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CLINICAL STUDY

Tumor treating fields plus temozolomide for newly diagnosed glioblastoma: a sub-group analysis of Korean patients in the EF-14 phase 3 trial

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Abstract

Background Tumor treating fields (TTFields) are anti-mitotic, non-invasive loco-regional cancer therapy comprising low intensity, intermediate frequency alternating electric fields. TTFields plus Temozolomide (TTFields/TMZ) extended survival versus TMZ alone in newly diagnosed glioblastoma (GBM) patients in the EF-14 trial. We report on Korean newly diagnosed GBM patients who participated in the EF-14 trial.

Methods Thirty-nine participants of the EF-14 trial were enrolled at 8 sites in South Korea. Patients (24 TTFields/TMZ; 14 TMZ alone) received: TTFields (200 kHz) for > 18 h/day; TMZ at 120–150 mg for 5 days per a 28 day cycle. Safety and efficacy were assessed.

Results Patient baseline characteristics were balanced in the 2 arms and the mean age was 52.1 years, 66.7% were male with a mean KPS of 90. Safety incidence was comparable between the 2 arms. In the TTFields/TMZ arm, 30% suffered from skin irritation versus 52% in the entire study population. No TTFields-related serious adverse events were reported. The median progression-free survival (PFS) in the TTFields/TMZ arm was 6.2 months (95% CI 4.2–12.2) versus 4.2 (95% CI 1.9–11.2) with TMZ alone (p = 0.67). Median overall survival was 27.2 months (95% CI 21-NA) with TTFields/TMZ versus 15.2 months (95% CI 7.5–24.1; HR 0.27, p = 0.01) with TMZ alone.

Conclusion Median OS and 1- and 2-year survival rates were higher with TTFields/TMZ and similar to the entire EF-14 population. About 30% of patients reported skin irritation, a lower rate than seen in the entire EF-14 population. These results demonstrate the efficacy and safety of TTFields in Korean newly diagnosed glioblastoma patients.

Clinical Trials Clinicaltrials.gov Identifier: NCT00916409.

Keywords Glioblastoma · Tumor treating fields · Korean GBM patients

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Introduction

Among cancers of the central nervous system, glioblastoma multiforme (GBM) is the most devastating of adult brain tumors. Glioblastoma, is the most commonly occurring type of malignant glioma, representing 56% of all gliomas [1], and patients diagnosed with GBM have an estimated 5-year survival rate of approximately 6% [2]. The average annual age-adjusted incidence rate for glioma in the United States—using data collected from 2010 to 2014—is 6.0 per 100 000 population with a significant amount of morbidity and mortality associated with the progression of the disease [1]. The incidence of glioma for all ages varies globally, with the highest rates in the United States, Canada, Australia, and Northern Europe and the lowest in Southeast Asia, India, and East Asia [3]. Glioblastoma has a poor prognosis with a median survival of only 15 months [4] following the standard treatment comprised of radiation therapy concurrent with temolozomide (TMZ) and TMZ adjuvant therapy after gross surgical resection—frequently referred to as the Stupp protocol [5].

Surgical resection, radiation therapy, and chemotherapy, components of the Stupp protocol [5], were until recently backbone treatment modalities for GBM. Tumor treating fields (TTFields) are a relatively new treatment modality for GBM that acts upon rapidly dividing glioma cells through the action of low-intensity, intermediate frequency (200 kHz) alternating electric fields [6–10]. Tumor treating fields act upon the microtubules and septin fibers of proliferating cancer cells to disrupt mitosis and induce mitotic cell death, mitotic catastrophe, formation of nonviable daughter cells and cellular stress [6–9, 11–14]. Ongoing research suggests that TTFields also inhibit DNA damage repair [15] and impair cellular migration and invasion through the inhibition of matrix metalloproteases (MMP) [16]. In vitro, TTFields application increases immunogenic cell death in cancer cells and suggests that combining TTFields with immunotherapies may enhance antitumor immunity [17]. There is also a possible synergistic effect between TTFields and radiation therapy (RT) when the TTFields are applied prior to or after RT, which suggests that GBM patients may benefit from the concomitant administration of TTFields with RT in the clinical setting [18, 19].

The phase 3 EF-14 study was an open-label, randomized trial comparing TTFields/TMZ to TMZ alone in 695 newly diagnosed GBM patients enrolled at 83 sites in North America, Europe, the Republic of Korea, and Israel. The study demonstrated that the addition of TTFields to maintenance TMZ therapy resulted in significant improvement in PFS and OS when compared to TMZ maintenance therapy alone [20, 21]. Among the 83 international study sites, 8 were located in the Republic of South Korea. The objective of this EF-14 phase III trial subgroup analysis was to evaluate the efficacy and safety of TTFields combined with TMZ during maintenance therapy versus TMZ alone in Korean patients.

Methods

This study is based on the subgroup of South Korean patients enrolled in the EF-14 trial. The EF-14 trial was a randomized, open-label study, that enrolled 695 newly diagnosed GBM patients whose tumor was either resected or biopsied, followed by radiation therapy and concomitant TMZ and then received maintenance TMZ therapy [20]. Patients were randomized 2:1 to TTFields plus maintenance TMZ chemotherapy (n = 466) or temozolomide alone (n = 229) [20]. Temozolomide (150–200 mg/m^2) was administered to both groups for 5 days on a 28-day cycle (6–12 cycles). In both treatment groups, the median time from randomization to treatment was 3.8 months [20]. Figure 1 shows the Optune® device for administering TTFields therapy in the EF-14 trial. Details regarding the study protocol and treatment administration are presented in the full set analysis of the EF-14 trial [20].

The EF-14 trial enrolled Asian patients at 8 sites in South Korea. Men and women, 18 years of age or greater, with newly diagnosed and histologically confirmed supratentorial GBM (WHO Grade IV astrocytoma) were eligible to participate [20]. Primary exclusion criteria were progressive disease following radiochemotherapy or a infratentorial tumor location [20]. The primary and secondary efficacy assessments in this subgroup analysis were progression-free

Fig. 1 The Optune® system is designed to be portable and minimize the intrusion of TTFields treatment for glioblastoma on the activities of daily living

survival (PFS) and overall survival (OS). One- and two-year survival rates as well as radiographic response rates were also calculated for the subgroup of Korean patients. The safety and tolerability of TTFields treatment was assessed based on the incidence and severity of adverse events.

Standard summary statistics were calculated as the number and percentage of responses in each level for categorical variables, and the sample size, mean, median, standard deviation, minimum, and maximum values for continuous variables. Statistical significance was calculated using Chi squared test for percentage values and *t* test for mean values. The PFS and OS survival curves were constructed using the Kaplan–Meier method.

Results

A total of 39 Korean patients were enrolled—24 in the TTFields/TMZ treatment group, one of whom one never started treatment, and 15 enrolled in the TMZ alone group. The baseline characteristics between the two treatment groups were balanced (Table 1) and generally matched the previously reported characteristics of the general study population [20]. The mean age of all Korean patients was 52.1 years and the majority were male (67%) and 51.3% had undergone a gross total surgical resection. The mean Karnofsky performance score (KPS) for Korean patients was 90 in the TTFields/TMZ and 92.7 in the TMZ alone groups. Antiepileptic use at baseline was 54.2 and 53.3% in the TTFields/TMZ and TMZ alone groups respectively and approximately 25% of patients in each group received corticosteroids at baseline. Recommended adherence to TTFields therapy was defined as having the transducer arrays applied to the scalp and administering TTFields therapy for ≥ 75% of the time over a month of treatment. Compliance with recommend therapy was achieved by 45.8% of Korean patients receiving TTFields/TMZ treatment during the first 3 months.

The median PFS in the TTFields/TMZ group was 6.2 months (95% CI 4.2–12.2) versus 4.2 (95% CI 1.9–11.2) in the TMZ alone group (p = 0.67). Median overall survival for Korean patients (Fig. 2) was 27.2 months (95% CI 21–NA) in the TTFields/TMZ group, which was significantly higher than the median OS of the TMZ alone group (15.2 months, 95% CI 7.5–24.1). The Hazard Ratio was 0.27 (0.098–0.750; p = 0.01).

The 1- and 2-year survival rates in the EF-14 Korean population (Fig. 3) were higher in the TTFields/TMZ group. The 1-year survival rates were 95.6% (95% CI 72.93–99.38) versus 73% (95% CI 43.62–89.05; $p = 0.033$) and the 2-year survival rates were 60% (95% CI 34.63–78.07) versus 30% (95% CI 8.916–54.90; $p = 0.041$) in the TTFields/TMZ and TMZ alone groups respectively.

Radiological response rates in the EF-14 Korean patients is summarized in Table 2. There was no statistically difference in the radiological response of EF-14 Korean patients between the TTFields/TMZ and TMZ alone groups. However, a greater percentage of patients in the TTFields/TMZ group (67% vs. 57%) showed stable disease as measured by radiological progression.

There were no differences between the TTFields/TMZ and TMZ alone groups of Korean EF-14 patients in the incidence of adverse events (Table 3). In the TTFields/TMZ group, 30% of patients reported skin irritation. Table 3 includes the adverse events by system organ class and preferred MEDDRA term.

Discussion

Based on epidemiological patient data from the Korean Central Cancer Registry (KCCR)—glioma comprised 12.7% of all primary brain and central nervous system tumors, and of these GBM represented 5.3% of all primary brain tumors and ~ 42% of all glioma reported for Korean patients in 2013 [22]. The current standard of care for GBM in South Korea includes radiation therapy concomitant with TMZ after surgical resection followed by maintenance therapy with TMZ [23, 24]. In a large retrospective analysis of 750 histologically confirmed GBM patients treated with concurrent chemoradiotherapy with TMZ and adjuvant TMZ was associated with a survival benefit for the Stupp protocol.

The Korean Society for Neuro-Oncology (KSNO) recently published a guideline for the treatment of GBM [25]. Prior to the KSNO guideline there was no practical guidelines for the treatment of GBM in Korea [25] and though the KSNO recommendations follow the Stupp protocol, the authors highlight limitations of their recommendations due to the unique medical circumstances in Korea. The National Health Insurance System of Korea limits the therapeutic options and does not cover TTFields, permitting only two treatment options—chemoradiotherapy with TMZ or standard radiotherapy alone—regardless of methylation status of MGMT promoter after surgical resection in newly diagnosed GBM patients [25]. The authors further highlight there is no standard and effective treatments for GBM recurrence in Korea or other countries, however there are fewer approved therapeutic regimens available for Korean patients and far fewer options for patients to participate in clinical trials.

In this subgroup analysis, Korean patients participating in the EF-14 trial had a median PFS of 4.2 months in the TMZ alone group during maintenance therapy and the OS rate was 15.2 months. More Korean patients in the EF-14 subset analysis were male and few had complete surgical resection prior to randomization in the study, which may account for the slightly

Table 1 EF-14 Korean participants subgroup analysis—Patient and treatment characteristics

Characteristic	No. (%) of patients			
	TTFields + TMZ (n = 24)	TMZ alone (n = 15)	All patients (N = 39)	*P*-value[a]
Age, years				
Mean (SD)	49.7 (13.90)	56.1 (13.44)	52.1 (13.91)	0.165
Median (range)	53.0 (22–75)	57.0 (28–74)	54.0 (22–75)	
Karnofsky performance score[b]				
Mean (SD)	90.0 (8.85)	92.7 (7.99)	91.0 (8.52)	0.348
Median (range)	90.0 (70–100)	90.0 (70–100)	90.0 (70–100)	
Sex (%)				
Men	15 (62.5%)	11 (73.3%)	26 (66.7%)	0.485
Women	9 (37.5%)	4 (26.7%)	13 (33.3%)	
Antiepileptic drug use at baseline	13 (54.2%)	8 (53.3%)	21 (53.8%)	0.959
Corticosteroid use at baseline	6 (25.0%)	4 (26.7%)	10 (25.6%)	0.908
Mini-mental state examination[c] score available, no. (%)				
≤ 27	8 (33.3%)	7 (46.7%)	15 (38.5%)	0.405
27–30	16 (66.7%)	8 (53.3%)	24 (61.5%)	
Extent of resection				
Biopsy	1 (4.2%)	1 (6.7%)	2 (5.1%)	0.875
Partial resection	10 (41.7%)	7 (46.7%)	17 (43.6%)	
Gross total resection	13 (54.2%)	7 (46.7%)	20 (51.3%)	
MGMT promoter region methylation status no. (%)	23 (95.8%)	13 (86.7%)	36 (92.3%)	
Methylated	8 (34.8%)	5 (38.5%)	13 (36.1%)	0.974
Unmethylated	13 (56.5%)	7 (53.8%)	20 (55.6%)	
Invalid	2 (8.7%)	1 (7.7%)	3 (8.3%)	
IDH1R132H tissue available and tested, No. (%)	22 (91.7%)	13 (86.7%)	35 (89.7%)	
Positive	2 (9.1%)	1 (7.7%)	3 (8.6%)	0.886
Negative	20 (90.9%)	12 (92.3%)	32 (91.4%)	
EGFR tissue available and tested, no. (%)	23 (95.8%)	13 (86.7%)	36 (92.3%)	
Positive	9 (39.1%)	4 (30.8%)	13 (36.1%)	0.616
Negative	14 (60.9%)	9 (69.2%)	23 (63.9%)	
Tumor tissue chromosomes ip and 19q, no. (%)	23 (95.8%)	13 (86.7%)	36 (92.3%)	
Co-deletion	1 (4.3%)	…	1 (2.8%)	0.318
Loss 1p only	1 (4.3%)	…	1 (2.8%)	
Loss 19q only	…	1 (7.7%)	1 (2.8%)	
Retained	21 (91.3%)	11 (84.6%)	32 (88.9%)	
Invalid	…	1 (7.7%)	1 (2.8%)	
Tumor position, no. (%)				
Corpus callosum				0.199
Frontal lobe	11 (45.8%)	6 (40.0%)	17 (43.6%)	
Occipital lobe	5 (20.8%)	…	5 (12.8%)	
Parietal lobe	4 (16.7%)	5 (33.3%)	9 (23.1%)	
Temporal lobe	9 (37.5%)	5 (33.3%)	14 (35.9%)	
Missing	…	1 (6.7%)	1 (2.6%)	
Tumor location, no. (%)				
Left	13 (54.2%)	8 (53.3%)	21 (53.8%)	0.747
Right	14 (58.3%)	7 (46.7%)	21 (53.8%)	
Treatment delivery				
Completed radiation therapy, no. (%)				
< 57 Gy	4 (16.7%)	…	4 (10.3%)	0.233
60 Gy (standard; ± 5%)	18 (75.0%)	14 (93.3%)	32 (82.1%)	

Table 1 (continued)

Characteristic	No. (%) of patients			
	TTFields + TMZ (n = 24)	TMZ alone (n = 15)	All patients (N = 39)	*P*-value[a]
> 63 Gy	2 (8.3%)	1 (6.7%)	3 (7.7%)	
Concomitant TMZ use, no. (%)				
Yes	24 (100.0%)	15 (100.0%)	39 (100.0%)	0.233
Time from diagnosis to randomization (days)				
Mean (SD)	34.0 (6.39)	33.3 (5.41)	33.7 (5.96)	0.755
Median (range)	32.5 (25–49)	35.0 (22–46)	33.0 (22–49)	
Number of TMZ cycles				
Mean (SD)	9.8 (8.02)	…	9.8 (8.02)	
Median (range)	8.3 (0–25)	…	8.3 (0-25)	
Duration of treatment with temozolomide, mo				
Mean (SD)	4.6 (3.11)	6.9 (5.34)	5.5 (4.20)	0.145
Median (range)	5.0 (0–15)	5.2 (0–23)	5.1 (0-23)	

EGFR epidermal growth factor receptor gene, *IDH1-R132H* socitrate dehydrogenase 1 (IDH1) R132H mutation site, *MGMT* O6-methylguanine-DNA-methyltransferase gene, *TTFields* tumor-treating fields

[a]Chi squared test for percentage values and T test for means values

[b]Karnofsky performance scores range from 0 to 100 in 10-point increments, with a higher score representing better performance status

[c]Scores range from 1 to 30, a higher score implies better cognitive function

poorer outcomes for patients in the EF-14 TMZ alone. In contrast, for Korean patients in the EF-14 TTFields/TMZ subgroup, the median PFS was 6.2 months and the median OS was 27.2 months which was significantly higher than the median OS of the TMZ alone group. In the full set of EF-14 participants that received TTFields/TMZ treatment, the median PFS from randomization was 6.7 months and the median OS from randomization was 20.9 months in the TTFields/TMZ group [20]. Outcomes for PFS and OS in the Korean patients receiving TMZ alone were comparable to the full set of EF-14 patients. However, the OS for the Korean patients receiving TTFields/TMZ was greater than that reported for the full set of EF-14 patients (27.2 months vs. 20.9 months).

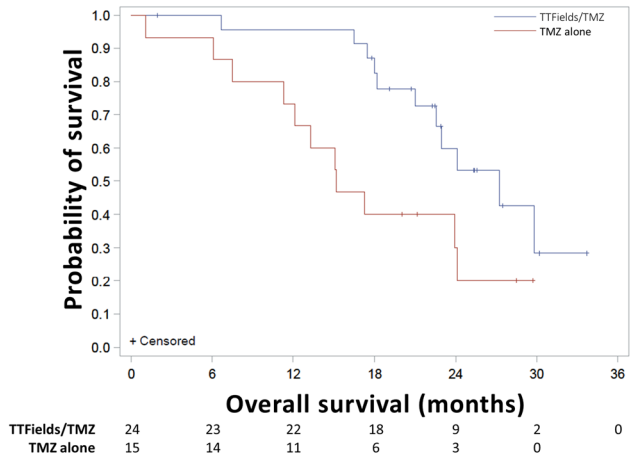

Fig. 2 Kaplan-Meyer curves for overall survival (OS) in EF-14 Korean participants. Median OS was significantly higher with TTFields/TMZ vs. TMZ alone in Korean patients

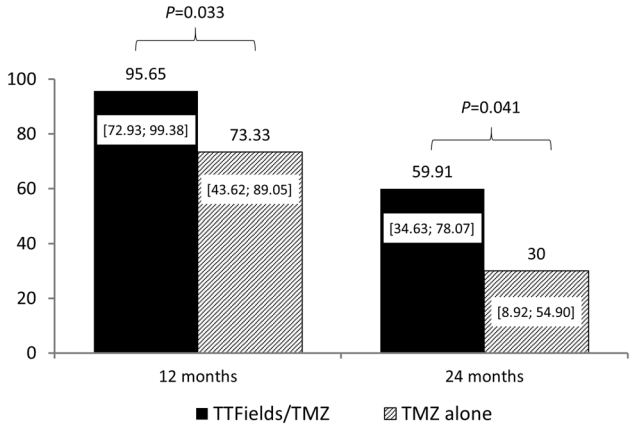

Fig. 3 One- and two-year survival rates in the EF-14 Korean patient population

There were no apparent differences in the incidence of adverse events between the two treatment arms of the Korean EF-14 patients. In the TTFields/TMZ group, 30% of Korean patients suffered from skin irritation, which was less than in the entire study population (44%) [20]. TTFields treatment compliance during the first 3 months of treatment was less among the Korean EF-14 patients when compared to full set of

Table 2 EF-14 Korean participants subgroup analysis—Adverse events by body system and severity (≥ 10% incidence in any group)

System organ class/preferred term	TTFields + TMZ (n = 24) no. (%)	TMZ alone (n = 15) no. (%)	All Patients (N = 39) no. (%)
Number of patients with ≥ 1AE	18 (78)	12 (80)	30 (79)
Blood and lymphatic system disorders	1 (4)	1 (7)	2 (5)
Cardiac disorders	0	1 (7)	1 (3)
Ear and labyrinth disorders	0	1 (7)	1 (3)
Gastrointestinal disorders	7 (30)	8 (53)	15 (39)
Constipation	3 (13)	2 (13)	5 (13)
Nausea	0	4 (27)	4 (11)
Vomiting	3 (13)	3 (20)	6 (16)
General disorders and administration site conditions	2 (9)	3 (20)	5 (13)
Hepatobiliary disorders	1 (4)	1 (7)	2 (5)
Immune system disorders	0	2 (13)	2 (5)
Infections and infestations	5 (22)	3 (20)	8 (21)
Injury, poisoning and procedural complications	8 (35)	1 (7)	9 (24)
Skin irritation	7 (30)	0	7 (18)
Investigations	3 (13)	7 (47)	10 (26)
Alanine aminotransferase increased	1 (4)	2 (13)	3 (8)
Platelet count decreased	1 (4)	2 (13)	3 (8)
White blood cell count decreased	0	2 (13)	2 (5)
Metabolism and nutrition disorders	2 (9)	7 (47)	9 (24)
Anorexia	1 (4)	2 (13)	3 (8)
Decreased appetite	0	3 (20)	3 (8)
Hypoalbuminanaemia	0	2 (13)	2 (5)
Musculoskeletal and connective tissue disorders	0	4 (27)	4 (11)
Nervous system disorders	9 (39)	8 (53)	17 (45)
Brain edema	2 (9)	2 (13)	4 (11)
Convulsion	1 (4)	3 (20)	4 (11)
Headache	6 (26)	4 (27)	10 (26)
Hemiparesis	0 (0)	2 (13)	2 (5)
Psychiatric disorders	2 (9)	2 (13)	4 (11)
Renal and urinary disorders	1 (4)	0	1 (3)
Respiratory, thoracic and mediastinal disorders	1 (4)	1 (7)	2 (5)
Skin and subcutaneous tissue disorders	5 (22)	4 (27)	9 (24)
Prupitus	1 (4)	2 (13)	3 (8)
Rash	1 (4)	2 (13)	3 (8)
Vascular disorders	1 (4)	1 (7)	2 (5)

Table 3 EF-14 Korean participants subgroup analysis—Radiological response rates

Radiological response	TTFields + TMZ (n = 24) no. (%)	TMZ alone (n = 15) no. (%)	All patients (N = 39) no. (%)
Best radiological response			0.4442
Progressive disease	6 (28.6)	3 (21.4)	
Stable disease	14 (66.7)	8 (57.1)	
Partial response	1 (4.8)	2 (14.3)	
Complete response	0 (0)	1 (7.1)	
Central clinical benefit	15 (71.4)	11 (78.6)	

EF-14 patients (46% vs. 75%). However, the Korean patients had a longer mean duration of TTFields treatment (9.8 months vs. 8.2 months), which may account for the higher OS seen among the Korean EF-14 patients receiving TTFields/TMZ. A prior subset analysis of EF-14 patients underscored the important treatment compliance demonstrating that higher levels of treatment compliance with TTFields plus TMZ were associated with increased durations of PFS and OS [26].

A limitation of this study is the relatively small sample size and that data are based on a subgroup analysis of the EF-14 trial; subgroup analyses are prone to type I errors limiting the accuracy of the results [27]. The protocol defined randomization schedule of 2:1 favored inclusion of GBM patients in the TTFields/TMZ group and accounts for the imbalance of Korean patients receiving TTFields (24 vs. 15 for TMZ alone) and further highlights the limitations imposed by the small sample size of this subgroup analysis. Tumor treating fields are approved for the treatment of newly diagnosed and recurrent GBM in Japanese patients and provides an opportunity for the collection and systematic analysis of real-world data for the use of TTFields in an Asian population of GBM patients.

This subgroup analysis was conducted to evaluate the efficacy and safety of the TTFields combined with TMZ during maintenance therapy for newly diagnosed GBM patients' Korean patients. There was no difference between the clinical outcome in the general study population and the 39 Korean patients randomized to the EF-14 study. The median OS and 1- and 2- survival rates were higher than those reported for the general EF-14 study population. In addition, adding TTFields to TMZ did not lead to increased toxicity and most adverse events were seen at a lower incidence in the TTFields/TMZ group than in the TMZ alone group. These results demonstrate the efficacy and safety of TTFields in Korean patients with newly diagnosed glioblastoma.

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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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