Retrospective clinical study for advanced brain-gliomas by adjuvant electro-hyperthermia treatment

Review Article

Dr. med. Hüseyin Sahinbas*, 2 Av. Aristide Briand 91440 Bures sur Yvette and CNRS Gif Sur Yvette 91190

*Correspondence: Dr. Sahinbas, Klinik für Hyperthermie und Supportiv Care, Institute of hyperthermia and nutrition research at the Marien Hospital Herne, Hospital of the Ruhr-University Bochum Massenbergstr. 19-21 44787-Bochum, Germany, telephone: +49 172 525 1940, Email: hssahinbas@googlemail.com;

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Summary

Gliomas are one of the most common primary brain-tumors. Despite surgery and radiotherapy (RT) with or without adjuvant chemotherapy (CT), malignant glioma remains an almost uniformly fatal disease characterized by a rapid and devastating clinical course. The standard management of brain-gliomas (BG) involves cytoreduction through surgical resection, when feasible, followed by RT. RT may remarkable (almost double) increase the median survival time (MST), while CT has no such robust effects.

Anyway the earlier well accepted PCV therapy (Procarbazine+CCNU(Lomustine)+Vincristine) is also shown inefficient on a large number of patients (n=339 and n=335 in the control- and active-arms, respectively). Despite advances in therapy, BG remain essentially a fatal disease, with a median survival time of 10 to 12 months and 2-year survival of only 8% to 12% even, [ii], [iii], [iv]. In a study where patients did not undergo debulking surgery, survival time was found to be less than 6 months and 2-year survival rate ended up at 0%

I. Introduction

Gliomas are a common primary brain tumor in humans. Despite surgery and radiotherapy (RT) with or without adjuvant chemotherapy (CT), malignant glioma remains an almost uniformly aggressive fatal disease characterized by a rapid and devastating clinical course, [i]. The standard management of brain-gliomas (BG) involves cytoreduction through surgical resection, when feasible, followed by RT. RT may remarkable (almost double) increase the median survival time (MST), while CT has no such robust effects.

The three studies of the Radiation Therapy Oncology Group (RTOG) retrospectively enrolled 1578 patients from 1974-1989, updated in 1991, show overall survivals under and over 50 years for anaplastic astrocytoma 49.4 m and 21.7 m, while for glioblastoma multiforme 13.7 m and 9.7 m, respectively.

The state-of-art of the treatment of malignant primary brain tumors, especially GBM could not offer effective, accepted curative methods yet. One reason for this may be the migrating tumor cells that spread into the surrounding normal tissues, creating the basis for inevitable recurrences, and further disseminations. Other reason of the lack of success is the insufficient chemoperfusion into the brain due to the brain-blood-barrier. On the other hand, study showed that genetic alterations in GBM affect cell proliferation and cell cycle control, as well as invasive metastatic growth. Furthermore, disruption of cell death pathways also contributes to the pathogenesis of GBM and may result in resistance to chemotherapy and radiation [v]. Therefore, innovative therapeutic strategies have been
Sahinbas: Brain Tumors Under Hyperthermia

based on drugs targeting cellular proliferation [vi], invasion and angiogenesis [vii].

Local therapy may have a temporary effect, but for a cure, the treatment must reach all the tumor cells and target many therapeutic ways.

The present situation in the glioma-area is well summarized by the title question of the recent editorial article of JAMA [viii]: “Where to GO from here?” Our present paper tries to indicate a possible alternative to go ahead: the brain hyperthermia (BHT) in combination with traditional tumor-treatment modalities like RT and CT.

Hyperthermia (HT) combined with RT and CT appears to become a promising method for cancer treatment, although the all molecular mechanisms of this process are not well understood. A number of studies showed that HT inhibits angiogenesis, enhances chemosensitivity and radio-sensitivity and induces a high concentration of drugs in a tumour [ix].

Due to the missing effective traditional therapies, HT could be one of the important targets to improve the treatment facilities. HT in general has a risk in tumor-treatment, namely it could increase the edema and the brain pressure, which could be fatal. Due to this reason the proper localization of the incident energy is essential. Numerous well localized, mainly interstitial, invasive (ablative) HT were applied for gliomas combined with laser techniques or as implant applications. As well some radiofrequency (RF) HT was applied intra- and extra-cranial as well as the ultrasound HT. It was also shown, that the electric capacitive coupling (called Electric Capacitive Transference) could be effective trans-cranially [x]. These clinical studies, including a randomized, controlled double-armed trial (with and without HT) [xi], had indicated the surprisingly good efficacy of HT treatment for brain-tumors: the median survival had grown from 76 to 85 weeks, and the 2-year survival was up to 31% vs. 15%. In consequence FDA in the USA had certified the brain-HT in its interstitial form.

Objective of this study had been to inquire whether or not a capacitative HT modality, as there are several makes on the market (e.g. Thermatron-Japan, Oncotherm-Hungary or Celsius42+ Germany) would be capable of showing promising results. Thus this article is to present a retrospective clinical study for 140 BG-patients. Intention was to study the feasibility of BHT for BG, and its effect on the survival times.

The Treatment Method

Electro-hyperthermia with short (RF) waves of 13.56 MHz was applied by capacitive coupling technique with keeping the skin surface on about 20 °C. The applied power ranged between 40 to 150 Watts in a pattern of step-up heating. It started with 40 Watts for 20 minutes and gradually raised up. After about six initial sessions high end applied power of up to 150 Watts have been reached in the last ten minutes of a treatment fraction which lasted 60 minutes overall. Tumor area was covered by the electrodes excluding a direct exposure of the eye-area from the field. BHT was performed in two/three sessions per week.

III. Case-report

47-year-old male patient has been seen with the pre-history of AA Neurologic examination. Laboratory evaluation was ok. Magnetic resonance imaging (MRI) showed a lesion of 8x6x5 cm in the temporal region. It is staged as anaplastic astrocytoma grade WHO II at 17.07.2001. Patient underwent a partial resection in July 2001. RT (60 Gy total dose) started on 15.08.01, with partial overlapping of BHT starting on 20.09.01 and being concluded on 14.12.01. Neurologic signs, observed in January 2002, did not completely resolve. From 04.03.02 until 19.04.02 a second BHT cycle was given in combination with Temodal° (Temozolomide). An MRI evaluation from January 23th 2009 showed a complete remission (CT) (Fig. 1.). Patient’s complaints have disappeared and all negative neurologic symptoms completely resolved. He has not required any further treatment from the time the adjuvant therapy was finished to date and appears for regular check-ups at our clinic. He is in normal health and has a good quality of life.

Figure. 1/a. Pretreatment imaging with MRI, T1 12.12.2001
IV. Material and Method

Description of the trial

Electro-hyperthermia with short (RF) waves of 13.56 MHz was applied by capacitive coupling technique with keeping the skin surface on about 20 °C. The applied power ranged between 40 to 150 Watts in a pattern of step-up heating. It started with 40 Watts for 20 minutes and gradually raised up. After about six initial sessions high end applied power of up to 150 Watts have been reached in the last ten minutes of a treatment fraction which lasted 60 minutes overall. Tumor area was covered by the electrodes excluding a direct exposure of the eye-area from the field. BHT was performed in two/three sessions per week.

The study is an open-label, single arm, monocentric, retrospective, Phase II study. The involved patients are intention-to-treat (ITT) population. Recruiting time was 56 months. The primary endpoints of the study were the overall survival time (OST) and the survival time from the first hyperthermia treatment (TST). The applied test was Kaplan-Meier log-rank. Inclusion criteria were: (1) Inoperable or subtotally resected or recurrent BG, (2) progression after radio- and/or chemo-therapy, (3) Karnofsky Performance Score (KPS) > 40%.

Distribution of the BG patients by their WHO-grade show mostly advanced cases: diffuse astrocytoma, (DA): 8 cases, (5.7 %); anaplastic astrocytoma, (AA): 40, (28.6 %); glioblastoma multiforme, (GBM): 92, (65.7 %); (see Fig. 2). Most of the patients failed to respond on the applied traditional therapies. Thus our patients in general were bad risks.

Age distributed near to normal (p<0.001 by Chi-square test for discrete variables), no outliers (p<0.05) present. The median age was 43.5 y (3-73), the mean-age was 43.2 y (Std.err=1.42), 15 (10.7 %) patients were below 18 y, and 8 (5.7 %) were over 68 y. The gender distribution was 50/90 female/male. Epidemiology acc. to literature [xii], [xiii] show BG in the elderly population more frequent (in Japan BG-incident is 2.40/100000/y over 70 y, while under is only 1.42/100000/y [xiv]) but this does not appeared in our case. A slight increase however from the normal distribution could be observed in the range of 50-70 year ages.

Pretreatments numbered up to 364 (~2.6/patient), and its distribution by main categories is shown in Fig. 3: chemotherapies in 117 cases (84 %), radiation in 129 cases (92 %) and surgery in 117 cases (84 %). (Two patients had no pretreatments due to individual reasons.) In mean, 69% of all patients had been treated by all three options.
BHT was applied adjuvantly in most of the cases. The distribution of adjuvant treatments is shown in Fig. 4. Chemotherapies (most of the cases TMZ) in 102 (73 %) cases, radiation in 5 (3.6 %) cases, and other supportive therapies were in 105 cases (75 %). The kind of conjoint supportive therapies is shown in Table 1. These started simultaneously to the BHT, and were applied for 3 months. Application of BHT as mono-therapy occurred in 2 cases (7 %) and only combined with these supportive therapies in 27 cases, (19 %). All standard therapies (be it surgery, radiation and/or Chemotherapy (TMZ) have been advised where possibly applicable. BHT just came in addition and since no major observable side effects were observed initially when BHT being managed as cautiously as applied in this protocol, ethical objections were of no concern.

Figure. 3: The pretreatment distribution by its kind (a) and by its combinations (b).
Figure. 4. The adjuvant/neoadjuvant treatment distribution with BHT by their kind (a) and by their combinations (b).

**Supportive drug**

<table>
<thead>
<tr>
<th><strong>Boswelia carterii (Olibanum)</strong></th>
<th><strong>Dose</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6 g/d</td>
</tr>
<tr>
<td><strong>Mistletoe (Lectinol)</strong></td>
<td>15 ng (3x/w) subcutan</td>
</tr>
<tr>
<td><strong>Selenium</strong></td>
<td>300μg/d</td>
</tr>
</tbody>
</table>

Table 1: The applied supportive therapy.

The BHT treatment cycles were in average 1.8 (1-9) while an average fraction number of 21.5 (2-108) single treatments. The median number of BHT treatment fractions was 15 single treatments. The median time elapsed to first BHT was 10.8 m (0.2-181) 21.7 m (std.err.=2.5) in average. The median follow-up time after the last BHT was 3.4 m (1day-49.1 months) in average 6.6 m (Std.err=0.8).

As in the pre-trial phase, no toxicity or other problems were observed during the treatment, only some 10-15 occasions were observed of reported headache, no increased oedema however, all incidences were clinically well controllable. In many cases the oedema was decreased and the intracranial pressure also seemed to be decreasing. No surgical or any other intervention was necessary during or after the BHT treatments for anyone of the patients. Most patients were quite relaxed during the treatment, some even felt asleep. All patients tolerated the treatment quite well and by and large reported a subjectively positive feedback on the treatment, but this was not objectively evaluated.

V. Results

The MST of OST and TST for all of the patients were 19.8 m (1.4-190) and 6.7 m (0.3-50), respectively. The average (mean) survival time (AST) of OST and TST were 31.7 (std.err=3.0) and 10.0 (std.err=0.9), respectively. The corresponding Kaplan-Meier (KM) plots are shown in Fig. 5. The same survivals categorized by their WHO-grade are shown in Table 2 and Figure 6.
Figure 5: a) OST (KM-survival plots from 1st diagnosis) and b) TST (KM-survival plots from 1st hyperthermia treatment) for all of the treated patients.

Table 2: Median and mean data of the survivals.

<table>
<thead>
<tr>
<th>WHO grade</th>
<th># Pts.</th>
<th>MST OST [m] (min.-max.) [m]</th>
<th>MST TST [m] (min.-max.) [m]</th>
<th>AST OST [m] (Std.err.) [m]</th>
<th>AST TST [m] (Std.err.) [m]</th>
</tr>
</thead>
<tbody>
<tr>
<td>DA</td>
<td>8</td>
<td>59.2 (22-190)</td>
<td>11.6 (1.1-41)</td>
<td>73.6 (18.8)</td>
<td>15.6 (5.2)</td>
</tr>
<tr>
<td>AA</td>
<td>40</td>
<td>25.8 (3.6-183)</td>
<td>9.1 (1.4-50)</td>
<td>43.3 (7.0)</td>
<td>13.4 (2.0)</td>
</tr>
<tr>
<td>GBM</td>
<td>92</td>
<td>16.0 (1.4-176)</td>
<td>6.1 (0.3-48)</td>
<td>23.0 (2.5)</td>
<td>8.0 (0.9)</td>
</tr>
</tbody>
</table>

Figure 6: a) OST and b) TST KM-survivals for patients with DA, AA and GBM.
The dose analysis (Fig.7) shows a relation not significant for OST (p=0.129) but significant for TST (p<0.01). Higher energy dose and longer treatments yielded better results.

![Graph showing dose dependence to DT for OST and TST](image)

**Figure 7:** a) Dose dependence to DT for OST (p=0.129) and b) for TST (p=0.003) survivals (KM survival plots).

No serious side effects were observed (see Table 3.) Patients tolerated the treatments well covering the whole treatment process.

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Rel. val.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Short term (&lt; 2h) asthenia after the treatment</td>
<td>9%</td>
</tr>
<tr>
<td>2. Local redness (rubor) of the skin</td>
<td>8%</td>
</tr>
<tr>
<td>3. Complications</td>
<td>15%</td>
</tr>
<tr>
<td>Subcutan fibrosis of fat tissue</td>
<td>1%</td>
</tr>
<tr>
<td>Skin burn (diam.&lt;1.5 cm) garde I-II</td>
<td>2%</td>
</tr>
<tr>
<td>Headache and vomiting (&lt; 2h)</td>
<td>12%</td>
</tr>
</tbody>
</table>

**Table 3:** The observed side effects during the study.

**VI. Discussion**

The expected MST for BG patients overall is 11.3 m, which is well behind our data of 19.8 m (gained by 75.2 %). According to the RTOG classifications [“], we divided the patients to two groups: age under- and over-50 years. The obtained patient’s distribution is shown in Fig. 8 pie-chart.

![Pie chart showing RTOG age-division](image)

**Figure 8:** Distribution of patients by 50 years age-threshold.
The OST definitely varies between the different age groups as the KM-plots show in Figure 9.

**Figure 9: KM plots by years threshold 50 years: for OST (p<0.0003)**

By categories the MST of OST was (except one category) systematically significantly superior (see Table 4 than the expected ones for corresponding stage BG patients: the under and over fifty-years patients median gains are - 28.5%, 24.0% for DA+AA and 39.4%, 46.4% for GBM, respectively. The KM-plots show well the significant differences. The gain is obviously large except the DA+AA patients under 50 years age. The reason of this discrepancy is not known. A next trial should look into this issue as well.

<table>
<thead>
<tr>
<th>WHO grade</th>
<th>Patients no.</th>
<th>MST OST [m]</th>
<th>(min.-max.) [m]</th>
<th>AST OST [m]</th>
<th>(Std.err.) [m]</th>
<th>MST RTOG [m]</th>
</tr>
</thead>
<tbody>
<tr>
<td>DA+AA (&lt;50y)</td>
<td>36</td>
<td>37.7</td>
<td>3.6-190</td>
<td>56.7</td>
<td>8.5</td>
<td>49.4</td>
</tr>
<tr>
<td>DA+AA (&gt;50y)</td>
<td>12</td>
<td>18.4</td>
<td>9.9-56</td>
<td>23.3</td>
<td>3.8</td>
<td>21.7</td>
</tr>
<tr>
<td>GBM (&lt;50y)</td>
<td>47</td>
<td>19.0</td>
<td>2.4-176</td>
<td>28.7</td>
<td>4.7</td>
<td>13.7</td>
</tr>
<tr>
<td>GBM (&gt;50y)</td>
<td>45</td>
<td>14.4</td>
<td>1.4-39</td>
<td>17.1</td>
<td>1.3</td>
<td>9.7</td>
</tr>
</tbody>
</table>

**Table 4: The main statistical characters by the RTOG division**

The results can be well compared to the available SEER [xvi] data. OST of our retrospective 140 patients are compared with SEER’s retrospective 28,970 patients, differentiated by grade categories as shown in Table 5.

<table>
<thead>
<tr>
<th>WHO grade</th>
<th>Patient number (n) (present)</th>
<th>MST OST (present) [m]</th>
<th>(min.-max.) [m]</th>
<th>Patient number (n) (SEER)</th>
<th>MST OST (SEER) [m]</th>
</tr>
</thead>
<tbody>
<tr>
<td>DA</td>
<td>8</td>
<td>59.2</td>
<td>22-190</td>
<td>2749</td>
<td>42.7</td>
</tr>
<tr>
<td>AA</td>
<td>40</td>
<td>25.8</td>
<td>3.6-183</td>
<td>3273</td>
<td>10.5</td>
</tr>
<tr>
<td>GBM</td>
<td>92</td>
<td>16.0</td>
<td>1.4-176</td>
<td>5801</td>
<td>10.2</td>
</tr>
</tbody>
</table>

**Table 5: Comparison of the data of SEER and our present study.**

In one of a recent publication [xvii], the 1 and 2 year survivals with TMZ shows 58% and 31%, respectively. Compare these results with ours, the gain is also remarkable. 71.7 % (66/92) and 30.4 % (28/92) for 1 and 2 years survival, respectively. (The two-year survival for GBM by RTOG study (no TMZ application) is only 17%. [xv]) The most recent TMZ randomized clinical trial for GBM [xviii], summarizing the results of 573 patients from 85 cooperating centers shows a gain of MST from 12.1 m (without TMZ) to 14.6 m (with TMZ). A former TMZ results [xvii] were similar, having MST in only RT group (n=24) 11.2 m, RT+CT (not TMZ) group (n=32) 12.7 m and for RT+TMZ group (n=23) 14.9 m. The two-year survival in the new study [xviii] increased form 10.4% (without TMZ) to 26.5% (with TMZ). Our present results are quite encouraging compared with the presently published best TMZ applications.
The long term survival of GBM is very rare, beyond three years was only 1.8% in a 279 patients trial [34]. In our case from 92 GBM patient 13 (14.1 %) had longer OST than 3 years, which is a remarkable gain.

Studying the MRI images we have some indicative hints to suppose an extended apoptosis initialized by the hyperthermia. This could be in good correspondence with some theoretical considerations [18], as well as with some experimental facts [19, 20, 21]. More considerable investigations on this line are in progress. The presented results are well comparable with other hyperthermia results published earlier on smaller groups (n=35) [13] and (n=17) [25].

Conclusions
These results well support feasibility and benefit of an adjuvant hyperthermia treatments in BG by numerous reasons:

- Capacitative Hyperthermia was applied for brain tumors, showing a valid treatment potential while being applied safely.
- A transcranially applied non-invasive electric field is capable to perform the treatment.
- No safety or considerable toxicity problem did occur. Eventual occurrence of increased oedema which was regarded as a general obstacle to hyperthermia applications in the past, has not proven to be a hazard in this kind of capacitative hyperthermia. No eye-damage and/or vision-complication have been observed. The treatment is safe and convenient to use.
- The survival time, as one of the most important parameters, was increased for the patients having no other treatment possibilities.
- Quality of life parameters, though not explicit investigated just taken by patients’s subjective feedback seemed not to worsen, on the contrary.

According to the data of this present retrospective study covering after all a fair number of brain-glioma patients (n=140) capacitative electro-hyperthermia is feasible to treat anaplastic astrocytoma and glioblastoma multiforme. This kind of hyperthermia has a quite attractive ratio of benefit/side effects. Comparing survival times from this data with the historical ones given from the large databases, one has to conclude a remarkable increase of overall survival. Further, the method is safe and stable; it is easy to use and well tolerated by the patients. It seems rewarding to put these data on touchstone for a proper evidence-based evaluation in conceptionalizing a prospective, randomized, controlled double-arm clinical trial.

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inhibitor batimastat

survival time


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