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TOPIC REVIEW

A systematic review of tumor treating fields therapy for high-grade gliomas

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Abstract

Introduction Tumor treating fields (TTF) is a unique treatment modality that utilizes alternating electric fields to deliver therapy. Treatment effects have been assessed in patients with newly diagnosed and recurrent glioblastoma in clinical trials and retrospective studies. While the results of these studies led to FDA approval for both populations, a portion of the neuro-oncology and neurosurgery community remains skeptical of TTF. Thus, this review aims to systematically summarize and evaluate prior studies investigating the efficacy and safety of TTF in patients with high-grade gliomas.

Methods A systematic review of the literature was performed according to PRISMA guidelines from database inception through February 2019. To be included, studies must have investigated the efficacy of TTF in adult high-grade glioma patients.

Results In total, 852 studies were initially identified, 9 of which met final inclusion criteria. In total, 1191 patients were identified who received TTF. Included studies consisted of two pilot clinical trials, two randomized clinical trials, and five retrospective studies. In randomized clinical trials, TTF improved survival for newly diagnosed glioblastoma patients but not for recurrent glioblastoma patients. Adverse skin reactions were the primary adverse effect associated with TTF.

Conclusion While TTF has been evaluated for safety and efficacy in a number of studies, concerns remain regarding study design, quality of life, and cost of therapy. Further investigation is needed regarding the therapy, and ongoing trials are already underway to provide more data regarding therapy outcomes and interactions in combination regimens.

Keywords Alternating electric fields · Glioblastoma · High grade glioma · TTF · Tumor treating fields

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Introduction

Glioblastoma is a devastating central nervous system cancer that affects over 17,000 people in the US annually and accounts for more than 60% of primary adult brain tumors [1, 2]. Even with standard therapy, prognosis is poor with a median survival of approximately 15 months [3, 4]. Survival at two and five years from diagnosis with established treatment is 26.5% and < 5%, respectively; long-term survival is rare [3].

The current standard of care for newly diagnosed glioblastoma patients was established in 2005, when the results of the EORTC/NCIC 26981 study demonstrated that radiation in combination with temozolomide (TMZ) significantly prolonged survival compared to radiation alone [3]. Since then, additional progress has been limited. Randomized clinical trials (RCTs) for dose-dense TMZ, bevacizumab, and everolimus have all failed to significantly improve

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survival beyond the standard regimen (i.e. radiotherapy and adjuvant TMZ) [5–7]. Additionally, there is currently no standard of care for recurrent glioblastoma, and the development of new therapies has been difficult due to the need to traverse the blood–brain barrier, tumor heterogeneity, and diffuse spread of microscopic disease, among other challenges [8, 9].

However, a unique treatment modality that has been evaluated in a number of studies is tumor treating fields (TTF) therapy. TTF involves the delivery of low-intensity, intermediate-frequency alternating electric fields to the tumor. These alternating electric fields hypothetically result in death or arrest of rapidly dividing tumor cells by disrupting mitotic spindle formation and cytokinesis [10]. Treatment is delivered via electrodes attached to the patient's scalp, powered by a portable battery. For effective therapy, the portable device is recommended to be worn for at least 18 h per day for 4 weeks [11].

Based on two pivotal clinical trials, TTF has been FDA approved for both recurrent and newly diagnosed glioblastoma patients [12, 13]. However, adoption of TTF into clinical practice has been lagging, and a portion of the neuro-oncology and neurosurgery communities remains skeptical of the treatment modality [14–16]. This study aims to systematically summarize and evaluate the existing literature regarding the clinical use of TTF.

Methods

Search strategy

A systematic review of the literature was performed in accordance with the PRISMA statement (see Online Resource 1) [17]. Databases queried included PubMed, Embase, Cochrane, Scopus, Web of Science, and ClinicalTrials.gov. The search timeframe included all studies from database inception through February 27, 2019. A comprehensive search string for keywords related to "high-grade gliomas" and "tumor treating fields" was utilized in the search (see Online Resource 2).

Inclusion criteria

To be included in the systematic review, studies must have: (1) involved human subjects; (2) utilized TTF; (3) provided progression-free survival (PFS) or overall survival (OS) data; (4) included patients with high-grade (WHO Grade III or IV) gliomas; and (5) included an adult patient population (≥ 18 years of age).

Exclusion criteria

After eliminating duplicate articles, we excluded (1) animal or simulation studies (no human patients); (2) TTF for non-glioma tumors; and (3) studies with < 5 patients. Studies that did not publish a full manuscript (such as conference presentations and abstract only publications) were also excluded. To avoid over-representation, if multiple studies analyzed a single patient population (e.g. secondary post-hoc analyses), only the single study that provided the most complete safety and efficacy data was included. However, the additional studies were still earmarked for discussion. Additionally, clinical trials currently listed as "Active" were noted separately.

Data extraction and analysis

Studies were first screened by title and abstract, and included studies were then screened by full text for final inclusion. Two authors (P.S. and T.W.) independently performed the screening and data extraction for all studies. Disagreements between the two reviewers were resolved by consensus involving another reviewer (D.M.). Factors recorded for each study included study design, glioblastoma status (newly diagnosed or recurrent), number of patients, treatment, sex, age, Karnofsky Performance Status (KPS), recurrence number at initiation of TTF, PFS, OS, adherence, TTF duration, and TTF related adverse effects. The review process was managed using Covidence.org (Covidence, Melbourne, Australia). A meta-analysis was not performed due to the heterogeneity in treatment regimens (e.g. TTF monotherapy vs various TTF combination regimens) and study design (e.g. starting time point for defining OS and PFS).

Risk of bias analysis

Risk of bias was assessed for the primary outcome for all studies that met final inclusion criteria. RCTs were assessed using the Risk of Bias 2 (RoB 2) tool, which evaluates studies in five domains and assigns an overall risk of "Low," "Some Concerns," or "High." Non-randomized studies were assessed using the Risk Of Bias In Non-Randomized Studies—of Interventions (ROBINS-I) tool, which evaluates studies in seven domains and assigns an overall risk of "Low," "Moderate," "Serious," or "Critical" [18, 19]. Risk of bias was not assessed for Ansstas et al. because this case series made no statistical comparisons between groups. Additionally, quality of included studies was assessed based on the 2011 Oxford Centre for Evidence-Based Medicine guidelines [20]. Each included study was reviewed and assigned an evidence level based on study design and quality. Quality and bias assessments were

performed by one author (P.S.), with oversight and review by another author (D.M.). A quantitative overall analysis of publication bias was not performed since fewer than 10 studies met the final inclusion criteria.

Results

Search results

Of the 852 unique studies initially identified using the search methodology detailed above, 9 met the final inclusion criteria (Fig. 1). While any study investigating TTF for high-grade gliomas was eligible for inclusion, only studies with Grade IV (glioblastoma) patients met all inclusion criteria. In these studies, 1191 patients were identified who received TTF.

Only two RCTs evaluating the efficacy of TTF have been completed: (1) EF-11 investigated TTF as a monotherapy vs. chemotherapy for recurrent glioblastoma patients, and the primary efficacy endpoint was OS; (2) EF-14 studied TTF for newly diagnosed glioblastoma patients, and the primary efficacy endpoint was PFS. Characteristics of these 2 studies are detailed in Table 1. The other included studies consisted of two pilot clinical trials and five retrospective studies (Table 2). The post-hoc portion of Wong et al. was excluded as it was a secondary survival analysis on the same patient population as EF-11 [21]. Clinical trials investigating

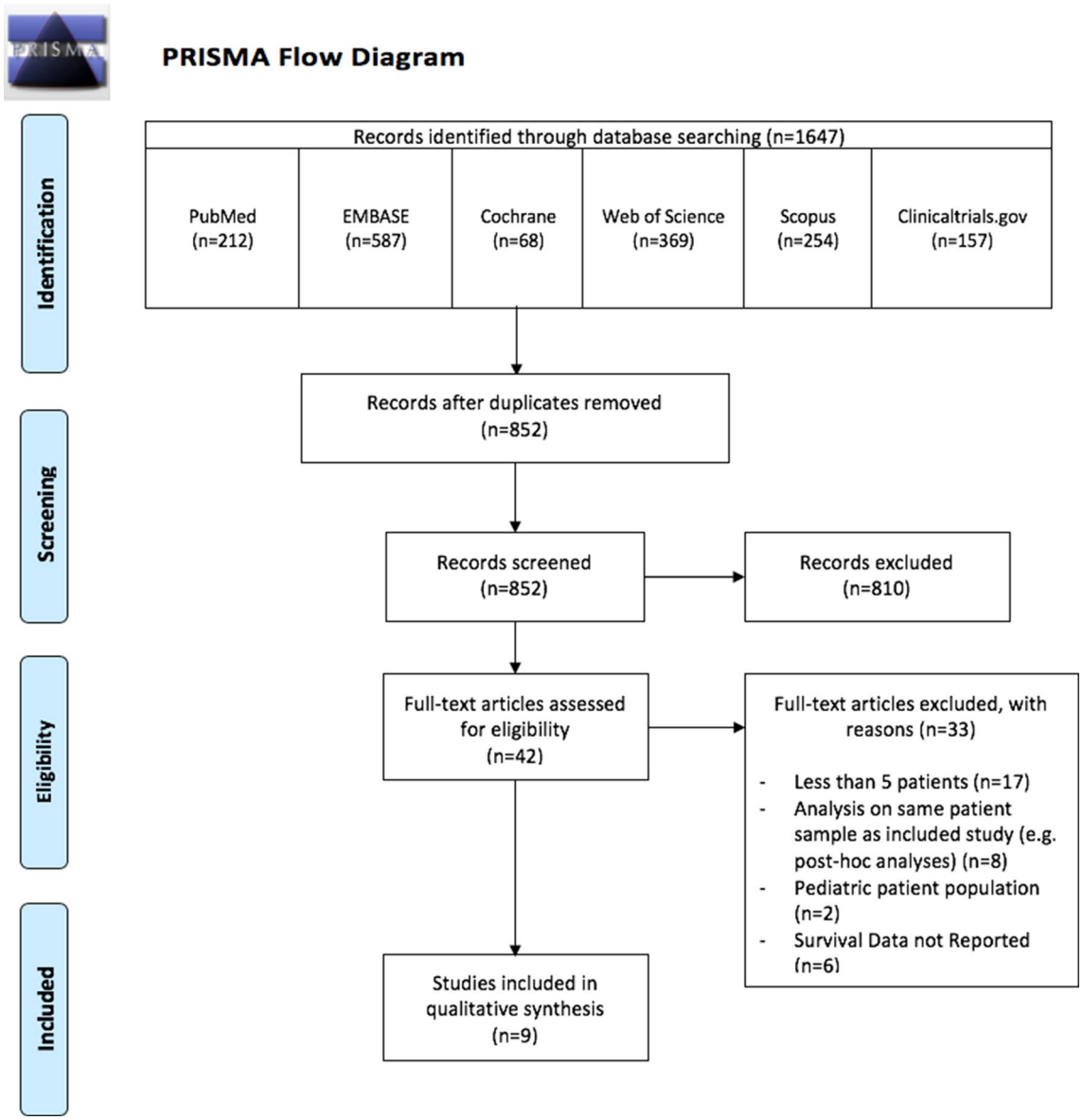

Fig. 1 PRISMA flow diagram outlining study screening

Table 1 Summary of randomized clinical trials assessing tumor treating fields efficacy

Study	Level of evidence	Overall risk of bias	Glioblastoma status	Number of patients	Treatment	Sex (% male)	Age median (range)
Stupp et al. [12]	1	Some concerns	Recurrent	120	TTF	77	54 (24–80)
				117	"Physicians Best Choice" chemotherapy	62	54 (29–74)
Stupp et al. [13]	1	Some concerns	Newly diagnosed	466	TMZ + TTF	68	56 (19–83)
				229	TMZ monotherapy	69	57 (19–80)

Study	Pre-treatment KPS median (range)	Recurrence number at TTF initiation	PFS, months median (95% CI)	PFS, significance	OS, months median (95% CI)	OS, significance	Adherence	TTF duration, months (median)	TTF adverse effects
Stupp et al. [12]	80 (50–100)	First 9% Second 48% Third or Greater 43%	2.2 (NA)	(p = .16)	6.6 (NA)	(p = .27)	Median 86%	NA	Low grade skin toxicity 16%
	80 (50–100)	First 15% Second 46% Third or greater 39%	2.1 (NA)		6.0 (NA)		NA	NA	NA
Stupp et al. [13]	90 (60–100)	NA	6.7 (6.1–8.1)	(p < .001)	20.9 (19.3–22.7)	(p < .001)	NA	8.2	Low grade skin toxicity 52%, High grade skin toxicity 2%
	90 (70–100)	NA	4.0 (3.8–4.4)		16.0 (14.0–18.4)		NA	NA	NA

KPS Karnofsky performance status, *TTF* Tumor treating fields, *TMZ* Temozolomide

TTF and registered as "active" on ClinicalTrials.gov are presented in Table 3. In total, 19 active trials were identified, 15 of which are currently recruiting participants.

Efficacy

Recurrent glioblastoma

Initial studies investigated the efficacy of TTF for recurrent glioblastoma patients. In 2007, a 10 patient pilot clinical trial of TTF demonstrated a median time to progression of 26.1 weeks and median OS of 62.2 weeks, which was markedly superior when compared to reported aggregate historical controls for recurrent glioblastoma patients (average time to progression 9.5 ± 1.6 weeks, average OS 29.3 ± 6 weeks) [10].

This provided the basis for EF-11, a phase III clinical trial comparing TTF monotherapy vs. "physician's best choice" chemotherapy for recurrent glioblastoma. Best choice chemotherapy was chosen for the control arm due to lack of an established standard of care for recurrent glioblastoma. The primary endpoint, OS, was not superior in the TTF arm compared to chemotherapy (median 6.6 months vs. 6.0 months, p = 0.27) [12].

After receiving FDA approval, the efficacy of TTF was also assessed in the Patient Registry Dataset (PRiDe), a large post-market registry which included all recurrent glioblastoma patients who began TTF between October 2011 and November 2013 [22]. The median OS reported in this study was 9.6 months, although the start date for OS was not specified in the manuscript, which was greater than the 6.6 months reported in the TTF arm of EF-11.

Newly diagnosed glioblastoma

For all included studies of newly diagnosed glioblastoma patients, TTF was applied alongside maintenance TMZ for patients who had completed concomitant radiotherapy and TMZ. Initially, a 10-patient study demonstrated a median PFS and OS of 155 weeks and > 39 months for TTF with maintenance TMZ, which was superior to a PFS of 31 weeks in concurrent controls and an OS of 14.7 months in historical control patients who received TMZ monotherapy [23]. OS of the concurrent control patients was not reported.

These results, combined with the demonstrated tolerability of TTF from EF-11, provided the basis for EF-14, a phase III RCT investigating TTF plus maintenance TMZ

Table 2 Summary of non-randomized studies assessing tumor treating fields efficacy

Study	Level of evidence	Overall risk of bias	Study design	Glioblastoma status	Number of patients	Treatment	Sex (% male)	Age median (range)
Kirson et al. [10]	4	Critical	Prospective	Recurrent	10	TTF	70.0%	53 (28–68)
Kirson et al. [23]	4	Critical	Prospective	Newly diagnosed	10	TTF + TMZ	NA	NA
					32	TMZ	NA	NA
Mrugala et al. [22]	3	Moderate	Retrospective	Recurrent	457	TTF[b]	67.6%	55 (18–86)
Wong et al. [21]	3	Serious	Retrospective[a]	Recurrent	35	TTF ± BEV	62.9%	57 (30–77)
Wong et al. [25]	4	Critical	Retrospective	Recurrent	3	TTF + BEV + TCCC	66.6%	56 (51–56)
					34	TTF + BEV	61.8%	57 (30 − 77)
Ansstas and Tran [27]	4	NA	Retrospective	Recurrent	8	TTF + BEV	62.5%	50 (35–62)
Lu et al. [26]	3	Serious	Retrospective	Recurrent	30	BBC + TTF	63.3%	Mean ± SD[c] 57.8 ± 11.6
					18	TBI + TTF	66.7%	Mean ± SD[c] 52.3 ± 9.9

Study	Pre-treatment KPS median (range)	Recurrence number at TTF initiation	PFS, months median (range)	OS, months median (range)	Adherence	TTF duration, months	TTF adverse effects
Kirson et al. [10]	90 (70–100)	NA	6 (0.7–28.5)[e]	14.3 (4.7–28.5)	NA	Average 12 (range 2.5–24)[f]	Skin toxicity, 90%
Kirson et al. [23]	NA (70–100)	NA	35.6 (NA)	> 39 (8/10 alive)	NA	Average 12 (range 2.5–24)[f]	Skin toxicity, 100%
	NA	NA	7.13 (NA)	NA	NA	NA	NA
Mrugala et al. [22]	80 (10–100)	First 33.3% Second 26.9% Third or greater 27.4% Unknown 12.5%	NA	9.6 (NA)	Median 70% (range 12%–99%)	Median 4.1	NA[d]
Wong et al. [21]	70 (50–90)	First 17% Second 29% Third or greater 54%	NA	4.3 (NA)	NA	NA	NA
Wong et al. [25]	70 (60–70)	First 0% Second 66.6% Third or greater 33.3%	8.1 (6.4–13.2)	10.3 (7.7–13.6)	66.7%	NA	NA
	70 (50–90)	First 17.6% Second 26.5% Third or greater 55.9%;	2.8 (0.1–20.7)	4.1 (0.3–22.7)	83.5%	NA	NA
Ansstas and Tran [27]	NA	NA	2.7 (NA)	7.2 (2–13.5)	Mean 74.2% (range 48.2–92.9%)	Median 5.2	NA
Lu et al. [26]	NA	NA	4.7 (NA)	11.8 (8.6–15.8)	NA	Mean ± SD[c] 9.0 ± 10.2	No TTF associated high grade adverse effects
	NA	NA	10.7 (NA)	18.9 (10.7–25.3)	NA	Mean ± SD[c] 17.5 ± 14.1	

KPS Karnofsky performance status, *TTF* Tumor treating fields, *TMZ* Temozolomide, *BEV* Bevacizumab, *TCCC* 6-thioguanine + Lomustine + Capecitabine + Celecoxib, *BBC* Bevacizumab ± Irinotecan or Lomustine, *TBI* Temozolomide + Bevacizumab + Irinotecan, *SD* Standard deviation

[a]Post-hoc analysis of Stupp 2012 was not considered

[b]Some patients may have received combination therapy in addition to TTF

[c]Median not provided

[d]Adverse effects were listed but causative therapy was not provided

[e]Value was reported as time to progression

[f]This value was reported as an aggregate for Kirson 2007 and Kirson 2009

Table 3 Active clinical trials assessing tumor treating fields registered on ClinicalTrials.gov

Identifier	Status	Study design	Estimated enrollment	Patient cohort	Intervention
NCT03705351	Active, not yet recruiting	Phase 1, single group	30	Newly diagnosed	TTF
NCT03642080	Recruiting	Observational	48	Newly diagnosed or recurrent	TTF
NCT03430791	Recruiting	Phase 2, nonrandomized, parallel assignment (two arms)	60	Recurrent	TTF + nivolumab vs TTF + nivolumab + ipilimumab
NCT03501134	Recruiting	Observational	20	Newly diagnosed or recurrent	TTF
NCT03477110	Recruiting	Phase 1, single group	35	Newly diagnosed	TTF
NCT03223103	Recruiting	Phase 1, single group	20	Newly diagnosed	TTF + mutation-derived tumor vaccine
NCT03405792	Recruiting	Phase 2, single group	29	Newly diagnosed	TTF + pembrolizumab
NCT03297125	Recruiting	Phase 4, nonrandomized, parallel assignment (two arms)	30	Newly diagnosed	TTF
NCT03258021	Recruiting	Observational	1000	Newly diagnosed	TTF
NCT03232424	Recruiting	Phase 1, single group assignment	10	Newly diagnosed	TTF
NCT03194971	Recruiting	Post-mortem (autopsy)	20	Newly diagnosed or recurrent	TTF
NCT03780569	Active, not recruiting	Single group	10	Newly diagnosed	TTF
NCT02663271	Recruiting	Phase 2, single group	18	Recurrent	TTF + pulsed BEV
NCT02903069	Active, not recruiting	Phase 1, single group	73	Newly diagnosed	TTF + marizomib (proteasome inhibitor) vs marizomib
NCT02343549	Recruiting	Phase 2, single group	46	Newly diagnosed	TTF + BEV
NCT02441322	Recruiting	Single group	30	Newly diagnosed or recurrent	TTF
NCT01925573	Active, not recruiting	Single group	7	Recurrent	TTF + BEV + hypofractionated stereotactic RT
NCT01954576	Recruiting	Single group	26	Recurrent	TTF
NCT01894061	Recruiting	Phase 2, single group	40	Recurrent	TTF + BEV

Identifier	Primary outcome	Secondary outcomes	Start date	Location
NCT03705351	AE/safety	PFS6, PFS24, OS	1-Nov-19[a]	Providence St. Vincent Medical Center
NCT03642080	Disease progression (MRI predictors of response)	–	1-Dec-18	New York Presbyterian
NCT03430791	Response (RANO)	–	5-Nov-18	Miami Cancer Institute
NCT03501134	Physical activity	QoL, sleep quality, mood state, functional capacity, daily steps	8-Aug-18	Duke University
NCT03477110	AE/safety	PFS, OS, event-free survival	4-May-18	Thomas Jefferson University
NCT03223103	DLT	AE/safety, OS, PFS, response (RANO)	1-Mar-18	Mount Sinai
NCT03405792	PFS	AE/safety, OS, glioma-specific immune reaction	23-Feb-18	University of Florida
NCT03297125	MRI predictors of response (standard vs advanced MRI)	–	1-Dec-17	Froedtert Hospital & Medical College of Wisconsin
NCT03258021	OS	AE/safety, compliance, PFS, QoL, reasons for refusal	31-Aug-17	University Hospital Frankfurt
NCT03232424	AE/safety	OS, PFS6, QoL	26-Jul-17	Hackensack University Medical Center

Table 3 (continued)

Identifier	Primary outcome	Secondary outcomes	Start date	Location
NCT03194971	Pathological signatures of TTF at autopsy	Pathological pattern of failure	1-Jun-17	Froedtert & the Medical College of Wisconsin
NCT03780569	AE/safety	OS, PFS	27-Apr-17	Tel Aviv Sourasky Medical Center
NCT02663271	PFS	AE/safety, KPS, mental status, response (RANO)	Aug-16	University of Florida, Washington University
NCT02903069	AE/safety, maximum tolerated dose	OS, PFS, response (RANO)	10-Feb-16	Multiple
NCT02343549	12 month survival	–	Jan-15	Levine Cancer Institute
NCT02441322	MRI radiologic response	OS, PFS, response (RANO)	Dec-14	University of Pennsylvania
NCT01925573	AE/safety	–	May-14	University of Maryland
NCT01954576	Response (RANO)	Genetic signature of response, PFS, QoL	10-Oct-13	University of Florida, Washington University
NCT01894061	PFS	Response (RANO), AE/safety, OS, TTP, neurocognitive function, QOL	12-Jun-13	Cleveland Clinic, Case Western, University of Cincinnati

TTF Tumor treating fields, *AE* Adverse effects, *PFS6* 6 month progression-free survival, *PFS24* 24 month progression-free survival, *RANO* Response assessment in neuro-oncology criteria, *QoL* Quality of life, *DLT* Dose limiting toxicity, *BEV* Bevacizumab, *KPS* Karnofsky performance status, *RT* Radiotherapy, *TTP* Time to progression

[a]Estimated start date

vs. maintenance TMZ monotherapy [13]. In this trial, TTF plus maintenance TMZ demonstrated significantly prolonged survival compared to TMZ monotherapy—median PFS was 6.7 months vs. 4.0 months, and median OS was 20.9 months vs. 16.0 months, respectively (both $p < 0.001$). Efficacy of TTF was similar across age, KPS, MGMT methylation, and other baseline factors. Thus, no prognostic indicators were identified for subpopulations of patients that may receive greater benefit from the treatment. Overall, the significant increase in PFS and OS demonstrated in EF-14 resulted in approval of TTF therapy for newly diagnosed glioblastoma patients.

Adherence

Treatment adherence has emerged as an important factor for TTF efficacy. Patients are recommended to wear the device for at least 18 h a day, corresponding to an adherence of ≥ 75%. This recommendation was first mentioned for human studies in the efficacy pilot for TTF for recurrent glioblastoma based on preclinical data suggesting that the treatment is most effective when applied continuously for at least 16 h [10]. However, the preclinical data was not presented in this pilot study.

Since then, numerous studies have established a relationship between adherence and survival. The PRiDe study reported a median survival of 13.5 months for those with ≥ 75% adherence and only 4 months for those with < 75% [22]. A post-hoc analysis of EF-11 also demonstrated a significantly prolonged median OS for patients with an adherence of ≥ 75% who had received more than a month of therapy [11], and a subgroup analysis of EF-14 stated that adherence was an independent prognostic factor for survival on multivariate analysis [24].

EF-11 had a median adherence of 86% and EF-14 reported that 75% of patients achieved 75% adherence or greater [12, 13]. However, patients in the PRiDe postmarket registry had a much lower adherence. Of the 287 patients with available adherence data, median adherence was 70% and only 44% achieved an adherence of over 75% [22].

Safety

Across all studies, the predominant adverse effect associated with the device was local low-grade scalp dermatitis. Mild to moderate skin irritation was reported in 16% of patients in EF-11, 52% of patients in EF-14, and 24.3% of patients in PRiDe [12, 13, 22]. The only report of high-grade skin toxicity was in EF-14, in which 2% of TTF patients reported a grade 3 adverse effect. The excellent safety profile of the device is what resulted in FDA approval of the device for recurrent glioblastoma; while survival was not superior to the chemotherapy control arm, there were significantly fewer severe adverse effects in the TTF arm relative to the control arm in EF-11 (6% and 16%, respectively) ($p = 0.022$) [12].

Additional studies

A number of smaller retrospective studies were also identified in this review. Wong et al. investigated the effects of dexamethasone on TTF efficacy and concluded that > 4.1 mg per day of dexamethasone may interfere with treatment [21]. In a second study, Wong et al. compared patients treated with TTF plus bevacizumab ($n = 34$) vs. TTF plus bevacizumab, 6-thioguanine, lomustine, capecitabine, and celecoxib (TCCC) ($n = 3$), and found an insignificant difference in median OS (4.1 months vs. 10.3 months, respectively) [25]. Lu et al. compared TTF with a triple-drug regimen of TMZ, bevacizumab, and irinotecan vs. TTF with bevacizumab-based chemotherapies for recurrent glioblastoma patients. While the former group had significantly prolonged median PFS compared to the latter from time of recurrence (10.7 months vs. 4.7 months, respectively), there was no significant difference in OS from time of recurrence [26]. Finally, Ansstas et al. reported a small case series of 8 patients who received TTF for recurrent glioblastoma refractory to bevacizumab, of which 5 were subsequently re-challenged with bevacizumab after progression on TTF [27]. Median OS was 216 days (7.2 months) following initiation of TTF. Since these studies were primarily focused on subgroup analyses or combination therapies and had much smaller samples sizes than the studies previously mentioned, they added limited insight into the effects of TTF.

Risk of bias

The overall risk of bias for both EF-11 and EF-14 was "Some Concerns." Neither study utilized sham therapy for control patients, so patients and providers were aware of assigned intervention. In EF-11, concerns regarded potential differences in baseline characteristics between groups and early discontinuation of TTF by some patients due to non-compliance. In EF-14, concerns regarded the long interval from diagnosis to randomization and withdrawal of consent by patients before and after randomization.

The PRiDe study had a "Moderate" risk of bias. While this study makes comparisons to EF-11, there are differences in baseline characteristics between the studies, including percentage of patients at first GBM recurrence (33.3% vs 9%, respectively). All other studies assessed had a "Serious" or "Critical" risk. Studies by Kirson et al. in 2007 and 2009 provided limited information on controls [10, 23]. Survival analyses by Lu et al. and Wong et al. did not adjust for covariates when assessing therapy outcomes [25, 26]. In the other included study by Wong et al., the single-institution survival analysis of patients receiving high vs. low dose dexamethasone did not control for potential confounders [21]. Additional details regarding these assessments are provided in Online Resource 3.

Discussion

TTF has received FDA approval for both newly diagnosed and recurrent glioblastoma patients, but physician support of the treatment modality remains divided. Although there have been several studies investigating TTF, only the two pivotal clinical trials (EF-11 and EF-14) and the PRiDe clinical registry had sizable patient populations and focused on outcomes directly related to TTF.

The treatment has demonstrated an excellent safety profile for both newly diagnosed and recurrent glioblastoma patients, but results regarding efficacy have been more contentious. EF-11 did not demonstrate an improvement in overall survival for recurrent glioblastoma patients on TTF vs. chemotherapy. However, recurrent glioblastoma patients in the PRiDe post-market clinical registry showed a survival that was greater than both the chemotherapy and TTF arms of EF-11. To explain this discrepancy, the authors mention that PRiDe patients were earlier in their disease course compared to EF-11 patients (33.3% vs. 9% at first recurrence, respectively). Also, many PRiDe patients received combination therapy, whereas only TTF monotherapy was allowed in EF-11. For newly diagnosed glioblastoma patients, the EF-14 clinical trial demonstrated that the addition of TTF to standard radiation and TMZ prolonged PFS and OS. While there is currently no published post-market clinical registry data for newly diagnosed glioblastoma patients, this study is now underway in Germany (NCT03258021).

One factor that significantly affected TTF efficacy in both patient populations is treatment adherence. While adherence was high in both EF-11 and EF-14, median adherence was below the recommended 75% in PRiDe. Given the median survival of 13.5 months for those with ≥ 75% adherence and only 4 months for those with < 75% in the PRiDe registry, low adherence is concerning and may suggest real-world barriers to achieving efficacious treatment.

Trial limitations

While the EF-11 and EF-14 trial results were sufficient for FDA approval of TTF, limitations in trial design and risk of bias must also be considered. Patients in EF-11 were late in the disease course—only 9% of patients in the TTF arm and 15% of patients in the chemotherapy arm were at first recurrence [12]. Given the lack of standard of care and limited benefit of chemotherapy at this stage, one may argue that patients on no treatment may also have similar survival and fewer adverse effects to those on chemotherapy [28]. In addition, MGMT methylation status, which has known survival implications for glioblastoma patients, was not assessed in this study.

Concerns have also been raised regarding certain aspects of EF-14 and the generalizability of its results. Inclusion

criteria specified that patients must have successfully completed standard radio-chemotherapy [13]. In addition, randomization occurred 3.8 months after diagnosis, and 8% of consented patients progressed in this interval. Thus, the randomized patient population may be biased towards individuals with a better prognosis. Prior carmustine wafer implants were allowed, though the number of patients with implanted wafers in each arm was not reported. In addition, the lack of a sham device in the control arm, which was excluded due to ethical concerns, is cited as a potential confounding factor [14]. One counterargument mentions that the magnitude of survival benefit is beyond what would be expected for a placebo effect and that other trials without a placebo arm had no difference in survival [14]. Another viewpoint is that the lack of sham therapy may influence survival due to the additional care necessitated by support for a novel device such as TTF, rather than due to a placebo effect [15].

Quality of life

In addition to efficacy and safety, quality of life (QoL) is also a centrally important facet of care for glioblastoma patients. EF-11 utilized the EORTC QLQ-C30 questionnaire to measure the effects of TTF on QoL at baseline and every 3 months thereafter, but data was only available for 27% of patients [12]. Since median treatment duration was 2.3 months, patients who remained on therapy for at least 3 months and who were eligible to complete the survey may represent a biased sample [22]. Importantly, when assessing changes between baseline and 3 months of therapy, there were no meaningful differences between the TTF and control arms in global health and social functioning. Thus, while patients on TTF may experience fewer severe systemic adverse effects compared to those undergoing chemotherapy, global health status / QoL may not be improved due to other burdens associated with TTF use.

For EF-14, QoL was assessed using the EORTC QLQ-C30 and the QLQ-BN20 (brain tumor module) surveys [29]. The survey was completed by 91.9% of patients at baseline, 65.8% of alive patients at 3 months, and 41.7% of alive patients at 12 months. This analysis demonstrated that there was no change from baseline in any of 9 QoL metrics for either the TMZ with TTF arm or the TMZ monotherapy arm except for itching, which was worse in the former arm. These results suggest that TTF prolongs survival without negatively impacting QoL for newly diagnosed glioblastoma patients.

Understanding the number of patients who have been offered TTF but denied or discontinued it, and why they did so, may also provide crucial insight into patient perceptions of TTF. For example, of the 1019 consented patients in EF-14, 46 removed themselves because they did not want to use the device and 53 "refused to participate" without further specification [13]. In EF-11, 27 patients discontinued treatment early, often within a few days, due to non-adherence or inability to handle the device [12]. One reason cited for therapy refusal is cosmetics [26]. Given that alopecia has been characterized as one of the most distressing adverse effects of chemotherapy, the greater cosmetic alterations required for TTF may have a notable impact on QoL [30–32].

Additional QoL data are greatly needed and new trials are already underway. For example, an actively recruiting trial at Duke University (NCT03501134) is utilizing activity-tracking technology to characterize the impact of TTF on sleep, daily activities, and overall QoL.

Cost

In addition to treatment effects, the financial implications of the device must also be considered. The estimated monthly cost for TTF is $21,000 per month [33]. In a post-hoc study performed using data from EF-14, the incremental cost-effectiveness ratio (ICER) for TTF was €549,909 ($610,399) per life-year gained [34]. By comparison, the ICER of concomitant and adjuvant TMZ when added to radiotherapy for newly diagnosed glioblastoma was €37,361 ($54,921) per life-year gained [35], and the ICER of carmustine wafers was €54,500 ($74,665) per quality-adjusted life-year gained [36]. Although these analyses had differences in methodology and setting, the comparison demonstrates the considerable cost difference between TTF and other treatments for newly diagnosed glioblastoma. However, the TTF cost analysis was retrospective and thus had limited access to potential cost factors such as hospitalizations and emergency room visits [37]. A prospective trial may provide a more accurate estimate of the real-world cost of therapy.

Additionally, Medicare recently released a Local Coverage Determination approving coverage for TTF in newly diagnosed glioblastoma patients for Medicare beneficiaries. Effective September 1, 2019, patients who meet criteria will be eligible for treatment coverage. Thus, the cost of therapy should be considered both at an individual and societal level.

Literature support

Concerns have also been expressed regarding the funding of TTF related publications. A study by Hayes et al. investigated the financial conflicts of interest between authors of TTF related studies and Novocure, the sole manufacturer of TTF devices [38]. Fifteen studies met the inclusion criteria for this analysis—9 studies were determined to have a favorable conclusion regarding TTF, while 6 were determined to be neutral. For the 9 favorable studies, 8 had at least one author who received more than $1000 from Novocure. In comparison, for the 5 neutral studies, only 1 of 9 authors had received any financial support from the TTF manufacturer, and no gifts exceeded $1000. Thus, the significant financial involvement of

Novocure with the body of literature on TTF may also contribute to physician skepticism.

Limitations

In addition to the limitations inherent in a systematic review, this review was limited by the small number of primary publications evaluating the efficacy of TTF for high-grade glioma patients. Notably, no studies were identified investigating TTF for Grade III glioma patients that met inclusion criteria. Furthermore, many included studies focused on TTF subgroup analyses or TTF combination regimens, and there were significant differences in study design and outcome definition within the included studies. Thus, an objective statistical meta-analysis was not performed.

Conclusion

Advancement of therapy for glioblastoma patients has proven to be difficult, and little has changed in the standard of care since the landmark EORTC 2005 trial establishing the role of TMZ in glioblastoma therapy. Given this landscape, TTF represents an entirely new modality that has demonstrated some promising results. The therapy provided a significant PFS and OS benefit for newly diagnosed glioblastoma patients in a phase III clinical trial and has repeatedly demonstrated an excellent safety profile. Furthermore, patients had high adherence to the therapy in clinical trials. However, the neuro-oncology and neurosurgery communities remain divided on their overall support of the therapy. Many physicians have concerns regarding the design of the pivotal trials that led to TTF approval, the cost of the device both on an individual and societal level, as well as the robustness of current analyses focusing on QOL impact. In addition, the financial ties between Novocure and TTF literature may raise questions of bias in the existing literature.

Ultimately, more data are greatly needed. As this review demonstrated, there are currently only 9 published studies describing the efficacy of TTF for glioblastoma that fit inclusion criteria. Additional studies have already been initiated to answer some of the most pressing issues, such as TTF effectiveness for newly diagnosed glioblastoma patients in routine clinical practice, its broader impact on QoL, and prognostic factors to determine which patients may benefit most from therapy. Emerging studies will allow physicians and patients to make better informed care decisions and will determine if TTF truly emerges as a new "standard treatment" for glioblastoma care.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

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