Prospective phase II trial for recurrent high-grade malignant gliomas with capacitive coupled low radiofrequency (LRF) deep hyperthermia

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Background

Treatment of malignant gliomas is in spite of many new approaches still disappointing. Median survival time (MST) of pts. with glioblastoma multiforme (GM) after diagnosis is 6 to 12 months.

Surgery is treatment of first choice, but in most cases healing is not possible. The aims of surgery are tumor debulking or decompression of the brain.

Radiation will double MST after surgery but high grade gliomas are not very radiosensitivesurvival.

Concomitant radiation with temozollamide could increase median survival time of pts with GM from 12.1 to 14.6 montths

Rationale for Hyperthermia

• Lower thermal doses (mild to moderate T):

- protein denaturation, esp. nuclear matrix
- increased blood perfusion → tumor oxygenation ↑
- reduction of intratumoral pressure
- reduction in DNA repair capacity
- anti-cancer immunogenicity, stimulation of innate and adaptive immun response
- increase in uptake of drugs

• Higher thermal doses:

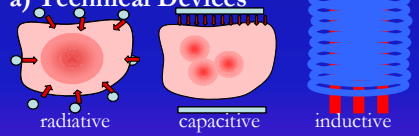
- cytotoxic, increases tumor necrosis & apoptosis
- vascular destruction & anti-angiogenic effects
- synergistic response to RTx/CTx/Itx/geneTx

• Non-thermal effects:

- electromagnetic coupling, interstitial heating

Methods & Technic

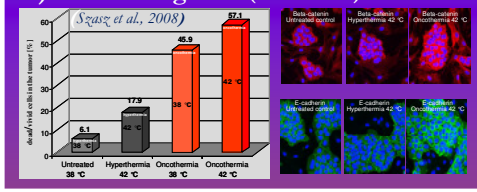
a) Technical Devices



Technical Decision Making:

- radiative	contraindicated (hot spots)
- capacitive	indicated, selective heating and non-thermal effects
- induktive	indicated with nanoparticels or liposomes containing Fe)

b) Electromagnetic (13.56 MHz) vs heat

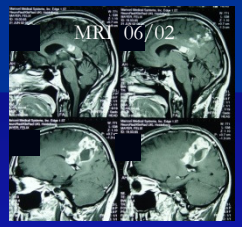


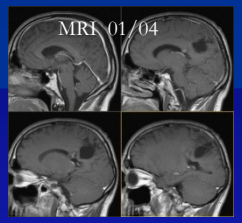
c) Treatment

- Deep hyperthermia was biweekly performed with 13.56 MHz capacitive coupled electrodes (Oncotherm®)
- Power: increasing from 20 to max. 100 Watts Treatment time: 60 minutes
- Treatment including RTx, CTx , *Boswellia caterii (6x* 400 mg/die), a selective inhibitor of leukotrienes

Case Report # :

Anaplastic Astrocytoma (WHO° III)





06/01 subt. resection
08/01 subt. res. of recur.
09-10/01 RTx (TD 60 Gy)
01-06/02 CTx (7xTemodal)

Since 06/02 LRF-DHT+ B.s.+Thal.+ELP

Statistics

- Prospective open-label, single-arm observational study
- Mono-centered phase II trial
- Intention-to-treat-analysis from relapse/progression

Aims

- 1. Median overall survival-time and survival rate
- 2. Response rate
- 3. Quality of life

Inclusion Criteria:

- Recurrent after surgery, RTx and/orCTx
- Progression after RTx and/or CTx in subtotally resected or inoperable cases
- Age > 15 years
- Karnofsky Perfomance Score ≥ 50

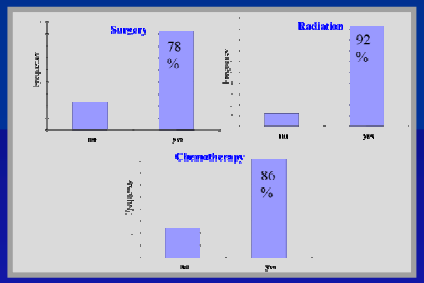
Exclusion Criteria:

- Uncontrolled epileptic seizures
- Tetraplegia
- KPS < 50%

Patient Characteristics

- Accrual time from 02/2000 to 04/2007
- 53 pts. with anaplastic astrocytoma(WHO°III)
- 126 pts. with glioblastoma multiforma (WHO°IV)
- Median age [range]:
  AA: 40 yrs GM: 49 yrs
- Karnofsky Performance Score [range]:
  AA: # GM: #

Primary Therapies:



Results:

Complete data where collected from all pts. and considered for evaluation if at least 1 cycle of LRF-DHT could be performed. The median follow-up time was for AA: # and GM # months. Median age: 43.9 yrs.

The median overall survival times (MST) with confidential intervals are listed in table 1 and the survival probabilities in table 2. Complete and partial remissions could be achieved in both groups by LRF-DHT alone.

Table 1: MST of patients with WHO°III & IV gliomas (Kaplan-Meier-Estimation)

MST from	AA ; N = 53 pts months±se [95%CI]	GM; N = 126 pts months±se [95%CI]
Newly diagnosed	38.2±3.5 [31.3;45.0]	20.3±1.7 [17.0;23.6]
1. LRF-DHT	10.6±2.0 [6.7;14.4]	7.6±0.9 [5.9;9.3]
Events/Censored N (%)	#/14 (26.4%)	#/25 (19.8%)

Overall Median Survival

(Kaplan-Meier-Estimation)

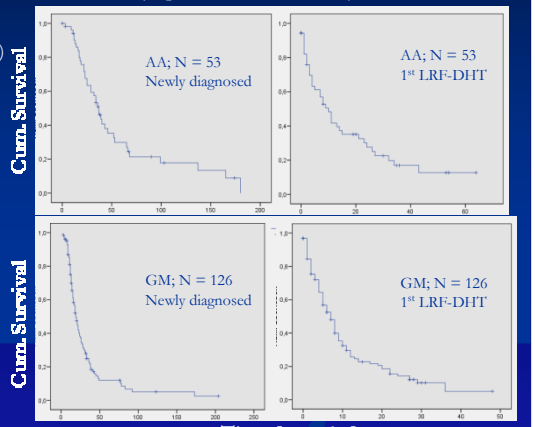


Table 2: Survival probability (Kaplan-Meier-Estimation)

From newly diagnosed	1 yr ±s.e.	2 yrs ±s.e.	3 yrs ± s.e.	4 yrs ± s.e.	5 yrs ± s.e.
AA WHO°III; N=53	100	83 ± 11	83 ± 11	64 ± 15	51 ± 16
GM WHO°IV; N=126	92 ± 8	83 ± 11	67 ± 14	53 ± 16	38 ± 18

Adverse effects:

A) Short-term (2h) asthenia after treatment (8-10%)
B) Local redness (rubor) of the skin (8%)
C) Edema of (fresh) scars (<1%)
D) Complications:
-subcutaneous fibrosis of fat tissue (1%)
- burning blisters stage I-II (2%)
- headache, fatigue & nausea (1-2 days) (12%)

Summary & Conclusions

- DHT with capacitive coupled electrodes with low radiofrequency (13.56 MHz) is feasible without any severe side effects, and even pts. at advanced stages of disease could be treated.
- Complete and long duration partial remissions or stable disease is possible.
- A significant prolongation of survival after relapse and progression after 1st line therapy could be demonstrated.
- Further randomized trials are warrented.

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Author Disclosure Information:
E.D. Hager, None; H. Sahinbas, None; D.H. Groenemeyer, None; E. Boecher, None.