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A Phase II Clinical Study on Relapsed Malignant Gliomas Treated with Electro-hyperthermia

GIAMMARIA FIORENTINI, PETROS GIOVANIS, SUSANNA ROSSI, PATRIZIA DENTICO, RAFFAELE PAOLA, GINA TURRISI and PAOLO BERNARDESCHI

Department of Oncology, San Giuseppe General Hospital, Empoli, Florence, Italy

Abstract. *The purpose of this study was to evaluate the activity and toxicity of electro-hyperthermia (ET) on relapsed malignant glioma patients. Twelve patients with histologically diagnosed malignant glioma entered the study. Eight patients had glioblastoma multiforme, two had anaplastic astrocytoma grade III and two had anaplastic oligodendroglioma. All patients were pre-treated with temozolamide-based chemotherapy and radiotherapy. Hyperthermia with short radiofrequency waves of 13.56 MHz was applied using a capacitive coupling technique keeping the skin surface at 20˚C. The applied power ranged between 40-150 Watts and the calculated average equivalent temperature in the tumours was above 40˚C for more than 90% of the treatment duration. One complete remission and 2 partial remission were achieved, with a response rate of 25%. The median duration of response was 10 months (range 4-32). The median survival of the entire patient population was 9 months, with 25% survival rate at 1 year. ET appears to have some effectiveness in adults with relapsed malignant glioma.*

Malignant gliomas (MG) represent a significant source of cancer related death and usually recur despite treatment.

Median overall survival after first-line therapy does not normally exceed 15 months and only slight improvements have been achieved over the last decade, despite advanced diagnostics and multimodal treatments with surgery, radiotherapy and chemotherapy (1, 2). The standard management of MG involves cytoreduction through surgical resection, when feasible, followed by radiotherapy.

Radiotherapy may increase the survival time, while chemotherapy has no such evident effect. Tumour progression is very rapid due to the fact that at the time of surgery tumour cells have already invaded normal brain tissue. Recurrent gliomas appear to be resistant to further surgery and chemotherapy is the most common treatment (3, 4).

In a meta-analysis and a retrospective study with recurrent MG patients, median overall survival after first tumour progression was 30 or 33 weeks (4, 5). Treatment of MG has, therefore, been among the most challenging fields in oncology for more than 20 years and has led investigators to develop innovative therapies designed to augment local control (6, 7). Although the biological effectiveness of heat in treating cancer has been known for decades and many of the corresponding molecular mechanisms are understood, thermal therapy has not yet been established in clinical routines (8). It seems that this discrepancy derives rather from technical limitations in achieving effective temperature distributions deep in the body than from a general lack of biological effectiveness.

Interesting reports showed that hyperthermia inhibits angiogenesis, enhances chemo- and radio-sensitivity and induces a high concentration of drugs in a tumour (9).

There has been much interest in studying the effects of heat on the brain (10, 11). To do this, proper localization of the incident energy is essential; numerous well-localized, mainly interstitial, invasive hyperthermia was applied for gliomas (12-17). Radiofrequency (RF) hyperthermia was also applied intra- and extra-cranial (16, 18). It was also shown that electric capacitive coupling, known as Electric Capacitive Transference, could be effective trans-cranially (18). These clinical studies, particularly those that were randomised, controlled double-armed with and without hyperthermia, indicated the efficacy of this treatment for brain-tumours (19). In consequence the United States Food and Drug Administration certified brain-hyperthermia in this interstitial form. Experience with electro-hyperthermia (ET) for MG is scarce, but one extended retrospective trial was recently presented showing palliative results.

Correspondence to: Giammaria Fiorentini, MD, Department of Oncology, S. Giuseppe General Hospital, via Paladini 40, I-50053 Empoli, Italy. Tel: +39 0571 702650, Fax: +39 0571 702671, e-mail: oncologiaempoli@usl11.toscana.it

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Hager *et al.* (20) treated 35 patients with 13.56 MHz capacitive coupled device hyperthermia. He reported that hyperthermia for MG is feasible and well tolerated. Even patients at far advanced stages of disease could be treated. He reported that after hyperthermia negative events were fewer (11% *vs.* 23%). A prolongation of survival and improvement of quality of life was also observed. The median survival time was longer in treated patients, with less side-effects than in untreated patients (20).

The purpose of this study was to evaluate the activity and toxicity of electro-hyperthermia on relapsed malignant glioma patients.

Patients and Methods

Patients were elegible to participate in this study if they were more than 18 years old and had a newly diagnosed relapse from histologically confirmed high grade glioma, an ECOG performance status ≥2, normal haematological and vital functions, and were able to give informed consent. From April 2003 to January 2006, twelve patients with relapsed malignant glioma entered the study. Eight patients had glioblastoma multiforme, two anaplastic astrocytoma grade III and two anaplastic oligodendroglioma. All patients were pretreated with temozolamide-based chemotherapy and radiotherapy. ET with short RF waves of 13.56 MHz was applied using the capacitive coupling technique keeping the skin surface at 20˚C (EHY 2000 device CE0123, Oncotherm, Traisdorf, Germany). The applied power ranged from 40 to 150 Watt and the calculated average equivalent temperature in the tumours was >40˚C for more than 90% of the treatment time. The targeted area was selectively treated using electrode system covering, excluding the eye-area from the field. ET was performed in three sessions per week. Treatment time and power ranged in every session. Treatment started at 40 Watt for 20 minutes, and step by step gradually and linearly raised up from 20 to 60 minutes and from 40 to 150 Watt in two weeks.

The responses were evaluated by CT scan every two months; complete remission (CR) was the complete disappearance of the tumour; partial remission (PR) was the reduction of at least 50% in the two greatest diameters. The WHO performance status scale was used to evaluate the functional recovery.

Results

Twelve patients had measurable disease and were evaluable for response and toxicity. After CT scan evaluation we obtained one CR lasting 32 months in a patient with anaplastic astrocytoma grade III, and 2 PRs (one anaplastic astrocytoma grade III and one glioblastoma), *i.e.,* a response rate of 25%. The median duration of response was 10 months (range 4-32). The median survival of the entire patient population was 9 months with 25% survival rates at 1 year. Seven patients received dexamethasone and suspension of mannitol infusions; three of them showed an objective clinical benefit increasing their performance status from 3 to 1 and two patients from 3 to 0 (WHO scale). The toxicity was mild: there was one case of persistent head pain, one of mild burn on the scalp causing an interruption of the therapy for one week, two patients, with bulky tumours, presented an epilepsy attack lasting 1 hour after the first application of hyperthermia. These two patients were successfully treated with infusions of dexamethasone, furosemide, mannitol and diazepam.

Discussion

The state of the art of relapsed MG treatment does not offer effective or accepted curative methods yet. One of the reasons of the lack of success is that the chemoperfusion into the brain is insufficient due to blood brain barrier (3-5). On the other hand, some studies showed that genetic alterations in malignant gliomas affect cell proliferation and cell cycle control, as well as invasive metastatic growth (3, 7). Therefore, innovative therapeutic strategies have been developed: radiotherapy with new drugs as an adjuvant setting (2), local chemotherapy with biodegradable carmustine wafers (6), gene therapy (7) and hyperthermia (8-20).

Haveman *et al.* reported that in animal studies the nervous tissue is sensitive to heat. Although inter-species variations may play a role, the data indicate that the maximum heat dose without obvious complications alter localised hyperthermia in regions of the central nervous system lies in the range of 40-60 minutes at 42-42.5˚C or 10-30 minutes at 43˚C (11).

Ley-Valle reported the results of heat increase obtained at the brain and tumour through a non-invasive technique, Electric Capacitive Transference. In the eight studied patients, the increases of temperature in the brain ranged between 0.7 and 1.5˚C in relation to the depth of the thermometric probe and the incident angle of the external electrode. Between tumoral and perilesional brain tissues, thermic increase ranged between 0.3 and 0.7˚C, with higher values at the tumour tissue. The observation that in no case the surrounding brain tissue registered a temperature over 39.2˚C supports the harmlessness of the technique regarding the potential damage to healthy brain tissue and seems to confirm previous data obtained in anatomo-pathological studies in animals (18).

Moran *et al.* reported that in 7 out of 13 patients treated with interstitial hyperthermia, the CT scans demonstrated a decrease or stabilisation of tumour volumes with a response rate of 66%, without any complete remission. In 4 of these patients, regression or stabilisation persisted until death from non-brain disease. They concluded that interstitial hyperthermia therapy for

intracranial tumours is technically feasible and may provide increased tumour control (16).

Tanaka *et al.* evaluated hyperthermia using a 13.56-MHz RF capacitive heating machine in 16 patients with malignant brain tumours. Intracranial heating during operation was performed in 4 patients. RF applicators with a cooling system were placed on the cerebral convexity and medial brain surface with the tumour between them. RF power was controlled to maintain the brain temperature under 40˚C. Under these conditions, the highest temperature in each tumour varied from 44 to 49˚C. After heating for about 60 minutes, 2 tumours showed regression on computed tomographic scans.

Extracranial heating was performed in twelve patients with glioblastoma. RF applicators were placed on the lateral sides of the scalp and applied to diametrically opposite sides of the tumour. Heating was performed for approximately 60 minutes in each session and was repeated twice a week for a total of 4 to 10 times in combination with radiation and ACNU chemotherapy. Six patients (50%) showed partial responses, but the combination with other modalities does not permit any conclusion about the efficacy of hyperthermia. The median survival of the entire patient population was 9 months, with 25% survival rate at 1 year (17).

Sneed *et al.* reported that the median survival had grown from 76 to 85 weeks, and the 2-year survival was up to 31% in a hyperthermia arm compared to 15% of arm treated only with brachytherapy (19).

In the present study, 12 patients were treated and three responses were observed (1 CR and 2 PRs), with a response rate of 25%. It is remarkable that the length of the median duration of response was 10 months. Severe toxicity during or after electro-hyperthermia was not observed, confirming previous data. One patient with CR is still alive and progression free at 32 months.

In conclusion, the interest in studying the effects of hyperthermia on the brain is well documented. Proper localisation of the incident energy seems to be important (8) and numerous studies of localised, mainly interstitial, invasive hyperthermia for gliomas have been undertaken (8, 12-20).

Our study demonstrates that electro-hyperthermia is a new external non-invasive method to treat MG without toxicity. Our data confirm the feasibility and the safety of this method. We obtained three responses in patients with advanced and heavily pre-treated disease. Electro-hyperthermia appears to be effective in adults with relapsed malignant glioma. Further studies are warranted to confirm these preliminary data.

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