Modulated electro-hyperthermia for the treatment of relapsed brain tumors

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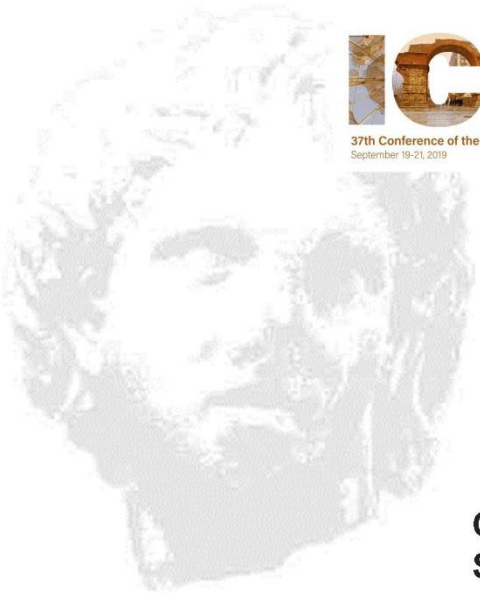
Aim
To motor the efficacy and safety of modulated electro-hyperthermia (mEHT) for the treatment of relapsed brain tumors.

Methods
We collected data retrospectively on 164 patients that were affected by recurrent malignant brain tumors: glioma and astrocytoma. Patients were included in the study if: informed consent signed, >18 years old, histological diagnosis of malignant glioma or astrocytoma, failure of previous temozolamide-based chemotherapy and radiotherapy, indication for treatment with mEHT as palliative setting.
mEHT was performed using a capacitive coupling technique that allowed to keep the skin surface at 26 C° and to reach 40-42.5 C° inside the tumor for > 90% of treatment duration (20-60 minutes) by applying a power of 40-150 Watts.

Results
The study sample included 164 patients with brain tumor, 115 of these (70%) had glioblastoma multiforme (GBM) and 50 (30%) had astrocytoma. mEHT was performed to 29 (25%) GBM and 28 (56%) of astrocytoma, whereas the remaining patients received the best supportive care (BSC).
Three months after mEHT, tumor response rate was 24% for GBM and 43% for astrocytoma, whereas it was 4% for GBM and 37% for astrocytoma for the BSC group. The median overall survival (OS) was 12 months (range 5-108) for GBM, and 17 months (6-156) for astrocytoma group. We observed 2 long-term survivors in the AST and 1 in the GBM group that were treated with mEHT.

Conclusions
mEHT may have promising efficacy for the treatment of relapsed malignant glioma and astrocytoma and can be a useful integrative therapy



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Θεσσαλονίκη
Salonicco

Modulated electrohyperthermia (mEHT) for the treatment of Relapsed Brain Tumors

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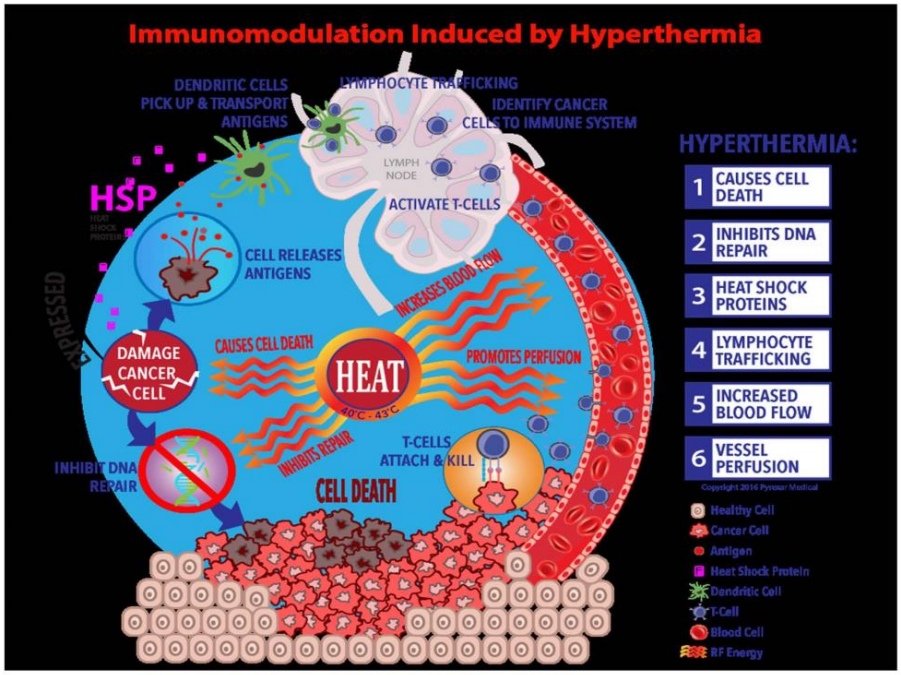


BACKGROUND

- Malignant Gliomas (MG) Therapy with hyperthermia is approved by the Food and Drug Administration .
- Studies on MG with mEHT, which combines the heat-therapy with an electric field, suggest a new way for research.
- Experts had found the mEHT method is feasible for not only palliative but reported also evidence of therapeutic response

STUDIES WHERE HT SEEMS EFFECTIVE IN MG (I)

- Radiofrequency hyperthermia is usefull for malignat brain tumors (Tanaka R, 1987)
- Thermotherapy of recurrent malignant brain tumors is usefull (Sneed 1992)
- Favourable effects of antineoplastic agents and hyperthermia on cytotoxicity toward chronically hypoxic glioma cells (Watanabe M, 1992)
- Survival benefit of hyperthermia in a prospective randomized trial of brachytherapy boost +/-hyperthermia for HG gliomas improves mOS with p = 0.008; hazard ratio 0.51 (Sneed, 1998)

STUDIES WHERE HT SEEMS EFFECTIVE IN MG (II)

- Concurrent hyperthermia and re-irradiation for recurrent high-grade gliomas suggested that is a safe and well-tolerated. (Heo J , Neoplasma, 2017)
- Hyperthermia induces traslocation of apoptosis-inducing factor (AIF) and apoptosis in human glioma cell lines (Fukami T, 2004)
- Improving efficiency of adriamycin crossing blood brain barrier by combination of thermosensitive liposomes and hypertehrmia (Gong W,2011)
- Efficacy and safety of intratumoral thermotherapy using magnetic iron-oxide nanoparticles combined with radiotherapy on patients with recurrent HG glioma (Mair-Hauff K, 2011)

STUDIES WHERE HT SEEMS EFFECTIVE IN MG (III)

•Non invasive intracranial hyperthermia with capacitive transference ECT intratumoral and cerebral thermometry gives favourable results (Ley-Valle, 2003) .

•Treatment of malignant glioma using hyperthermia (Sun J, 2013)

•Thermotherapy-induced reduction in glioma invasiveness is mediated by tumor necrosis factor-alpha. (Qin LJ, 2015)

•Enhanced Energy Localization in Hyperthermia Treatment Basec on Hybrid Electromagnetic and Ultrasonic System: Proof of Concept with Numerical Simulations.(Nizam-Uddin N, 2017**).**

•Pulsed-wave low-dose ultrasound hyperthermia selectively enhances nanodrug delivery and improves antitumor efficacy for brain metastasis of breast cancer.(Wu SK, 2017)

STUDIES WHERE MEHT SEEMS EFFECTIVE IN MG (I)

- Regional mEHT in combination with chemotherapy induces a mOS of 44,2 and 23,2 months in relapsed HG gliomas (Sahinbas, 2005) .
- Phase II clinical study on relapsed HG gliomas treated with mEHT reported a RR of 25% (Fiorentini, 2006).
- mEHT combined with alkylating drugs in relapsed HG gliomas reported that is tolerable and feasible (Wismeth, 2010).
- Clinical and economic evaluation of mEHT concurrent to dose-dense temozolomide regimen in the treatment of recurrent glioblastoma: a retrospective analysis of a two-center German cohort trial with systematic comparison and effect-to-treatment analysis (Roussakov SV, 2017).

STUDIES WHERE MEHT SEEMS EFFECTIVE IN MG (III)

mEHT inhibits glioma tumorigenicity through the induction of E2F1-mediated apoptosis. (Cha J, 2015, Int J Hyperthermia .

Retrospective observational Clinical Study on Relapsed Malignant Gliomas Treated with Electro-Hyperthermia (Fiorentini G, Int J Neurooncol Brain Tumors, Vol I, Issue 1, p11-13, 2017)

Modulated Electrohyperthermia in Integrative Cancer Treatment for Relapsed Malignant Glioblastoma and Astrocytoma: Retrospective Multicenter Controlled Study. (Fiorentini G, Integr Cancer Ther, 2019 Jan-Dec;18:1534735418812691).

AIM

to motor the efficacy and safety of modulated electrohyperthermia (mEHT) for the treatment of relapsed brain tumors

METHODS

• we collected data retrospectively on 164 patients that were affected by recurrent malignant MG.

• Patients included if informed consent signed, >18 years old, GBM or astrocytoma, failure of previous temozolamide-based chemotherapy and radiotherapy, indication for treatment with mEHT as palliative setting.

• mEHT was performed using a capacitive coupling technique that allowed to keep the skin surface at 26 C

Treatment parameters

Practical parameters	value
step-up power (from-to [W])	40-150
average energy-dose (kJ)	540
Therapeutic temperature (°C)	40-42.5
treatment time /session	60
treatment frequency (weakly)	3
treatment cycle (weeks)	8
follow-up time (months)	16

Description of the sample

Basic character (AST)	n	%
Males	24	48
Females	26	52
mEHT treated	29	58
Historical control	21	42
Data AST group	**n**	**%**
MGMT methylated	13	26
MGMT non methylated	13	26
MGMT no data	24	48
IDH1 mutated	15	30
IDH1 wild type	12	24
IDH1 no data	23	46

Description of the sample

Basic character (GBM)	n	%
Males	71	62.3
Females	43	37.7
mEHT treated	29	25.4
Historical control	85	74.6
Data of GBM group	**n**	**%**
MGMT methylated	26	22.8
MGMT non methylated	28	24.6
MGMT no data	60	52.6
IDH1 mutated	14	12.3
IDH1 wild type	20	17.5
IDH1 no data	80	70.2

The complementary therapies

Complementary therapies	All	AST		GBM	
		mEHT	no mEHT	mEHT	no mEHT
BSC	32	9	3	18	2
RT	8	0	1	0	7
CHT	0	0	0	0	0
TMZ	5	1	1	0	3
RT+TMZ	66	1	10	1	54
CHT+TMZ	1	0	1	0	0
CHT+TMZ+RT	47	14	5	10	18
CHT+TMZ+RT+FOTEMUSTINE	1	1	0	0	0
CHT+TMZ+RT+ DOTATOC	2	1	0	0	1
ND	2	2	0	0	0

The abbreviations as follows: BSC – best supportive care including dexamethasone, 18% glycerol infusion, mannitol, holistic therapy and psychosocial support, RT – radiotherapy, CHT – chemotherapy with platinum derivatives, TMZ – temozolomide therapy, ND – no data.

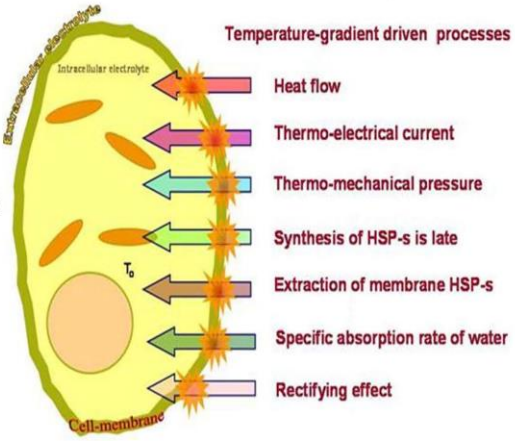
ELECTRO - HYPERTHERMIA (TRANSLATIONAL)

Regional non-invasive EHT

Selective killing effect to tumor cells – specific absorption and nano range heating (Koga 1993, Head 2000, Szasz O. 2017)

Stimulation of natural killer cell-induced apoptosis based on activation of heat-shock-proteins (Young 1990, Multhoff 2005, Baronzio 2006)

Intratumoral reduction of micro-circulation (Yoshimasa 2001).

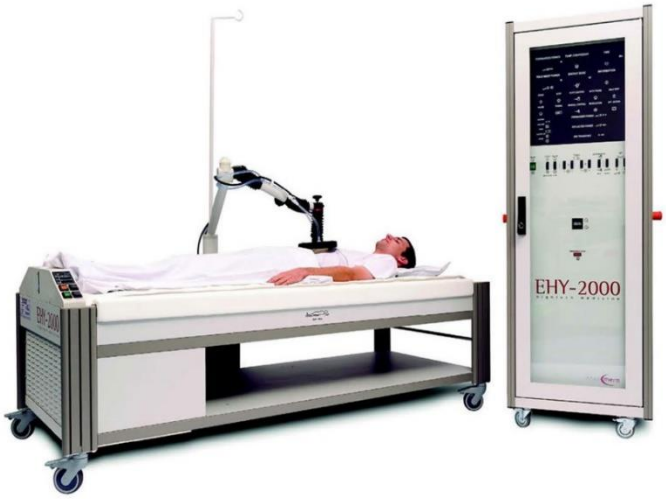


Regional EHT and ACNU have synergistic effects in a rat model (Schem, 1995)

Regional EHT plus chemotherapy have additive effects on inhibition of proliferation (Mella, 1990)

Regional EHT improves the antitumor effect of metronomic cyclophosphamide in a rat transplantable brain tumor (Borkamo 2008)

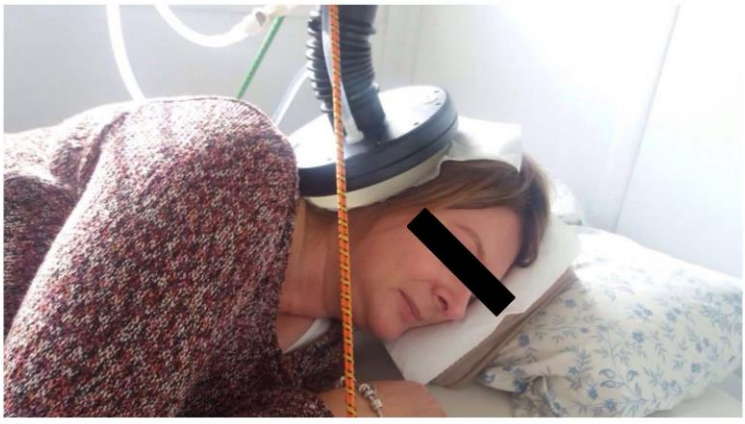
ELECTRO HYPERTHERMIA



Treating area: **REGIONAL (Deep seated tumors)**

Invasivity: **NON-INVASIVE**

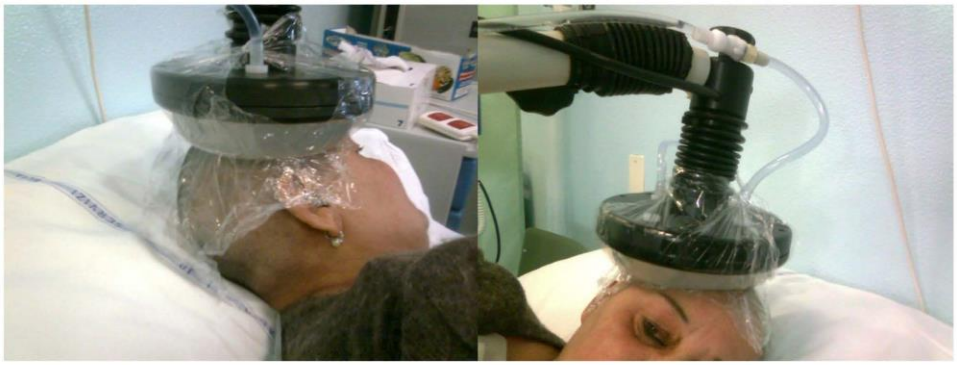
mEHT



Treating area: **Brain tumor (Pons site)**

Invasivity: **NON-INVASIVE**

mEHT



Treating area: **Brain tumor (frontal-parietal site)**

Invasivity: **NON-INVASIVE**

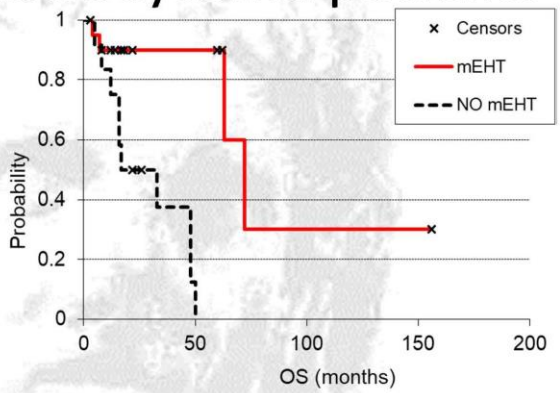
RESULTS

- 164 consecutive patients with relapsed MG, 115 of these (70%) had GBM and 50 (30%) had astrocytoma.
- mEHT was performed to 29 (25%) GBM and 28 (56%) of astrocytoma, whereas the remaining patients received the best supportive care (BSC).
- Three months after mEHT, tumor response rate was 24% for GBM and 43% for astrocytoma, whereas it was 4% for GBM and 37% for astrocytoma for the BSC group.
- The median overall survival (OS) was 12 months (range 5-108) for GBM, and 17 months (6-156) for astrocytoma group. We observed 2 long-term survivors in the AST and 1 in the GBM group that were treated with mEHT.

ASTRO response at three months

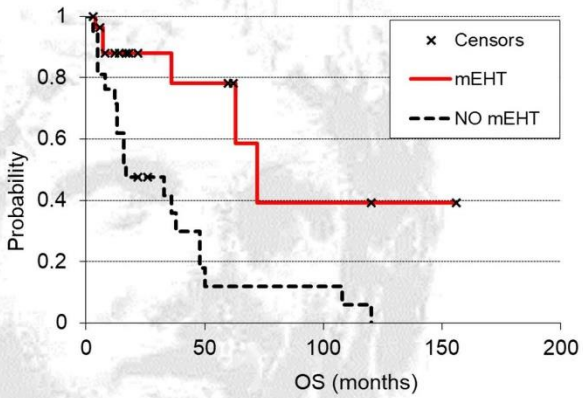
Response (AST)	mEHT		conventional		P-value
	(n)	(%)	(n)	(%)	
CR	2	6.9	1	4.8	
PR	10	34.5	6	28.6	0.0004
SD	9	31	5	23.8	
PD	6	20.7	8	38.1	0.42
NO data	2	6.9	1	4.8	-
OS median (Range)	72	(3-156)	17	(3-120)	0.0006

Duration of the response for astrocytoma patients



Median/Mean are 72/87.9 and 17/28.5 for with and without mEHT respectively. The results are statistically significant (p=0.00036). Events real/expected (Cox-mantel log-rank test) were 4/9.7 and 10/4.3 in groups with and without mEHT, respectively

OS of the AST group

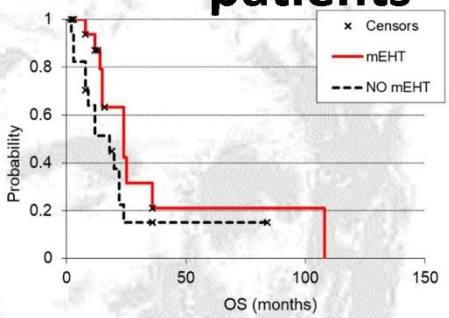


Median/Mean are 72/91.6 and 17/34 for with and without mEHT respectively. The results are statistically significant (p=0.0006). Events real/expected (Cox-mantel log-rank test) were 6/14.3 and 19/10.7 in groups with and without mEHT, respectively.

GBM response at three months

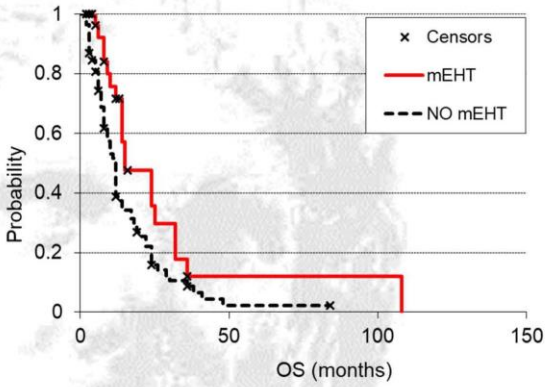
Response (GBM)	mEHT		conventional		P-value
	(n)	(%)	(n)	(%)	
CR	1	3.4	2	2.4	
PR	6	20.7	2	2,4	0.123
SD	11	37.9	13	15.3	
PD	11	37.9	63	74.1	0.858
NO data	0	0.0	5	5.9	-
OS median (Range)	15	(2-108)	12	(2-84)	0.026

Duration of the response for GBM patients



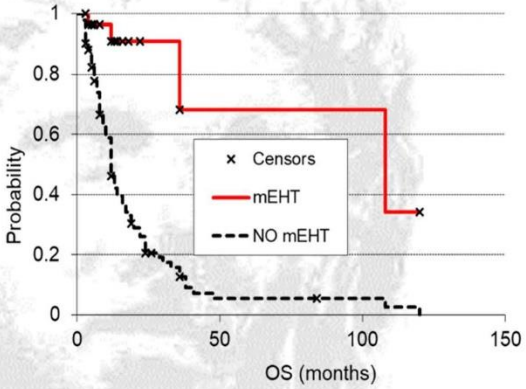
Median/Mean are 24/39.1 and 18/23.9 for with and without mEHT respectively. The results show the difference, but they are statistically not significant (p=0.123). Events real/expected (Cox-mantel log-rank test) were 10/13.4 and 13/9.6 in groups with and without mEHT, respectively.

OS of GBM group



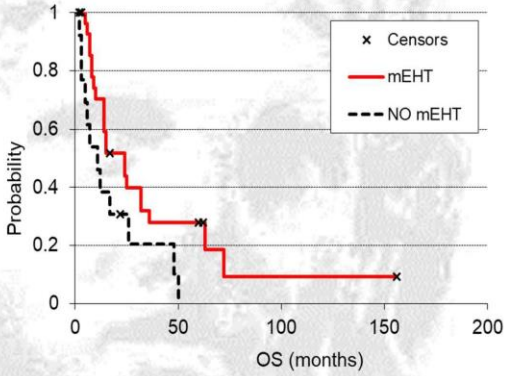
Median/Mean are 15/29 and 12/15.8 for with and without mEHT respectively. The results are statistically significant (p=0.026). Events real/expected (Cox-mantel log-rank test) were 19/28.2 and 68/58.8 in groups with and without mEHT, respectively.

Effect of temozolomide (TMZ) for glioblastoma patients



Complementary therapy contains TMZ. Median/Mean are 108/86.7 and 12/20.5 for with and without mEHT respectively. The results are statistically significant (p=0.00001). Events real/expected (Cox-mantel log-rank test) were 4/20.4 and 75/58.6 in groups with and without mEHT, respectively

Complementary therapy without TMZ



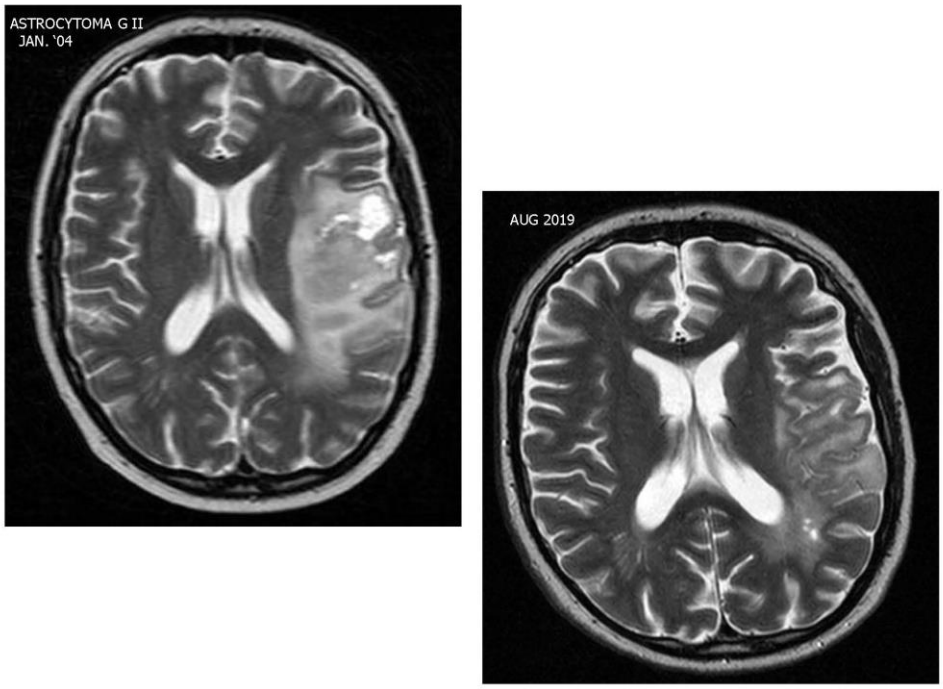
Median/Mean are 24/38.9 and 11/17.85 for with and without mEHT respectively. The results are statistically significant (p=0.039). Events real/expected (Cox-mantel log-rank test) were 21/25.8 and 12/7.2 in groups with and without mEHT, respectively.

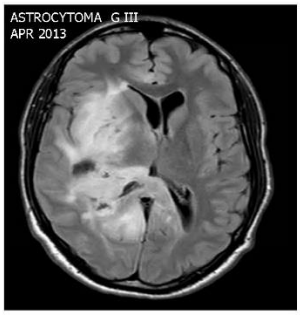
Safety

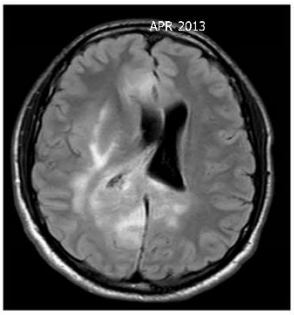
• The safety profile was confirmed by the small total number of adverse events (5%).

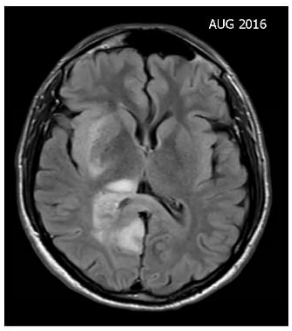
• mEHT toxicity was mild (G1).

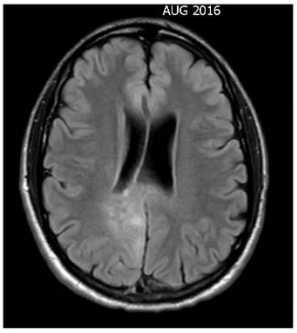
• We observed one (1%) head pain, one (1%) scalp burn, five (3%) epilepsy that was resolved with medication including diazepam 10 mg in 100 ml of saline and levetiracetam in tablets without any further attack

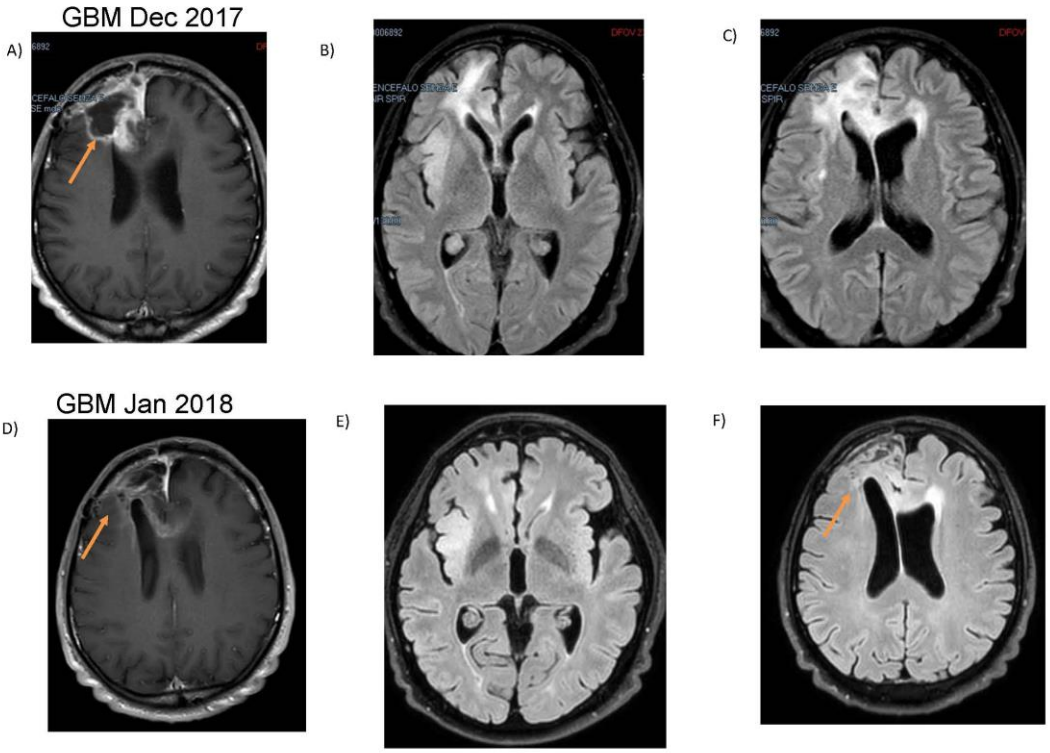



ASTROCYTOMA G III
APR 2013

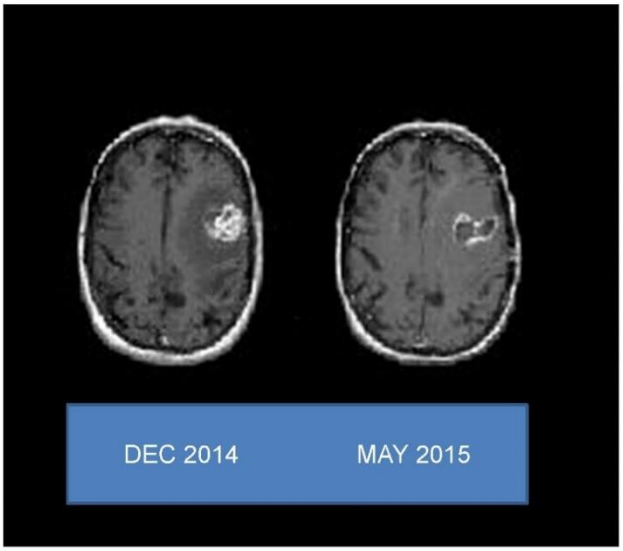

APR 2013

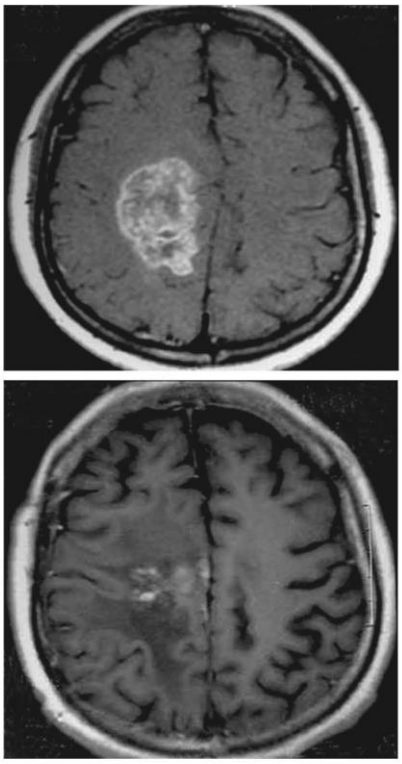

AUG 2016


AUG 2016


GBM Dec 2017
A)
B)
C)
GBM Jan 2018
D)
E)
F)

RELAPSED GBM G III Partial Remission





RELAPSED GMB
OCT 2010

RELAPSED GMB
FEB 2011

Partial remission

CONCLUSION

- mEHT was a safe and effective treatment of recurrent MG as integrative therapy.
- Both AST and GBM had higher tumor response rates after mEHT than after BSC, reporting few- and mild-intensity adverse events.
- The survival and quality of life were improved as well.
- The main limitation of the study was the retrospective data collection, for this reason, further randomized prospective studies with larger number of patients are also required.

ευχαριστίες

Thank you