Oncothermia for advanced brain gliomas
(Review of ten years experience)

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Introduction

None of the established state-of-the-art treatments in malignant primary brain tumors, especially in glioblastoma multiform (GBM), could show effective or commonly accepted curative potential until today, [1]. The earlier well accepted PCV combined chemotherapy (Procarbazine + CCNU (Lomustine) + Vincristine) was shown to be inefficient (n=339 and n=335 in the control- and active-arms, respectively) [2]. 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% [3]. The three studies of the Radiation Therapy Oncology Group (RTOG) retrospectively enrolled 1578 patients from 1974-1989, updated in 1991, show overall survival for anaplastic astrocytoma of 49.4 m for patients under the age of 50 years and 21.7 m. for those being older, while for glioblastoma multiforme 13.7 m and 9.7 m were obtained, respectively. The editorial question of JAMA [4] in 2005 is actual even now: “Where to go from here?” Our objective is showing feasible way to go, summarizing the results obtained till now by modulated electro-hyperthermia (oncothermia) in various clinics in EU.

Hyperthermia (HT) combined with conventional therapies seems to be a promising method for glioma treatment by enhancing chemo- and radio-sensitivity [5]. Controlled, randomized, double-armed clinical studies study of Sneed et al. [6], indicated a surprisingly good efficacy of invasive (interstitial) HT treatment for brain-tumors: the median survival had improved from 76 to 85 weeks, and the 2-year survival went up to 31% vs. 15%. In consequence, the FDA certified HT to the brain in its invasive interstitial form.

Feasibility of oncothermia

Invasivity of HT made complicated this method, but the transcranial non-invasive applications had definite unwanted side effects: the possibility of the edema promoted dangerous intracranial pressure and the heat-sensitivity of eyes. Both problems are successfully controlled by a new hyperthermia paradigm: by oncothermia. Its thermodynamical approach is theoretically established, ([7]), and applied successfully in numerous malignancies [8]. Oncothermia is a non-invasive modulated RF-current, capacitive coupled at 13.56 MHz carrier frequency, (Fig. 1) [9], [10], [11], [12]. and it is successfully applied transcranially for various brain malignancies [13]. The applied protocol was unified step-up heating, 40-150 W RF-power with water-bolus cooling. Treatment is applied in combination with chemo- and/or radio-therapy or used as monotherapy if the conventional therapies fall.

Fig. 1. The individually tuned and fractal modulated radiofrequency current self-selectively targets and kills the tumor cells.
The preclinical experiments had shown good efficacy of tumor killing (see fig. 2) as well as surprisingly the method could be applied the near-eye areas also, which is generally contraindicated for hyperthermia therapies. The case-report examples at near-eye localizations are shown in fig. 3 and fig. 4. The method shows successful applications in paediatric cases as well, [14].

These results are consequences of the applied modulated electric field, having active tumor killing even in low temperatures [15], [16]. There are some indicative hints to suppose an extended apoptosis initialized by the oncothermia [17], [18]. This could be in good correspondence with some theoretical considerations proposing a gain of the apoptotic processes by hyperthermia [19], as well as with some experimental facts showing the relevance of the enhanced apoptotic activity [20], [21].

These facts allow special well controlled treatments and safe operation applying the method for humans.

Oncothermia is a new method in the treatment of brain gliomas with favourable toxicity profiles and show is promising preliminary results. A well designed Phase I study shows the safety of the method in cases of advanced, relapsed brain gliomas [22]. It is shown, the dose escalation up to daily treatments has no extra hazard.
Clinical results

Some open-label, single arm, monocentric, retrospective, intention-to-treat frame clinical studies had been published in ASCO [23], [24], and in other highly ranked conferences, [25], [26], [27], [28], [29], [30], [31], [32], [33]. Results for anaplastic astrocytoma and for glioblastoma multiform are shown on fig. 5. and fig. 6., respectively.

Fig. 5. Results of median survival time for advanced anaplastic astrocytoma in different, independent clinics used the same oncothermia protocol.

Fig. 6. Results of median survival time for advanced glioblastoma multiform in different, independent clinics used the same oncothermia protocol. Data from large database (SEER USA) and from other treatment results are shown for comparison.

The results are pretty coherently above the statistical values of the large databases SEER [34] and the gold-standard radiotherapy (RT) and RT+PCV. The results of oncothermia show advantages in comparison with the recent publications on Temiozolomide [3], [35], too.

The first-year survival rates compared to SEER [34] and EUROCare [36] databases as well as to the most recent chemotherapy of Temiozolomide shows also definite and significant advantages (more than 25% increase) of oncothermia (fig. 7.).
Fig. 7. First year survival ratio (%) for advanced brain gliomas treated in different, independent clinics used the same oncothermia protocol. Data from large databases (SEER USA; Eurocare, EU) and from recent temiozolomide treatment results are shown for comparison.

According to the RTOG classifications [37], we divided the patients to two groups: age under- and over-50 years. In this division oncothermia is also better, (fig. 8.).

No serious side effects were observed [32]. Patients tolerated the treatments well during the whole treatment period. Most of the patients were well relaxed, some even fell asleep during the treatment. Patients reported better quality of life, but this information was not objectively measured.

Conclusion
The results are strongly indicating the feasibility and the benefit of the oncothermia showing a valid treatment potential and safe application. Oncothermia is a potential way to escape from the present impasse situation and treat brain gliomas successfully. Performing prospective, randomized clinical trials in the future is mandatory.

Oncothermia treatment has numerous benefits:
1. Oncothemia was applied for brain tumors, showing a valid treatment potential and safe application.

2. A transcranially applied non-invasive electric field is able to perform the treatment.

3. No safety or mentionable toxicity problem has occurred. The development of an oedema, which was the general block of hyperthermia applications in the past, is not the case with oncothermia. There was not any eye-damage and/or vision-complication which was also a risk in the radiative hyperthermia methods. The treatment is safe and convenient to use.

4. The survival time, as one of the most important endpoints of the studies, was increased.

5. The quality of life of every patient who was treated with oncothermia was not worsened, even according to their subjective reports.

Acknowledgement
Author is thankful for the diligent and smart physicians dealing with oncothermia and making possible to collect this review. Special thanks have to be made for Groenemeyer Institute, Witten- Herdecke University, Bochum, Germany; Fachklinik Dr. Herzog, Nidda, Germany; Klinikum Nord-Nurnberg, Nurnberg, Germany; Biomed Clinic, Bad Bergzabern, Germany; HTT-Med Clinic, Budapest, Hungary; Neurology Clinic, Regensburg University, Germany.

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