Review on the Use of Modulated Electro-Hyperthermia as a Stand-Alone Therapy in a Palliative Setting: Potential for Further Research?

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Abstract:
Background: Hyperthermia (HT) in oncology was originally applied as a stand-alone treatment (monotherapy), but achieving temperatures required to cause cellular destruction (>43˚C) proved to be challenging. Lower temperatures may increase the risk of dissemination of the treated tumours. Hyperthermia in the current context of oncology therefore aims to achieve moderate temperatures of 39˚C - 41.5˚C and is applied in combination with chemotherapy (ChT) and/or radiotherapy (RT). Modulated electro-hyperthermia (mEHT) applies amplitude modulation to an electric field generated by a capacitive coupled set-up, to selectively heat tumours. As mEHT does not ap- pear to increase the risk of disease dissemination, it has been investigated as a stand-alone treatment for patients with advanced disease and who have exhausted all other treatment options. This report is a descriptive review of pa- pers in oncology which report on the use of mEHT as a stand-alone treatment in a palliative setting. We aim to establish whether there is motivation for the development of trials to further investigate mEHT as a monotherapy in a palliative setting.
Methods: A literature search was conducted using the key words "Oncothermia", "modulated electro-hyperthermia" and "monotherapy", and case reports were excluded. Only studies which applied mEHT without ChT or RT; for palliative intent; when conventional therapies have failed; or when no further options are available, were included.
Results: Six phase I/II studies on tumours of the liver, brain, pancreas, and stomach were included. The studies demonstrated the safety of mEHT; disease stabilisation; and improved quality of life.
Conclusion: mEHT may have a role in the palliative management of certain tumours in the absence of any other treatment options. The development of robustly designed studies on mEHT for palliative management of oncology patients is motivated.

Keywords:
Modulated Electro-Hyperthermia, Palliative Care, Monotherapy, Cancer

1. Introduction

Investigations into the thermal sensitivity of tumours (both spontaneous and induced), date back to as early as 1903 [1] [2] and it is now well-known that tumour cells have a higher sensitivity to heat than their healthy counterparts. This variation in thermal sensitivity is also observed between different tumour cell lines [3] [4] [5]. Hyperthermia (HT) in the current context of oncology refers to the moderate (39˚C - 41.5˚C) heating up of tumours in order to sensitise them to the prescribed treatment regimens [6]. The dose control, protocols, and thermometry vary depending on the heating technique applied. Hyperthermia was however originally applied as a monotherapy with the treatment goal of inducing temperatures of ≥43˚C, resulting in the direct damage and destruction of the tumour cells [1] [2].

Positive results using HT as a monotherapy were presented at the International Symposium on Hyperthermic Oncology in Kyoto in 1988 [7]. In 1990, Gabriele et al. published a paper on the use of HT (microwave or radiofrequency) as a monotherapy for 60 superficial recurrent tumours. A complete response (CR) was noted in 10 (16.6%) tumours and a partial response (PR) in 14 (23.4%) tumours [8]. In a phase I study on superficial recurrent tumours, Manning et al. demonstrated a local response following treatment with HT alone. However the same study demonstrated that the combination of HT and external beam radiation (EBRT) yielded superior results [8]. Sannazzari et al. reported similar results in their study on HT (using microwave heating), with or without EBRT for the management of locally recurrent breast cancer [9]. The use of radiofrequency (RF) heating techniques in HT can be traced as far back as the 1930s [10] with initial reports showing positive results following the application of RF-HT as a stand-alone therapy [11] [12] [13].

Despite the positive results, there have been some obstacles. The high temperatures required to induce direct cellular damage frequently cause damage to the surrounding healthy tissues and result in hot spot formation [14]. Achieving cytotoxic temperatures in tumours using the currently available technology is challenging [15]. A handful of studies have shown that the local response does not always result in an increased survival time and it has even been suggested that heating the tumour and increasing the blood flow may increase the risk of dissemination of the tumour [16] [17].

In combination with chemotherapy (ChT) or radiotherapy (RT), HT has however continued to show improved outcomes for a range of malignancies [18] [19]. When combined with other treatment modalities, the risk of disseminated disease appears to be reduced [18] [20] [21]. Interest in HT as a monotherapy has subsequently declined and HT is now almost exclusively applied synergistically with RT or ChT. Most studies show an improved local control with no significant difference in toxicity when HT is added to either RT or ChT [10] [18] [19]. However in at least one study, no difference in local control was reported and higher (although not

significantly), acute and late toxicity was reported in the group treated with HT plus RT compared to RT alone [22]. Although the benefits of HT combined with RT or ChT on local disease control are widely documented, a at least two studies have shown questionable survival benefitsm[23] [24] [25]. Discrepancies in results have been attributed to variations in techniques and thermometry [26] and to the lack of a temperature reference point [27].

Several mechanisms of sensitisation to ChT and RT by HT have been de- scribed. At temperatures ranging from 39˚C - 42˚C, HT interferes with protein synthesis [28] and inhibits DNA and RNA synthesis and repair [28] [29]. Hyperthermia therefore complements RT and certain cytotoxic drugs which cause DNA double-strand breaks, by inhibiting the repair of the breaks [30] [31] [32]. Increased blood perfusion seen at temperatures between 38˚C and 42˚C increases oxygen and drug delivery to the tumour [15], however at temperatures of 43˚C and above, vasoconstriction occurs and oxygen perfusion declines [33]. Moderate HT (<43˚C) therefore provides another mechanism of radio-sensitisation as hypoxia plays a central role in radio-resistance [33] [34]. Additionally, the failure of DNA replication and repair in the S-phase of the cell cycle, caused by the application of HT, results in mitotic catastrophe [33]. Hyperthermia there- fore also has the potential to sensitise the otherwise more radio- and chemo-resistant cells in the S-phase of the cell cycle to the damaging effects of RT and certain cytotoxic agents [18]. Hyperthermia promotes the release of intra-cellular Heat Shock Protein 70 (HSP70) into the extracellular matrix where it is involved in a complex cascade of reactions triggering a local and systemic immune response to the malignant cells [35]. Frey et al. describe the immunomodulating mechanisms of HT involving the extracellular HSP70 which has an epitope that acts as a signal for Natural Killer (NK) cells, and leads to enhanced NK cell proliferation, migration, and killing activity [36]. Additionally HSP70 appears to play a role in the activation of the tumour suppressor gene p53 [37] [38] [39]. As a result of the immunomodulating effects of HT, the addition of HT to RT may promote the abscopal effect, an immune-mediated response following the local irradiation of a tumour that results in a systemic response to metastatic, non-irradiated lesions [18]. When combined with ChT, the increase in metabolism of the heated cells results in an increase in the reaction rate of the drugs [40]. The effects of HT on ChT does however depend largely on the type of ChT used [41].

This paper reviews the application of modulated electro-hyperthermia (mEHT) applied as a monotherapy with palliative intent. Modulated electro-hyperthermia is a widely used, mild-to-moderate (<41.5˚C) heating technique which utilises amplitude modulated (AM) RF (13.56 MHz) in a capacitive-coupled set up, with impedance matching [40]. The technique induces an increase in temperature high enough to improve perfusion [42], and to induce chemo- [42] and radio[43] sensitisation, safely, even in high risk populations [44]. Although the exact mechanisms of action are not currently fully understood, the improved out- comes despite the milder, and therefore safer, temperatures of mEHT are believed to be attributed to the AM of the carrier frequency, the effects of the electric field on the cell membranes [45] [46], and the subsequent modulating effects on the immune system [47] [48].

In vitro and in vivo murine experiments have demonstrated the tumour-killing effects and immune-modulating effects of mEHT as a monotherapy without the increased risks of metastases in murine models [45] [46] [49] [50] [51] [52] and have shown mEHT to be superior to conventional heating techniques when ap-plied at the same temperature [45] [46]. As a result of the safety and the ease with which treatments are applied, researchers have investigated mEHT applied as a monotherapy for palliative intent, in cases where no further treatment options are available. Numerous case studies have been published on the use of mEHT for the management of patients with locally advanced disease who have failed conventional treatments. The case studies report tumour regression and disease stabilisation for tumours of the colon, rectum, liver, pancreas, lung, bladder, ovaries, stomach, and kidneys [53].

The objective of this review is to explore the potential for mEHT to be applied as a monotherapy for palliative intent, when conventional therapies have failed, and when no further options are available. Examples of patients who may benefit from mEHT as a monotherapy, should it prove effective, include patients with organ failure, recurrent/resistant disease, treatment toxicity, and disease progression requiring palliative or supportive treatment.

2. Methodology

This is a descriptive review of studies published on the use of mEHT as a stand-alone therapy in oncology. Inclusion criteria: A literature search was con- ducted using the key words “Oncothermia”, “modulated electro-hyperthermia”, and “monotherapy” in PubMed. Only studies which applied mEHT as a mono- therapy for palliative intent; when conventional therapies have failed; or when no further options are available, were included. Exclusion criteria: Human, clinical case-reports have shown the potential for mEHT to be used as a

monotherapy [applied after failure of conventional treatments. For the purpose of this re- view however, case-studies were excluded. The literature search returned six studies eligible for inclusion in the review. The studies were on liver metastases (from colorectal cancer), primary liver tumours, brain tumours, pancreatic tumours and gastric tumours. All reviewed reports used the EHY2000+ (Oncotherm GmbH, Troisdorf, Germany) device.

3. Results

All of the studies, with the exception of the study on brain tumours, applied a step-down heating protocol. This involves applying a high power output at the start of the treatment, and reducing the power as the patient feels discomfort at the treatment site. This reduces the risk of dissemination by inducing a transient high temperature and causing vasoconstriction at the beginning of the treatment. The step-down heating method is described elsewhere in the literature [54] [55] [56]. Treatments to the brain applied a step-up heating protocol, as this is considered safer in more sensitive areas. Treatments were administered two to three times per week, with at least 48 hours in between treatments in order to prevent the development of thermo-tolerance [37] [57] [58] [59]. In the reviewed studies, the treatment duration depends on the size of the applicator used (30 cm applicator requires 60 minutes of treatment time and the 20 cm applicator requires a treatment time of up to 90 minutes, with the exception of head and neck treatments), and the treatment location. Sensitive areas such as the brain are treated for 45 - 60 minutes while areas with effective cooling mechanisms, such as the lung, require up to 90 minutes, regardless of the applicator size. Table 1

Location	*n*	Protocol	Treatment frequency
Liver metastases (colorectal primary) [60]	80	Step-down heating starting from 130 W, for 60 min	2/week; 8/cycle; cycles repeated every 5 - 6 weeks until dx progression
Liver primary [61]	8	80 W - 130 W for 60 min	2/week for 5 weeks.
Brain [62]	12	Step-up, starting at 40 W for 20 min; increasing linearly to 150 W for 60 min over 2 weeks	3/week for 8 wks followed by a CT, repeated until dx progression
Brain [63]	149	Step-up, starting at 40 W for 20 min; increasing linearly to 150 W for 60 min over 2 weeks	3/week for 8 wks followed by a CT, repeated until dx progression
Pancreas [64]	6	Step-up, starting at 60 W for 40 min; increasing linearly to 150 W for 90 min over 2 weeks.	3/week for 8 wks followed by a CT, repeated until dx progression
Gastric [65]	25	60 min	3/week

Table 1. Summary of protocols for mEHT applied as a monotherapy.
Abbreviations: CT: Computed Tomography dx: Disease; Min: Minutes; W: Watt; wks: weeks. summarises the protocols that were applied in the reported studies which used mEHT as a monotherapy.

3.1 Liver Metastases from Colorectal Cancer

Eighty participants, who had failed prior treatment, were enrolled in a single arm, prospective, phase II study evaluating mEHT treatments for the palliative management of liver metastases from colorectal cancer. Of the 80 participants, 36% (n = 29) also presented with extra-hepatic lesions. The cycle of mEHT treatments (described in Table 1), was repeated until disease progression was observed. Thirty seven percent (n = 30) of the participants were eligible for palliative chemotherapy during the follow up (median time to first chemotherapy dose: 4.5 months), and subsequently received 5-Fluorouracil + Folinic acid + Mitomycin-C. Long lasting disease stabilisation was noted with a median overall survival time of 24.1 months from the time of first diagnosis of metastases, and the administration of ChT did not significantly change the overall survival. Fifty one percent (n = 41) of participants survived two years and 31% survived three years, which, according to the authors' report, is significantly better than the expected survival rates of 36% and 19% respectively. The authors noted that the mild increase in temperature alone was unlikely to be responsible for the bene- fits seen in the sample, and hypothesised that the interactions with the electro- magnetic field may also contribute to the positive outcomes noted [60].

3.2 Hepatocellular Carcinoma

Ferrari et al. presented results on a phase II study investigating mEHT as a palliative treatment option for primary, chemo-refractory, hepatocellular carcinoma at the annual meeting of the American Society of Clinical Oncology in 2007. Twenty-two participants with non-resectable tumours were enrolled. Fourteen participants were eligible for retreatment with chemotherapy (Oxaliplatin: 50 mg/m2) and mEHT, and eight participants were treated only with mEHT. One cycle of treatment consisted of 10 mEHT treatments, administered twice per week for five weeks (treatment duration: 60 minutes), and the median number of cycles administered was 1.5 (range: 1 - 4). Four participants developed a skin reaction after mEHT with three developing a mild superficial burn which was treated with local steroids. The authors reported one complete response and stable disease in 25% of the participants, with a median survival time of 20.5 weeks (range: 5 - 81). Improved well-being was reported in 50% of the participants treated with mEHT and the authors concluded that mEHT was a safe modality which could be explored further for chemo-refractory hepatocellular carcinoma [61].

3.3 Brain

A phase II study on the application of mEHT for the management of 12 relapsed malignant glioma patients by Fiorentini et al., demonstrated the safety of mEHT to the brain. All participants were previously treated with RT and temozolamide (TMZ). Eight of the participants had glioblastoma multiforme (GBM), two had anaplastic astrocytoma grade III, and two had anaplastic oligodendroglioma. Adverse events reported were persistent head pain in one (8%) participant, mild burn on the scalp in one (8%) participant, and two (17%) participants experienced seizures that were successfully treated with dexamethasone, furosemide, mannitol, and diazepam. One complete remission and two partial remissions were achieved, with a response rate of 25% and a median duration of response of 10 months (range 4 - 32) [62].

Following the results of this 2006 study, Fiorentini et al. proceeded with a phase II, retrospective study investigating mEHT as a monotherapy treatment for relapsed malignant glioma and astrocytoma tumours, compared to best supportive care (BSC), involving dexamethasone, 18% glycerol infusion, mannitol, holistic therapy, and psychosocial support. The researchers enrolled 149 consecutive participants, of which 111 (74%) had GBM, and 38 (26%) had astrocytoma (AST). Palliative care using mEHT was administered to 28 (25%) GBM patients and 22 (58%) AST patients, and BSC was administered to 83 GBM and 14 AST participants. Tumour response was based on the RECIST, v.1.1 criteria and was evaluated by CT or magnetic resonance imaging (MRI) after three months of treatment. A tumour response of 29% and 48% of GBM and AST participants respectively was seen in the mEHT group, and 4% and 10% of GBM and AST patients respectively in the BSC group. The authors report a five-year overall survival of 83% in the AST participants treated with mEHT versus 25% in the participants treated with BSC. In the GBM group, the five-year survival was 3.5% after mEHT, versus 1.2% after BSC [63].

3.4 Pancreatic Cancer

Patients with stage III-IV pancreatic adenocarcinoma were retrospectively di- vided into two groups: those treated with mEHT and those who did not receive mEHT, in this multicentric observational study. Of the 34 participants treated with mEHT, six (15%) received only mEHT and the rest received ChT plus mEHT. Tumour response was evaluated at three months by CT or MRI studies. A total of 499 mEHT treatments were

administered. Adverse events included skin pain in 12 (2%) of the treatments, grade 1 burns in six (1%) of treatments, and grade 2 burns in two of the treatments. All adverse events were resolved within a week of discontinuing treatment. Of the 34 participants treated with mEHT, only two progressed (8%) compared to 23 (34%) in the non-mEHT group. The median overall survival of the mEHT group was 18.0 months (range: 1.5 - 68) and 10.9 months (range: 0.4 - 55.4 months) in the non-mEHT group [64].

3.5 Gastric Cancer

Modulated electro-hyperthermia was applied as a monotherapy to 25 patients with unresectable/recurrent gastric cancer. Outcomes evaluated were tumour volume, symptom experience, and performance. Nine patients had distant metastases on enrolment. Survival time in these nine patients was significantly better than an analysis of a matching retrospective historical arm. Patients treated with mEHT reported improved performance and symptom experience as well as a reduction in tumour size [65].

4. Discussion

This report discusses six phase I/II studies in which mEHT is applied as a monotherapy for some or all of the participants. The safety of mEHT treatments has been established in these studies and elsewhere in the literature when applied alone or when combined with ChT and/or RT [44] [66] [67] [68]. The risk of adverse events is low when applying mEHT in cases in which there are no further treatment options. The results suggest that patients with refractory disease, and in whom there are no further treatment options, may benefit from mEHT as a stand-alone treatment. The benefits may include disease stabilisation, palliation, and a prolonged overall survival. It is however difficult to draw definitive conclusions, due to the variation in study designs and the lack of data from a prospective, randomised controlled trial.

While some of the mechanisms of action of HT are applicable to mEHT, HT and mEHT have some fundamental differences in their effects on cells and tis- sues. This is largely attributed to the differences in temperature achieved and technology applied. Different HT techniques have different actions resulting in variations in outcomes [32] [46] [69]. The mechanisms of action of both mEHT and HT are however still not fully understood. When considering mEHT as a monotherapy, the temperature alone is unlikely to play a major role in the cellular destruction, given that the increase in temperatures seen during mEHT is- mild (achieving only fever-range temperatures) [55], and does not reach 43˚C (the temperature required to cause direct damage and necrosis to the cells). Several preclinical studies on mEHT have however shed light on the immune-related effects of mEHT. These effects include the induction of apoptosis [69], and of deoxyribonucleic acid (DNA) fragmentation, apoptotic bodies, and nuclear shrinkage, which further suggests the induction of programmed cell death pathways [70] [71]. The mEHT-induced programmed cell death appears to be mostly caspase-dependent [46] [49], but in HT29 murine xenografts an independent pathway was observed via the induction of apoptosis inducing factor (AIF) [70]. Modulated electro-hyperthermia triggers the release of damage associated molecular pattern (DAMP) proteins and results in an increase in the cell-membrane expression of HSP70 [49]. The release of HSP70 from cells into the extracellular environment [46] triggers an influx of antigen presenting dendritic cells and killer T-cells (CD8+) which are primed for the recognition of the malignant cells. This could contribute to a systemic immune response to the tumours [49] [71]. These immunogenic effects are believed to be due to the effect of the electromagnetic field and amplitude modulation on the membranes of tumour cells [32] [46] [72]. Minnaar et al. reported on the complete metabolic resolution of metastases outside of the treatment field in 24% (14/54) of participants treated with chemoradiotherapy and mEHT to the cervix in a phase III randomised controlledtrial [73]. These results further hint to the potential effect of mEHT on the immune response to metastatic disease, and the possibility that mEHT can potentiate immune-related effects of ionising radiation. In a three
year follow-up of the participants, 35/99 [35.4%] participants in the mEHT group were alive and disease free compared to 14/102 [13.7%] participants in the control group (OR: 3.4; 95% CI: 1.71 - 6.91l p = 0.001) [74].
The literature contains several case reports of spontaneous tumour regressions in the absence of any treatments [75] [76] [77]. Challis et al. reported on 489 cases of spontaneous regression described from 1900 to 1987 [78] and in 2001, Hobohm published an extended meta-analysis in which he suggested that the presence of feverish conditions in many of the spontaneous regressions indicates a link between immune stimulation and tumour regression [79]. In his paper,
Hobohm suggests the investigation into fever therapy in order to induce remissions. Cases of spontaneous remissions in non-solid tumours have also been re- ported [80] [81] [82]. Nakhla et al. reported on 20 cases of spontaneous regressions in chronic lymphocytic leukaemia (CLL) patients [83]. Del Giudice et al. hypothesise that B-Cell Receptor signaling may play a role in the spontaneous regression of CLL and Hirishanu et al. suggest in their case report that cancer immune surveillance contributed to the spontaneous regression of CLL, in the absence of any other apparent exogenous triggering events [81]. In 2001, Printz

reported on the link between immunological factors and the spontaneous regression of melanomas [84]. Fever, or the fever range of heating, has been cited as a common factor in several spontaneous regression cases [75] [79] [85] [86].

A possible connection between fever and spontaneous regressions is the effects of the heat on the immune system [86] [87] [88] [89]. It may therefore be a possibility that the immune stimulation in the presence of the moderate heat caused by mEHT may contribute to the stabilisation of disease or perhaps even to the spontaneous regression noted in some cases treated only with mEHT.

Although these studies suggest that mEHT may have potential to stabilise disease and manage symptoms, caution must be exercised with regards to pre- scribing, or over-prescribing, mEHT in such cases.
Any potential benefits to the treatments must be carefully balanced against the cost, travelling, the time, and the potential stress on patients with such advanced disease. When appropriately prescribed, mEHT may offer patients and physicians additional treatment options for the palliative management of advanced disease, with minimal risks of adverse events and treatment-related toxicity.

5. Conclusion

Evidence-based statistics are not available for the use of mEHT as a monotherapy. Theory and literature however build an interesting case for the potential benefit of applying mEHT as a monotherapy when standard treatments have failed and when patients have no further options. Determining which cases may benefit from mEHT is an important research question and understanding how mEHT works as a monotherapy may improve the development of protocols for combined therapies. The development of randomised studies on mEHT is needed to confirm these effects and to develop guidelines for the application of mEHT as a monotherapy. Future research on mEHT in a palliative setting could also consider inclusion of immune-modulating agents in the study protocols, in order to enhance the immune-related effects of mEHT.

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Conflict of Interests Statement

MS is the medical director of the company that manufactures the mEHT devices: Oncotherm GmBH. The rest of the authors confirm that they do not have any conflicts of interest.

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