SAFETY AND EFFICACY OF THE APPLICATION OF THE TUMOR-TREATING FIELDS (TTFIELDS) MECHANISM ASSOCIATED WITH TEMOZOLOMIDE AFTER THE STANDARDIZED PROTOCOL OF CHEMOTHERAPY AND RADIOTHERAPY IN PATIENTS WITH RECENTLY DIAGNOSED GLIOBLASTOMA

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Abstract: Tumor-Treating Fields is an antineoplastic treatment modality that consists in the application of alternating electric currents directly to the skin in the tumor region. Glioblastoma multiforme is the most common primary brain tumor. Treatment options are limited. A bibliographical review addressing what is significant and new in the medical literature regarding the treatment of glioblastoma with the Tumor-Treating Fields or Novocure mechanism is presented, based on the main research portals. The main objective of this study was to establish the safety and efficacy of the Tumor-Treating Fields approach in the treatment of recently diagnosed glioblastoma. After confirming its safety and efficiency the secondary objective was to establish this approach as the treatment of choice for this pathology. The main articles in English concerning this issue were searched on the portals PUBMED, Cochrane, Lilacs, and Embase. The investigated approach should be added to the first line treatment of glioblastoma in association with microneurosurgery, radiotherapy, and temozolomide.

Keywords: TTFields; Oncology; Glioblastoma; Radiotherapy.

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INTRODUCTION

The glioblastoma multiforme, or glioblastoma, according to the terminology used in the World Health Organization of 2016[1], is the most common primary brain tumor. A total of 23,380 new cases of primary malignant tumors were reported in the USA in 2014, with 14,320 deaths. Glioblastoma represents 45.6% of the total number of notified intracranial malignant tumors. The life expectancy of these patients in 5 years is about 5% .[2]

According to the Central Brain Tumor Registry of the United States, in an epidemiological survey about the incidence of tumors of the central nervous system performed between 2009 and 2013, glioblastoma reached an average annual incidence of 10,996 cases from a total of 54,980 patients in the observed period. This tumor represented 14.9% of all the reported cases.[3]

Along the last decade, very low improvement in life expectancy was reached, despite the technological advances obtained with the available therapeutic treatments. The treatment options for this tumor are still limited.

In 1995, Brem *et al*[4] introduced the carmustine wafer therapy applied to the tumor bed during the intraoperative phase. An average survival rate of 6.5 months was reached against 4.7 months for the recurrence of the tumor (disease-free survival rate) with this approach. However, this therapy is associated to an increase in toxicity in association with other drugs used in the gliobastoma treatment.[4]

Stupp *et al*[5] (2005) presented the temozolomide treatment for gliobastoma, which added 4 months to the disease-free survival rate in patients with glioblastoma. This drug is associated to some adverse reactions such as hair loss, nausea, vomits, anorexia, lymphopenia, and opportunistic infections. Ever since the gold standard treatment for glioblastoma consists in the maximum safe resection, radiotherapy with 60 Gray, and temozolomide in at least 12 cycles.[5]

In 2009, Friedman *et al*[6] introduced the treatment for glioblastoma recurrence with the monoclonal antibody that blocks the endothelial growth factor receptor (EGFR), bevacizumab.[6]

The Avaglio study, in 2014, showed an improvement in the disease-free survival rate in the patients treated with the intravenous drug. This drug might be associated to some health problems such as arterial hypertension, pulmonary embolism, hemorrhagic phenomena, poor wound healing, chronic perforation, and renal failure.[7]

The present study aims to assess the safety and efficacy of the implementation of the Tumor Treating Fields therapy or TTFields, associated to temozolomide, after the chemotherapy and radiotherapy standardized protocols, in patients with recently diagnosed glioblastoma.

METHODOLOGY

A bibliographical review was made using the terms “Glioblastoma” and “Tumor Treating Fields” in the Pubmed research portal, in English, resulting in 40 articles. The following groups of cooperation in investigation of cancer of the central nervous system were used as research sources: NCCN, EANO, SNO, and SNOLA. Regarding the articles available in Pubmed, this study has analyzed the following types of articles: A. 5 *in vitro* studies; B. 1 detailed report; C. 6 case series; D. 19 reviews or overviews; E. 6 technical notes (impedance studies, computational studies, virtual tumors for the development of resonance planning software); F. 2 trials; G. 1 cost analysis.

LITERATURE REVIEW

Mechanism of Action

A study performed by Kirson *et al* (2004)[8], from the University of Haifa, Israel, investigated the influence magnetic fields in the disruption of the cell division cycle.[8]

Mitosis is divided in four stages: prophase, when chromatin condensation and DNA (deoxyribonucleic acid) duplication takes place; metaphase, when the equatorial plate is formed, sustained by microtubules; anaphase,

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when the DNA is divided between the cell poles, with duplication of the centromeres and formation of the chromosomes of the daughter cells; and finally the telophase, when the nuclear and cell membranes close in the daughter cells.

The work of Kirson *et al* (2004)[8], divided in three parts, showed the interruption of mitosis after treatment with TTFields. In general, this investigation showed a sequence of anomalies in the dividing cells, shown by the immunohistochemical assay with antibodies against microtubules, actin, and DNA, namely: polyploid prophase; nondisjunction metaphase; multiple spindle metaphase; asymmetric anaphase.

In another moment of the same work, melanoma cell cultures were inoculated in the dorsum guinea pigs in the laboratory. Comparing the animals that received the TTFields treatment with those that were not submitted to any treatment, the former ones presented a reduction in tumor growth.[8]

In 2007, Kirson *et al* [9] performed a new study to assess the result of the treatment with TTFields in different tumors. Culture cells were selected from three groups: cells *in vivo* from a melanoma of rat tissue, cells *n vitro* from a human breast carcinoma, and *in vivo* cells from a human glioma in rats. In quiescent cells (out of mitosis) there was no interference of the proposed treatment, while in cells in mitosis the cell poles were hardly separated during anaphase, preventing the DNA separation and the formation of the daughter cells.[9]

Regarding cell cultures, their number was smaller in the group treated with TTFields than in those without any therapy. The optimal frequency for treatment was 150-200 kHz, with an ideal intensity of 1-2 V/cm. A group of 40 rats was inoculated with intracranial glioblastoma cells was treated for 6 days with 200 kHz, with an intensity of 2V/cm. Magnetic resonance exams of the brain revealed the reduction of the tumors.

In order to assess the safety of the studied treatment an investigation was performed applying the TTFields therapy to the thorax and cranium of rabbits. Heart rate, weight, temperature, ECG, blood count, and biochemistry of

the patients were monitored. Pathology exams were performed in the post-mortem and no pathological change was detected in the samples.[9]

Still in the same study, Kirson *et al* (2007) [9] performed a pilot study of 10 patients with recurrent gliobastoma. The criteria of patient inclusion were: more than 18 years; Karnofsky index of at least 70; treatment for at least 18h per day, case evaluation by a radiologist certified by the institution that performed the study, use of temozolomide in 100% of the cases. The authors found a disease-free survival rate of 50%, with an average time for disease progression of 26 weeks. Patients with severe comorbidities, using cardiac pacemaker, and with infratentorial tumor were excluded.

In order to validate and implement TTFields as the golden standard treatment for glioblastoma, two major trials have been made: EF 11 and EF 14. Later, a *post-hoc* analysis or a modified analysis of the treatment intention of the EF 11 population was performed.

EF 11 TRIAL

Stupp *et al* (2012)[10] performed a phase III, prospective study, with patients from 28 institutions of 7 countries. In this study patients from two groups were analyzed: a group with patients with recurrent glioblastoma treated with TTFields and a group of patients with recurrent glioblastoma treated with the best drug of choice of the assistant physician. Considering that the average survival rate of patients with recurrent glioblastoma rarely goes beyond 3 to 5 months, the primary endpoint analyzed was global survival.

In this study, 237 patients with recurrent glioblastoma were evaluated. In general, the population studied had an average Karnofsky index of 80 and an average age of 54 years. The minimum age analyzed was 18 years old, without any limit of previous therapies. There were 120 patients in the TTFields group and 117 in the chemotherapy group. The previous treatment included radiotherapy with or without temozolomide. The major drugs used in the chemotherapy group without the TTFields treatment were bevacizumab, irinotecan, nitrosureas, carboplatin, and temozolabide. Patients with infratentorial lesions, implanted

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electronic devices, and adjustable ventriculoperitonial shunt were excluded.[10]

A randomization of 1:1 of TTFields versus the best drug of choice of the assistant physician was performed. The methodology used was the Novo TTF-100-A with frequency of 200 kHz and intensity of 0.7V/cm. All the patients from the TTFields group were submitted to trichotomy. Magnetic resonance exams were performed with 60 days to assess the treatment efficiency, besides the neurologic and laboratory exams and the ECG.[10]

The results showed a survival rate of 6.6 months in the TTFields group against 6.0 months in the chemotherapy group. The survival rate in 1 year was 20% of the cases in both groups. The radiologic response was better in the TTFields group than in the chemotherapy group. [10]

The average disease-free survival rate was of 2.1 months in the TTFields group, while in the chemotherapy group it was of 2.1 months, with p = 0.16 (Confidence Interval - CI 95%). The disease-free survival rate in 6 months was higher in the TTFields group (21%) than in the chemotherapy group (15%), with p=0.13 (CI 95%).[10]

The EF11 trial failed to show a statistically significant increase in the global survival rate and in the disease-free survival rate. In addition, the study selected patients with advanced stage disease, with a heterogeneous population, besides several chemotherapy lines.[10]

EF 11 POST HOC TRIAL

Posteriorly, an evaluation of the results of a subgroup of the study was carried out in the secondary analyses of the EF 11 Trial. In the “Post-Hoc Analyses of Intention To Treat Population” of the EF 11 Trial, Kanner *et al* (2014)[11] selected those patients that had concluded a complete 28-day cycle with 18 h per day of the proposed treatment with the TTFields therapy, compared to those patients that had completed at least one chemotherapy cycle, among the initial population of the study. For these subpopulations, a global average of de 2 additional months of survival (7.8x6) was recorded

in the TTFields subgroup (p=0.045, CI 95%). Further, the death risk was 30% lower for this group, with p=0.12 (CI 95%). [11]

EF 14 TRIAL

In 2015, Stupp *et al*[12] published encouraging results about the glioblastoma treatment. Ten years after the remarkable work that transformed temozolomide in the golden standard treatment for this pathology, EF 14 Trial was presented. In this study, 695 patients from the United States, Canada, Europe, and South Korea were followed between July 2009 and November 2014 in a 2:1 randomization.[12]

Two groups were formed with patients recently diagnosed with glioblastoma, after receiving the prescribed treatment with surgery or biopsy, radiotherapy (60Gy) and chemotherapy with temozolomide for 6 to 12 months. Among the analyzed populations, 466 patients were selected for the group treated with TTFields associated to temozolomide and 229 patients received only temozolomide.[12]

The group treated with TTFields associated with temozolomide presented a global average survival rate of 20.5 months against 15.6 months of survival in the group that used only temozolomide, with p=0.004 (CI 99.4%). The average disease-free survival rate for the TTFields group was of 7.1 months against 4.0 months in the temozolomide group, with p=0.001 (CI 98.7%).[12]

LONG-TERM EFFECT OF TTFIELDS

Rulseh *et al* (2012)[13] described a series of cases of 20 patients treated with the TTFields therapy, some of them with 7 years of survival (4 patients). Younger patients and those with a better Karnofsky index presented more promising results.[13]

BEVACIZUMAB ASSOCIATED WITH TTFIELDS

Bevacizumab is a humanized monoclonal antibody targeted against the receptor of the endothelial growth factor that is responsible for the tumor genesis. A phase III study showed an improvement in the disease-free survival rate, with reduction of the corticosteroid dosage, although without an increase in the global survival rate, with the use of bevacizumab. The potential health problems were the

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following: pulmonary embolism, poor wound healing, kidney failure, arterial hypertension, besides symptoms such fever and skin rash. Omar (2014)[14] described 2 cases of patients in second line treatment for glioblastoma using the association of bevacizumab and TTFields. According to this study, there was an important radiologic improvement in the aforementioned cases, but with a low survival rate.[14]

INFLUENCE OF THE STATUS OF THE MGMT ENZYME GENE PROMOTER

In 2017, Clarck *et al* [15] described an *in vitro* study with cells derived from patients with glioblastomas, for tumors expressing or not the methylation of the O6-Methyguanine-DNA Methyl Transferase (MGMT) enzyme. The cell cultures received temozolomide and the TTFields therapy. The anti-neoplastic effect of the TTFields treatment was considered additive to the effect of the temozolomide for the glioblastoma.[15]

COST-EFFECTIVENESS STUDY

Bernard-Arnoux *et al* (2016)[16] published a study with data about the cost of the TTFields therapy in a public hospital in France. To analyze the cost of this treatment they created the ICER (Incremental Cost-Effectiveness Ratio) index, based on the lifetime gained. Considering that the lifetime gain provided by TTFields was of 4.08 months (0.34 year) in the EF 14 *Trial*, at a cost of 186.476 euros per patient, the ICER was of 549.909 euros per year of life gained by the patient.[16]

CONCLUSION

Based on the reviewed articles, this work assures the safety and efficiency of the Tumor-Treating Fields therapy for the treatment of glioblastoma. This therapy should be associated to a microsurgery with maximum safe resection, at least 12 monthly cycles of temozolomide, and radiotherapy with 60 Gy (Gray).

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