

In 2017, Stupp published final results from this trial, including all 695 subjects.[10] From the time of randomization, median progression-free survival was 6.7 months in the TTF/TMZ group, and 4.0 months in the TMZ only group (HR, 0.63; 95% CI, 0.52-0.76; P < .001). Median overall survival was 20.9 months in the TTF/TMZ group as compared to 16.0 months in the TMZ only group (HR, 0.63; 95% CI, 0.53-0.76; P < .001). The application of TTF therapy in addition to TMZ treatment compared to TMZ treatment alone was not associated with an increase in adverse events (48% vs 44%, P = 0.58). Mild to moderate skin irritation was observed in 52% of patients who received TTF/TMZ treatment.

RECURRENT GLIOBLASTOMA

The literature on the efficacy of TTF therapy in patients with recurrent GBM consists of small, single-arm studies and two RCTs.

Randomized Controlled Trials

The use of TTF and the corresponding effects on living tissue have been studied in clinical settings.[11-13] For example, in 2007, Kirson, 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.[11] 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.[11]

These preliminary findings served as a basis for a 2012 prospective Phase III multinational RCT by Stupp (EF-11), 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).[4] 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 and median Karnofsky performance status (KPS) of 80%. More than 80% of participants had failed 2 or more prior chemotherapy regimens (≥ second recurrence), and 20% had failed bevacizumab prior to study enrollment.[4]

Two hundred 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.[4] Chemotherapy agents considered as active control during the trial included platinum-based chemotherapy (i.e., carboplatin); nitrosoureas; 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 to 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 1 full treatment course.[4]

The primary study end point in this RCT was OS.[4] Secondary end points included progression-free survival (PFS) at 6 months, total time to progression (TTP), 1-year survival rate, quality of life (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.[4]

Ninety-seven percent (116) of 120 participants in the TTF group started treatment and 93 participants (78%) completed 1 cycle (4 weeks) of therapy. Discontinuation of TTF therapy

occurred in 27 participants (22%) due to noncompliance or the inability to handle the device.[4] 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 1 individual completed a full treatment course. Twenty-one participants (18%) in the active control group did not return to the treating site and details on disease progression and toxicity were not available.[4]

This RCT did not reach its primary end point of improved survival compared to active chemotherapy.[4] 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 [CI], 0.66 to 1.12; p=0.27). For both groups, 1-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. PFS 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% to 22.4%) compared to 9.6% (95% CI, 3.9% to 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.[4]

Longitudinal QOL data were available in 63 participants (27%).[4] There were no meaningful differences observed between the groups in the domains of global health and social functioning. However, cognitive, emotional, and role functioning 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.

In summary, this RCT failed to demonstrate the primary end point of improved survival with TTF therapy in comparison to chemotherapy.[4,14] Limitations of the trial included a somewhat heterogeneous patient population, with participants included after progression of 1 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.

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 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. 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.[4,7] 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.

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.[15,16] For example, Wong et al., published a subgroup analysis of the previously described RCT to determine characteristics of responders and nonresponders in the treatment and active control groups.[17] Tumor response was assessed by the Macdonald criteria. More patients in the TTF arm were considered responders (14/120 vs 7/117 in the chemotherapy arm.) Median response time was longer for those in the TTF arm than the chemotherapy arm (7.3 months vs 5.6 months, $p<0.001$), and there was a strong correlation (Pearson's r) between response and OS in the TTF arm ($p<0.001$) but not in chemotherapy arm ($p=0.29$). Compared with the chemotherapy arm, a higher proportion of responders in the TTF arm had a prior low-grade histology (36% vs 0%). These differences in treatment responder groups suggest that TTF therapy may differentially benefit certain types of GBM; however, the small numbers of responders in both groups limits generalizations that can be drawn from this analysis.

Nonrandomized Studies

In 2017, Kesari conducted a post hoc analysis of the EF-14 trial to evaluate the efficacy of TTF in patients who had the first recurrence.[18] Some patients in the temozolomide alone group crossed over to receive TTF plus chemotherapy after the first recurrence, resulting in 144 patients who received TTF fields plus chemotherapy and 60 patients who received chemotherapy alone for recurrent GBM. Patient characteristics and second-line treatments were well-balanced between the groups, with bevacizumab the most common second-line therapy. The median OS in patients treated with systemic therapy alone was 9.2 months. In comparison, the group of patients who received TTF therapy in addition to systemic therapy had a median OS of 11.8 months ($p=0.043$).

A study published in late 2014 included OS data from 457 patients included in the Patient Registry Dataset (PRiDe), a postmarketing registry of all recurrent GBM patients who received NovoTTF therapy in a real-world, clinical practice setting in 91 centers.[19] The median OS rate in the PRiDe clinical practice dataset was reported as significantly superior to that attained in the TTF pivotal trial (9.6 months vs 6.6 months; HR=0.66, 95% CI, 0.05 to 0.86; $p<0.001$). One- and 2-year OS rates for TTF in PRiDe were significantly longer than those in the TTF group in the pivotal RCT (44% vs 20% at 1 year; 30% vs 9% at 2 years, respectively). The PRiDe investigators reported no novel or unexpected treatment-related adverse events compared with the pivotal RCT. These results, although promising, are limited by a lack of randomized comparison group with which to isolate the direct effect of TTF therapy upon symptom improvement and overall outcomes.

In addition, two very small case series have also been published of long-term survival (>6 years) with TTF therapy.[20,21] Since the approval of the NovoTTF device, additional case reports and very small case series (n=3-5) have been reported.[22-24]

NOVOTAL™ SYSTEM

Nonrandomized Studies

In 2016, Connelly published a small feasibility study using the NovoTAL™ System with nonstandard non-contrast enhancement and advanced imaging.[25] All patients presented with gliomas (grades 2-4) and had previously received standard therapy prior to initiation of TTFields. A standard pre- and postcontrast MRI scan was acquired and used for TTFields treatment planning, in conjunction with other imaging modalities. Eight patients were reported on in this series: three underwent T2 imaging, one underwent FLAIR, one used diffusion weighted imaging, and one used MR-perfusion imaging. This case series demonstrates that treatment planning beyond the extent of contrast enhanced MRI is clinically feasible but it must be prospectively compared to standard treatment planning in a clinical trial setting, in order to determine the impact on patient outcomes.

In 2015, Chaudhry evaluated physician performance in conducting transducer array layout mapping using the NovoTAL™ System compared with mapping performed by the Novocure in-house clinical team.[26] Fourteen physicians (seven neuro-oncologists, four medical oncologists, and three neurosurgeons) evaluated five blinded cases of recurrent glioblastoma. Concordance for each physician versus Novocure on 20 MRI measurements was 0.96 (standard deviation, SD ± 0.03, range 0.90-1.00), indicating very high agreement between the two groups, indicating that physicians prescribing TTFields, when trained on the NovoTAL™ System, can independently perform transducer array layout mapping required for the initiation and maintenance of patients on TTFields therapy. This study did not address clinical utility.

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK

The National Comprehensive Cancer Network (NCCN) clinical practice guidelines on Central Nervous Systems Tumors (v.1.2019) recommend TTF therapy in conjunction with standard brain radiation therapy and current/adjuvant temozolomide for patients with supratentorial disease with good performance status. This is a category 1 recommendation.

The guidelines recommend considering TTF for diffuse or multiple recurrent glioblastoma; and for local unresectable recurrent glioblastoma (category 2B recommendation). In the guidelines discussion section, it is noted that due to a lack of clear efficacy data for TTF in the Stupp RCT, the panel is divided about recommending it for the treatment of recurrent glioblastoma.[3]

SUMMARY

The research on the safety and efficacy of tumor treating fields (TTF) therapy, and the associated optimizing software for patients with glioblastoma has some limitations. However, the small number of studies published do show that TTF therapy improves progression-free and overall survival in select adult patients with newly diagnosed glioblastoma who are receiving concurrent temozolomide (TMZ) treatment. Therefore, TTF therapy and TTF-associated mapping software may be considered medically necessary when criteria are met.

There is not enough research to show that tumor treating fields (TTF) therapy and TTF-associated mapping software for indications other than those specified in criteria improves

overall health outcomes. More research is needed. Due to a lack of evidence and clinical practice guidelines based on research, the use of TTF and TTF-associated mapping software is considered investigational when criteria are not met.

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CODES

NOTE: There is no specific code for the NovoTAL™ System software program. While some may submit using CPT code 77261, the appropriate CPT code for this service is unlisted code 77299.

Codes	Number	Description
CPT	77261	Therapeutic radiology treatment planning; simple
	77299	Unlisted procedure, therapeutic radiology clinical treatment planning

Codes	Number	Description
HCPCS	A4555	Electrode/transducer for use with electrical stimulation device, used for cancer treatment, replacement only
	E0766	Electrical stimulation device, used for cancer treatment, includes all accessories, any type

Date of Origin: *January 2014*