Modulated electro-hyperthermia as a monotherapy: A potential for further research?

Carrie A Minnaar[1]; Gyula P Szigeti [2]; Jeffrey A Kotzen[3]; Ans Baeyens[4]

[1]University of the Witwatersrand, Radiation Sciences: Radiobiology, Johannesburg, South Africa.

[2] Semmelweis University, Institute of Human Physiology: Clinical Experimental Research, Budapest, Hungary.

[3] Wits Donald Gordon Medical Centre, Radiation Oncology, Johannesburg, South Africa.

[4] Ghent University, Basic Medical Sciences, Ghent, Belgium

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Carrie A Minnaar[1]; Gyula P Szigeti [2]; Jeffrey A Kotzen[3]; Ans Baeyens[4]
[1] University of the Witwatersrand, Johannesburg, South Africa;
[2]Institute of Human Physiology, Clinical Experimental Research, Semmelweis University, Budapest, Hungary
[3] Wits Donald Gordon Medical Centre, Johannesburg, South Africa
[4] Ghent University, Ghent, Belgium

Introduction
The benefits of hyperthermia (HT) combined with chemotherapy or radiotherapy in oncology are widely documented, with several Phase III studies and reviews published demonstrating improved local control and survival. The history of HT and its progression from a monotherapy to a complimentary treatment are discussed. We address the question of whether there is still a place for monotherapy studies with a special focus on the modulated electro-hyperthermia (mEHT) technique. Our objective in this paper is to explore the potential for mEHT to be applied as a monotherapy for palliative intent, in cases where conventional therapies have failed and no further options are available for the patients (e.g. due to recurrent disease, organ failure, treatment toxicity or disease progression).

Methods
Modulated electro-hyperthermia (mEHT, trade name oncothermia) is a complementary hyperthermia treatment that is used in combination with conventional oncology treatments. The protocol used in the studies discussed on mEHT in this paper is the step-down method, not the standard step-up heating protocol used when mEHT is combined with radiation therapy (RT) or chemotherapy (CT). The application of mEHT as a monotherapy would be for palliative intent only: for disease stabilisation and the management of symptoms.

Results
We discuss animal models showing potential for disease stabilisation and human cases which show that mEHT as a monotherapy is safe with limited and acceptable adverse events. Four phase I/II studies on mEHT as a monotherapy are discussed which also showed a potential for disease stabilisation and symptomatic management: 1) Colorectal liver metastases n=50, median survival 16 months. 2) Malignant glioma, n=12, 25% response rate, 1 complete response, 25% 1-year survival, 42% improved performance. 3) Hepatocellular carcinoma, n=8, improved quality of life and disease stabilisation. 4) Gastric carcinoma, n=25, symptomatic and performance improvement, reduction in tumour volume. The effect of mEHT as a monotherapy on disease stabilisation, and occasionally even regression, may be potentiated by the immune responses elicited by mEHT.

Conclusion
Randomized studies and evidence-based statistics on mEHT as a monotherapy are not available. However, the available literature provides enough motivation for the development

of future trials on the topic and investigations into the future use of mEHT as a monotherapy for disease stabilisation and palliation, when there are no further treatment options available.

Keywords: mEHT, monotherapy, palliation, complementary therapy, step-up heating, step-down heating

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1. University of the Witwatersrand, Radiation Sciences: Radiobiology, Johannesburg, South Africa.
2. Semmelweis University, Institute of Human Physiology: Clinical Experimental Research, Budapest, Hungary.
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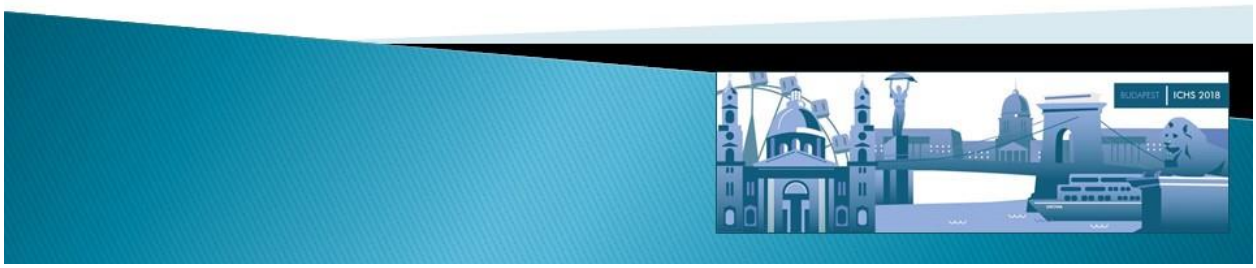


Disclosures

The authors are not aware of any circumstances which may lead to a conflict of interest

Introduction

HT Progressed from a monotherapy to a complimentary treatment …

Is still a place for monotherapy studies?

Specific interest in modulated electro-hyperthermia (mEHT):

- mEHT is a complementary hyperthermia treatment
- Used in combination with conventional oncology treatments
- Step-up heating protocol used when mEHT is combined RT / CT

History

- Historically, absence of other options, HT applied as a monotherapy.
- Tumour thermosensitivity investigations date back to as early as 1903
- Tumours showed signs of destruction after high temperatures (>44°C) administered for short periods (≤30 min)
- 1920s: heat sensitivity of different tumours – Malignant cells more heat sensitive

History

RF techniques in hyperthermia has been discussed in literature since the 1930s

1927, RF was shown to have a special selectivity for malignant tissue; destroying the tumour without damaging their healthy tissue in rat models

Results were promising but healthy tissue damage was a problem.

- *HT was applied as a monotherapy, using RF or microwave, 60 superficial recurrences in 57 patients after treatment failure.*
  - *10% CR*
  - *23.4% PR*

History

Some suggested heating tumours (increases blood flow) may increase risk of dissemination

- Two laboratory studies: HT (monotherapy) = increased rate of metastases from mammary carcinomas of C3H mice and on rat's sarcoma.

Why is HT not widely accepted as a monotherapy?

- Better outcomes in combined treatments
- When combined with other treatment modalities, the risk of distant metastases appears to be reduced.

Objective

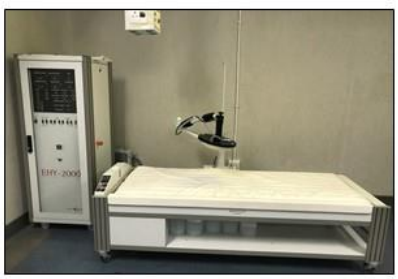
To explore the potential for mEHT to be applied as a monotherapy

-For palliative intent;
-When conventional therapies have failed;
-No further options are available;

Recurrent disease,
Organ failure,
Treatment toxicity or
Disease progression.

Methodology

- **Technology**: Modulated Capacitive coupling, RF:13.56MHz (Oncotherm GmBH, Driosderf, Germany)
- Studies using the step-down protocol are reviewed
- The application of mEHT as a monotherapy would be for palliative intent only: for disease stabilisation and the management of symptoms



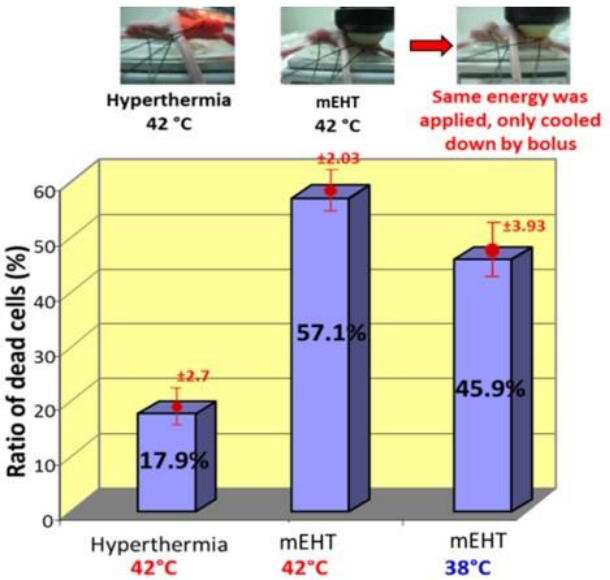
Results: Animal Models

- Potential for disease stabilisation
- Almost all *in vitro* and *in vivo* (murine) experimental studies were performed using monotherapy protocols with success.

Andocs G. *et al* (2009):

- Synergy of the electric field and thermal effects of mEHT *in vivo*
- HT29 (humancolorectal tumour) cell line derived xenograft in nude BALB/c (nu/nu) mice

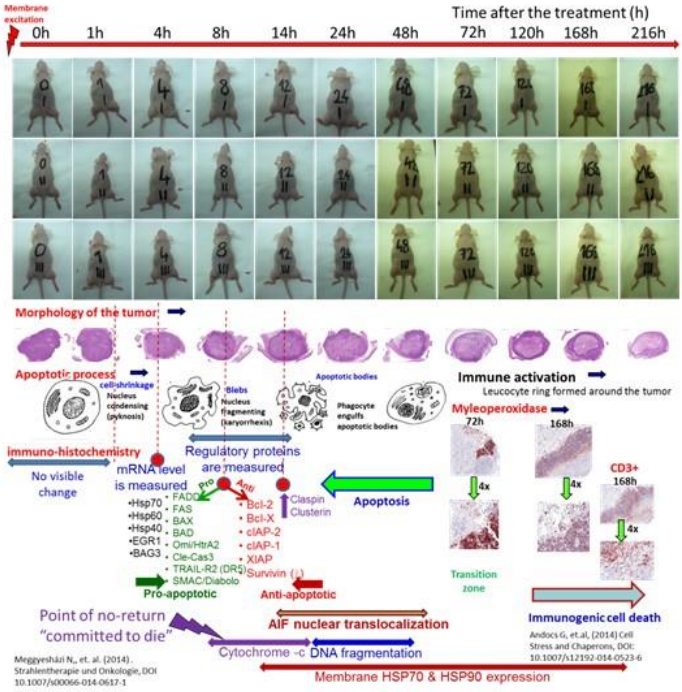
Results: Animal Models



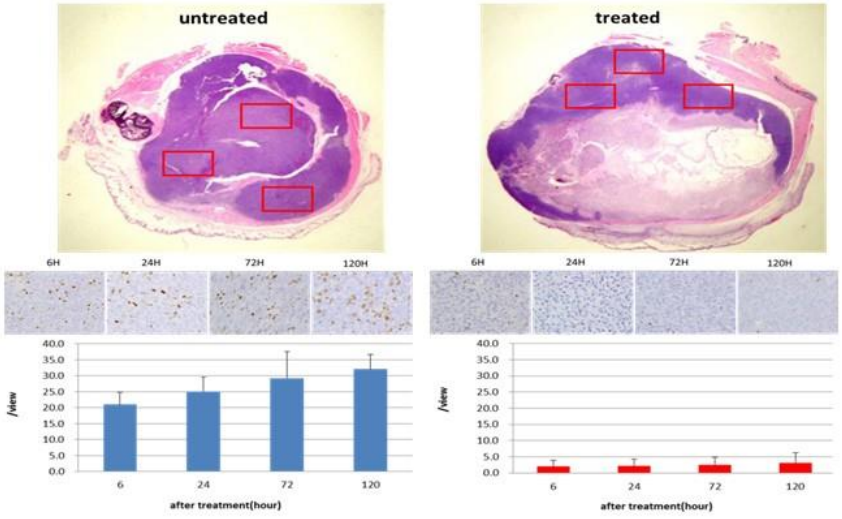
Results

Follow up study:
Same HT29 cell line
Time-course monotherapy experiment
To describe molecular mechanisms of mEHT induced cell death

Apoptotic process is shown:
At 72 hours post treatment the apoptotic processes have slowed and a
non-specific antitumor immune reaction was observed.



Results: Animal models



Result of the measurement of Ki-67 proliferation marker protein. Samples were taken from both the untreated (a) and treated (b) tumors, and from their vivid part containing dividing cells. (Shown with red rectangular shapes on the tumor cross sections.)

Results: Human studies

- Several mEHT monotherapy cases have been published after failure of the gold standards of treatments.
- mEHT as a monotherapy is safe with limited and acceptable adverse events.
- Is there high level evidence?
- Four phase I/II studies on mEHT as a monotherapy are discussed which also showed a potential for disease stabilisation and symptomatic management

Results: Colorectal Liver Metastases

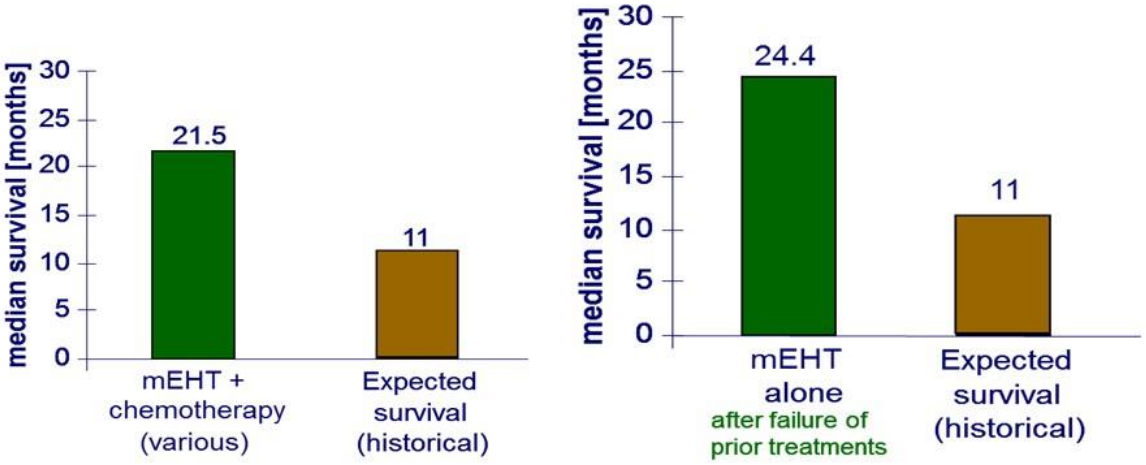
Location: Germany

Methods: Prospective trial, n=80; Palliative intent
The results were compared to a historic arm
Pts all failed the previously administered (with curative intent) cytotoxic therapies.

- 37.5% of patients (n=30) were eligible for palliative CHT + mEHT.
- 62.5% (n=50) received only mEHT

Results: Median Survival 16 months.
Both groups showed more than double the survival time, compared to the historical data.
(mEHT alone had highest higher survival time)

Results



Clinical study for colorectal liver metastases (Bad
Chemotherapy + mEHT: (left),
mEHT alone: (right).

Results: Brain

Location: Italy
Methods: Malignant glioma patients. n:12;
Histologically diagnosed malignant glioma
(8 pts GBM; 2: astrocytoma gr III; 2 anaplastic
Oligodendroglioma).

- Pre-treated with Temozolamide-based CHT + RT
- mEHT: 40-150 Watts

Results: 1 CR; 2 PR
Overall response rate of 25%
Median duration of response: 10 months (range 4-32).
Median survival was 9 months,
(with 25% at 1 year)

Results: Brain

Location: Italy
Methods: 24 consecutive patients:
19 (79%) GBM 13 Gr <4; 6 Gr 4,
5 (21%) Astrocytoma
Tumor response 2 after mEHT
Results: 2 (8%) CR (astrocytomas) and
5 (21%) PR (2 astrocytoma; 3 GBM)

- Overall Response rate: 29%
- The median duration of response was 16 months (range 6-120).
- The median survival: 19.5 months (range 2-156), 55% survival rate at 1 year, and 15 % at two years. We observed 3 long survivors at 156, 60, 62 months in atrocytomas.

Results: Hepatocellular carcinoma (Poster)

Location: Italy

Methods: A prospective study; n=22; Hepatocellular carcinoma (Stage C: BCLC classification) patients who failed treatment.

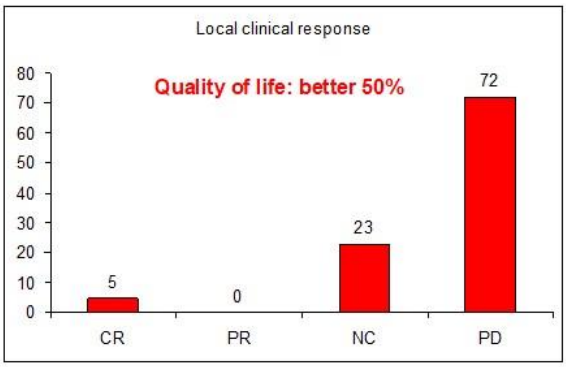
- Non-operable: 68%.
- Portal vein-thrombosis: 70%.
- Distant metastasis: 9%.),

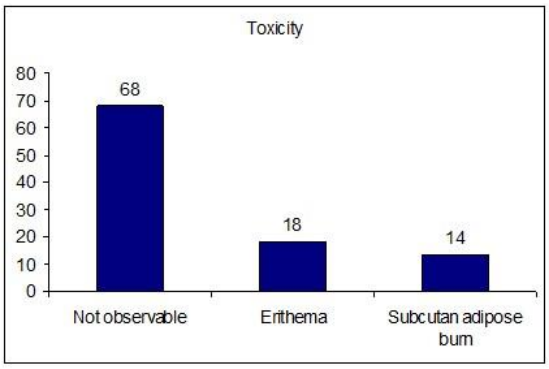
Patients eligible for further CHT (n=14, 64%) received mEHT + oxaliplatin reduced from 85 to 50 mg/m^2 (42% dose reduction).

Patients not eligible for CHT (n=8, 36%), received only mEHT.

- 80-140 W, 60 min/session, 2 sessions/week.
- 10 sessions/cycle, Median of 1.5 cycles (1-4

Results: HCC phase II study (n=22)





Results: Improved quality of life in 50% of pts (LEFT)

Acceptable toxicity (RIGHT) Erythema (18%); subcutaneous adipose burns (14%).

- Disease stabilisation: 1 CR; 5 SD; 16 PD
- Median survival was 20.5 weeks (5-81+)

Results: Gastric carcinoma

Location: Japan

Methods: mEHT for unresectable /recurrent gastric ca, treated 3/week for 60 minutes; n=25;

Results: Improved symptoms + performance
Reduced tumour volume

9 pts had distant metastases: Survival time was significantly better ($p<0.01$) than 42 historical control patients who also had peritoneal dissemination.

Results: Traditional Chinese Medicine

- **Location**: China (several studies show mEHT has + TCM = a strong synergy with in colorectal malignancies
- **Methods**: Prospective randomized; n=156; TCM = control arm and mEHT = study arm.
- **Results**: mEHT could be applied as a stand-alone treatment in refractory and non-refractory cases with promising outcomes.

Conclusion

- Randomized studies and evidence-based statistics on mEHT as a monotherapy are not available.
- We hypothesise that the effect of mEHT as a monotherapy on disease stabilisation, and occasionally even regression, may be due to immune responses elicited by mEHT.
- Protocols must be developed to test this hypothesis.

Discussion

- Available literature provides sufficient motivation for the development of trials and investigations into the use of mEHT as a monotherapy for:
  - disease stabilisation,
  - palliation,
  - no further available treatment options.
- Understanding how mEHT works as a monotherapy may improve the development of protocols for combined therapies.

Thank You