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Case Report

Tumor Treating Fields (TTFields) Therapy and Lomustine Chemotherapy for the Treatment of Unresectable Progressive Glioblastoma

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Glioblastoma · Tumor Treating Fields · Lomustine · Case report

Abstract
Introduction: Tumor Treating Fields (TTFields) therapy used concomitantly with maintenance temozolomide through second progression after radio-chemotherapy is associated with improved survival outcomes compared to adjuvant temozolomide alone in individuals with newly diagnosed glioblastoma (GBM). Lomustine (CCNU) is frequently used as monotherapy or concomitant with other chemotherapy regimens as second-line treatment for recurrent GBM. ***Case Presentation:*** We report a 59-year-old female patient diagnosed with *MGMT*-promoter methylated, isocitrate dehydrogenase-wildtype GBM (World Health Organization Grade 4) who received TTFields therapy concomitant with first- and second-line chemotherapy following partial resection. The patient experienced tumor pseudoprogression/progression after three cycles of maintenance temozolomide/TTFields therapy and again after a further two cycles of procarbazine/CCNU/TTFields therapy, and was then switched to CCNU/TTFields therapy. During 18 months of treatment with concomitant TTFields therapy and CCNU, the patient experienced regression/reduction of both tumor volume and perifocal edema with tolerable hematotoxicity and was able to maintain a high rate of TTFields therapy usage. The patient ultimately died after developing chemotherapy-related acute myeloid leukemia. ***Conclusion:*** This patient case is reflective of the EF-14 study outcome using TTFields therapy beyond first progression concomitantly with chemotherapy. The observations from this case suggest that TTFields therapy concomitant with CCNU is a valuable treatment modality in patients with GBM, in this context.

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Introduction

Tumor Treating Fields (TTFields) are alternating electric fields that disrupt cellular processes critical for cancer cell viability and tumor progression [1]. Administration of TTFields therapy with temozolomide, after radio-chemotherapy, significantly increased median progression-free survival, median overall survival, and long-term survival in patients with newly diagnosed (nd) glioblastoma (GBM) in the pivotal/phase 3 EF-14 study (NCT00916409) [2]. Of note, patients in the EF-14 study were permitted to receive TTFields therapy concomitant with second-line treatment after first progression; a post hoc analysis of this subset of patients revealed prolonged overall survival in this setting [2, 3].

The efficacy of temozolomide and lomustine (chloroethyl-cyclohexyl-nitroso-urea [CCNU]) has been demonstrated in ndGBM [4], and CCNU is frequently used as second-line therapy in recurrent GBM, often alone or in combination with procarbazine and/or vincristine, despite its association with delayed (4–6 weeks) cumulative leukopenia and thrombocytopenia [5]. In a preclinical glioma model, TTFields treatment has been shown to enhance the effectiveness of temozolomide and CCNU, supporting the rationale for clinical use [6]. Indeed, a bicentric retrospective analysis of 16 patients with ndGBM found that combination treatment with TTFields therapy, lomustine, and temozolomide was generally safe and effective [7]. Furthermore, in the EF-14 study, nitrosoureas drugs including CCNU were the second most common second-line chemotherapy after bevacizumab [3]. Based on this evidence, it is relevant to seek to understand more about the feasibility and efficacy of TTFields therapy concomitant with CCNU. Here, we report on a patient with partially resected GBM who received TTFields therapy concomitant with first- and second-line chemotherapy. The novelty of this case study lies in the fact that these data add to the growing body of evidence of the feasibility of TTFields therapy concomitant with CCNU, a commonly used agent in GBM. This case report was prepared following the case report (CARE) guidelines; a CARE checklist has been completed by the authors for this case report and is attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000540669) [8]. Written informed consent was obtained from the participant's next-of-kin for publication of the details of their medical case and any accompanying images.

Case Report

A 59-year-old female European patient presented with memory loss in November 2018. Additional symptoms at clinical examination included a 2-month history of headache and difficulty with written language. The patient had a prior medical history of nodular goiter and immunogenic hyperthyroidism Graves' type for which the patient received antithyroid drugs. Following examination, magnetic resonance imaging (MRI) revealed a large, heterogeneous, space-occupying lesion in the left temporo-occipital region with clearly contrast-enhanced margins (3.9 × 5.2 cm transverse dimension, 4.0 cm craniocaudal dimension) and perifocal edema, as shown in Figure 1a. Additionally, two smaller contrast-enhancing lesions in the splenium of corpus callosum and to the right of the trigonum suboccipital were found. While the tumor in the left occipital region was amenable to neuro-navigated resection, the contrast-enhancing lesions in the right hemisphere were deemed unresectable due to their critical locations (shown in Fig. 1a). Histopathological analysis of the resected tumor identified *MGMT*-promoter methylated, isocitrate dehydrogenase-wildtype GBM.

The patient received radio-chemotherapy (total radiation dose of 54 Gy to the extended former tumor lesion, delivered using 2 Gy daily fractions, followed by a sequential boost of 6 Gy, up to cumulative 60 Gy to the narrower tumor region, delivered using 2 Gy daily

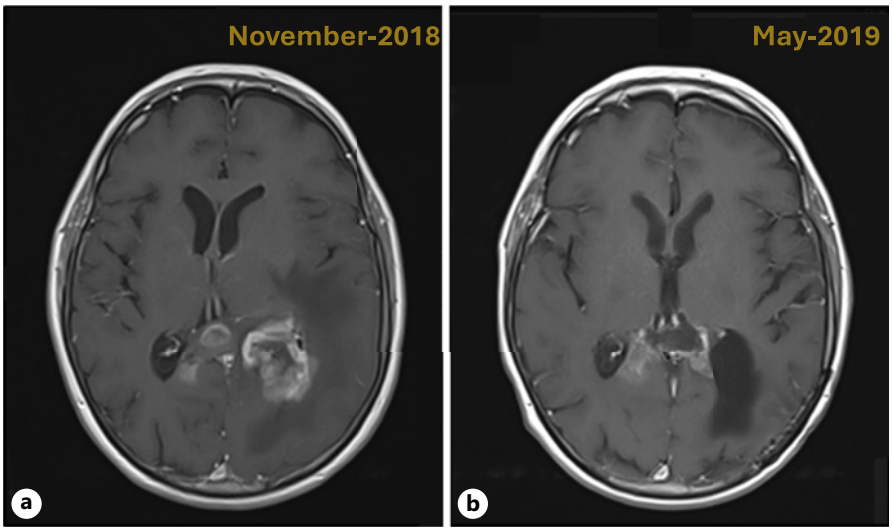

Fig. 1. Pre- and postoperative contrast-enhanced T1-weighting MRI scans. **a** Preoperative MRI taken at baseline (November 2018) and perifocal edema. **b** Postoperative MRI taken in May 2019.

fractions; temozolomide 75 mg/m^2 body surface area) and adjuvant temozolomide (200 mg/m^2) concomitant with TTFields therapy. After three cycles of temozolomide, unresected tumor progressed (imaging was assessed to be likely pseudoprogression; however, progression could not be excluded) and chemotherapy was changed to procarbazine/CCNU (procarbazine chemotherapy 60 mg/m^2 on days 8–21; 110 mg/m^2 CCNU on day 1).

Further progression occurred after two cycles, following which CCNU (110 mg/m^2) supplemented with ondansetron for nausea prevention was administered; TTFields therapy continued without treatment interruption. Other supplementary medication included continuous administration of L-thyroxine and apixaban (apixaban starting 2019) and for a limited period pantoprazole, dexamethasone, and sertraline. A schematic overview of the administered treatments and contrast-enhanced T1-weighting MRI scans are shown in Figures 2 and 3.

One year following initial diagnosis, MRI revealed no contrast-enhancing tissues in the resection cavity, regression of perifocal edema, and stable contrast-enhancing lesions, in comparison with the last follow-up. CCNU was continued alongside TTFields therapy, with high rate of device usage (an average of 81% in an exemplary time period, shown in online suppl. Fig. 1), beyond the suggested threshold of 50% [9]. Average TTFields therapy device usage was based on usage reports collected every month by Device Support Specialists and provided to the main treating physician. The patient experienced persistent hemianopsia with memory and orientation impairment (necessitating daily help from a relative); otherwise, the patient was generally in good physical health.

Radiologic follow-up examinations in February 2020 reported a regressive tumor volume in the right hemisphere; therefore, CCNU and TTFields therapy were continued. In February 2022, the patient was diagnosed with chemotherapy-related acute myeloid leukemia (t-AML) with a complex aberrant karyotype and a TP53 mutation, among others. The patient was subsequently treated with azacitidine and regular blood transfusions. Thrombocytopenia-induced intracerebral bleeding resulted in motor deficits. The patient's general condition deteriorated over subsequent weeks, accompanied by infections. Side effects related to azacitidine treatment included bone marrow toxicity, infections, local reaction at injection site, and gastrointestinal symptoms. In March 2022, the tumor regressed further without the detection of new lesions (shown in Fig. 3). The patient died in May 2022 due to t-AML.

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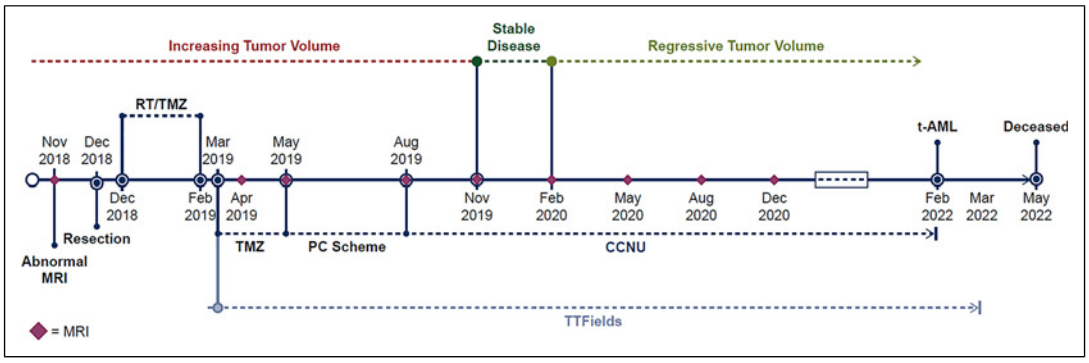

Fig. 2. Schematic overview of administered treatment.

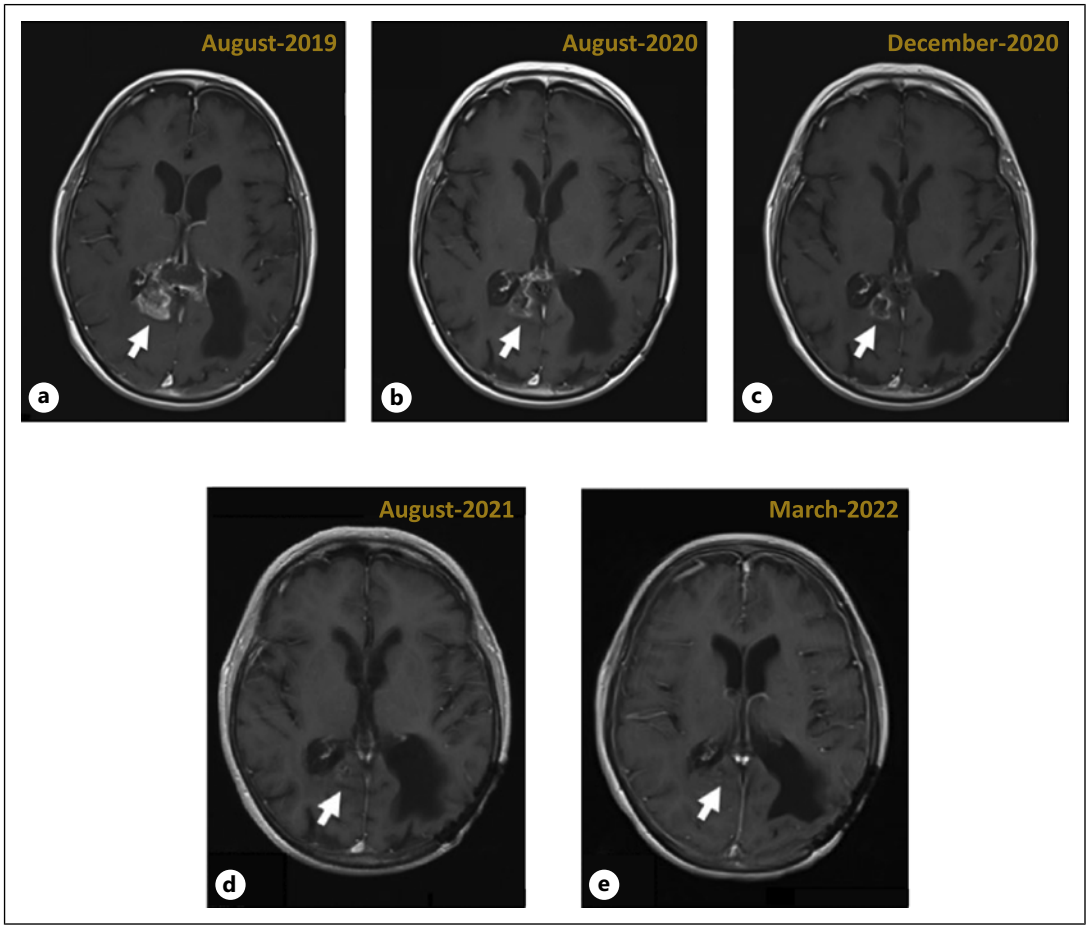

Fig. 3. Contrast-enhanced T1-weighting MRI scans showing regression of the unresected tumor. **a** August 2019. **b** August 2020. **c** December 2020. **d** August 2021. **e** March 2022.

Discussion

Treatment of GBM, the most common primary brain tumor in adults, remains challenging, with disease progression frequently occurring after resection and first-line standard-of-care treatment [10, 11]. TTFields therapy is an established option for the treatment of GBM,

offering beneficial outcomes beyond first tumor progression with lower systemic toxicity profiles than traditional chemotherapies [2, 12, 13].

The observations from this case study further support the findings from the EF-14 study (NCT00916409) and support the use of TTFields therapy concomitant with second-line treatment after first disease recurrence in patients with GBM (post hoc results showed improved overall survival [11.8 vs. 9.2 months; hazard ratio: 0.70; 95% confidence interval, 0.48–1.00; p = 0.049] compared with chemotherapy alone) [2, 3]. The case presented here and findings from clinical studies show that treatment with TTFields therapy has a low toxicity safety profile. Importantly, this case study demonstrates that TTFields therapy continued concomitantly with CCNU beyond the first progression was found to be beneficial.

Of note in this case is the observation that the patient showed evidence of regression of perifocal edema following treatment with chemotherapy concomitant with TTFields therapy. Increased tumor volume is linked to poorer outcomes [14], while higher edema levels at diagnosis are independently associated with decreased survival in patients with GBM [15]. Conversely, greater reductions in peritumoral edema lead to symptomatic improvement in patients with GBM [6]. As such, the reduction in tumor volume and perifocal edema regression observed in this patient, taken together with past preclinical findings [6] and real-life experiences with combination of CCNU and temozolomide in patients with ndGBM [16], suggests that TTFields therapy and concomitant CCNU use may be beneficial in patients with GBM. It should be noted that larger scale studies would be needed to confirm this observation.

While our findings are promising, our report is subject to several limitations, the most obvious being the observation of only a single patient. It should be noted however, that as the patient's death was ultimately due to chemotherapy-related complications (t-AML) and not disease progression per se, the outcome could not have been influenced by the addition of TTFields therapy, nor was there any evidence that TTFields therapy exacerbated any effect of the chemotherapy [7, 16]. This fact may have impacted the perceived added benefit of TTFields therapy, since the patient died before the full benefit could be assessed, perhaps dampening the actual effect. Additionally, we cannot exclude the possibility of true tumor progression, as opposed to pseudoprogression, resulting from cancer treatment as no further testing was carried out to evaluate this. Future studies would seek to confirm our experience in a larger sample of patients in the real-world setting.

Conclusion

In this case study, TTFields therapy continued concomitantly with CCNU beyond the first progression was found to be beneficial. This observation further supports the results from the EF-14 study and the recommendation to continue TTFields beyond first progression concomitantly with systemic therapy. TTFields therapy concomitant with chemotherapy is a valuable treatment modality to improve clinical and radiological outcomes of patients with GBM.

Statement of Ethics

Written informed consent was obtained from the participant's next-of-kin for publication of the details of their medical case and any accompanying images. Ethical approval is not required for this study in accordance with local or national guidelines.

Conflict of Interest Statement

Ertan Mergen was previously engaged by Novocure GmbH as a speaker, and this activity was unrelated to this publication.

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Author Contributions

Ertan Mergen contributed to the conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, and writing of this publication. Sonja Landrock and Barbara Chizzali contributed to the conceptualization, investigation, methodology, resources, software, visualization, and writing of this publication.

Data Availability Statement

All data supporting the findings of this case report were included in this article. Further inquiries can be directed to the corresponding author.

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