Modulated electro-hyperthermia (mEHT) in monotherapy for painful bone metastases. A new promising indication?

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Abstract

Introduction: Painful bone metastases (PBM) have a great negative impact in patient's quality of life. Pain drugs for PBM are usually not enough and have serious side effects. Up to date, radiotherapy is the most effective treatment for PBM, but has some important limitations (toxicity, dose limits…).

Material and methods: We prospectively included 10 patients with different types of primary active tumors with PBM and tested mEHT as an "analgesic" treatment for PBM. 9 patients had solid tumors and 1 had a multiple myeloma with only one vertebral body affected. All patients had pain which was not responding to systemic and/or analgesic treatment.

Table 1. Patient characteristics and results

	*Sex	Primary Tumor	Systemic Treatment	**mEHT NO bone / Progression		mEHT Bone / Pain Response	
1	F	GYN	YES	UTEROUS	YES	FEMUR	**YES**
2	F	BREAST	YES	BREAST	NO	VERTEBRA	**YES**
3	M	MYELOMA	NO	NO	-	VERTEBRA	**YES**
4	F	BREAST	YES	LIVER	YES	HIP	**YES**
5	F	BREAST	YES	BRAIN	YES	VERTEBRA	NO
6	F	BREAST	NO	NO	-	VERTEBRA	NO
7	F	LUNG	YES	NO	-	RIBS	**YES**
8	F	SARCOMA	YES	NO	-	HIP	**YES**
9	F	BREAST	NO	NO	-	HIP	**YES**
10	F	BREAST	YES	NO	-	VERTEBRA	**YES**

**SEX: F: Female, M: Male.*

***Patients treated with mEHT at other "no bone" sites with tumor and evidence of progression at those sites after mEHT treatment.*

Results: All patients with solid tumors had stage IV (AJCC) and the patient with myeloma had stage III (ISS). All patients received between 5 and 12 mEHT treatments at PBM sites. Seven patients were under systemic treatment. 80% of the patients had significant pain response to mEHT treatment.

Three patients had radiotherapy scheduled and after mEHT treatment, did not need to receive it. Patient's pain response to mEHT was not related to systemic tumor response. Despite tumor progression at other sites treated with mEHT, mEHT was very effective on pain control for treated PBM. It's remarkable, that the patient with the no solid tumor (myeloma), had a significant pain response after mEHT treatment in monotherapy.

Conclusions: mEHT can be a very safe and effective treatment for PBM as a combined treatment, but also in monotherapy. Contrary to the common belief that mEHT does not works in hematological tumors, mEHT may have a role also in no solid tumors as multiple myeloma. These findings open a very interesting path of research.

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November 5, 2020

Modulated electro-hyperthermia (mEHT) in monotherapy for painful bone mestastases. A new promising indication?

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Radiation oncologist at HUMV
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President of ICHS 2020

BONE METASTASES

- Bone is **the most frequent site of metastasis of the most common cancers** in men and women.
- Although bone metastases are sometimes asymptomatic, their **consequences are most often devastating, impairing both life quality and expectancy**, due to the occurrence of the skeletal-related events, including bone fractures, hypercalcemia and spinal cord compression.

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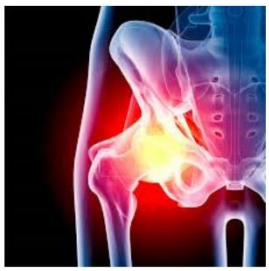
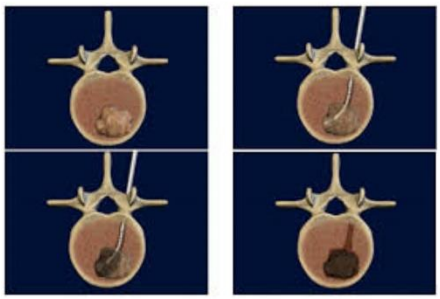
MAIN TREATMENTS FOR PAINFUL BONE METASTASES

- **Analgesics:** usually opioids → important side effects.
- **Bisphosphonates, calcitonin**
- **Systemic treatment** (chemotherapy, immunotherapy…) → very frequently not enough…
- **Radiotherapy**
  - Very effective
  - Dose limit
    - Organs at risk
    - Only once, twice…



MAIN TREATMENTS FOR PAINFUL BONE METASTASES



- **Radiofrequency (*"Agressive heat…"*)**
  - If live tissue is heated **beyond the threshold for protein denaturation (57–60°C) for a few seconds, coagulation necrosis occurs.**
  - Because heating above these critical levels **is not selective** and kills both normal and neoplastic cells, thermal ablations are limited among other things, by risk of side effects.

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MAIN TREATMENTS FOR PAINFUL BONE METASTASES

- **Hyperthermia**:
  - Studies mainly combined with radiotherapy.
    - **Good side**: usually more effective than radiotherapy alone.
    - **Bad side:** Radiotherapy limitations.
- **Hyperthermia alone**?
  - Almost nothing published…

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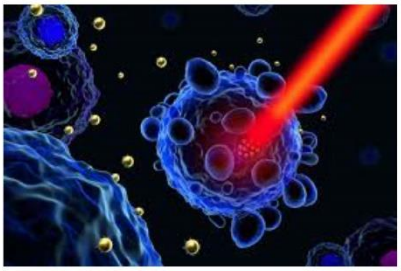

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We have some comments in different studies about metastatic bone pain and mEHT but not a specific study for this….

Hindawi Publishing Corporation
Conference Papers in Medicine
Volume 2013, Article ID 392480, 12 pages
http://dx.doi.org/10.1155/2013/392480

Conference Paper

Cases That Respond to Oncothermia Monotherapy

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Received 17 January 2013; Accepted 29 April 2013

Academic Editors: G. F. Baronzio, M. Jackson, D. Lee, and A. Szasz

This Conference Paper is based on a presentation given by Tae Sig Jeung at "C Society 2012" held from 12 October 2012 to 14 October 2012 in Budapest, Hur

Tumor mass was regressed at the right lung and spine. However, tumors progressed in the left lung because oncothermia was not given at the left lung.

Back pain to the right chest was subsided after oncothermia. Many cases showed the reduction of the metastatic bone pain with oncothermia.

It is possible to apply oncothermia to reduce metastatic bone pain with a variety of cancers.

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MOLECULAR PLAYERS IN CANCER-INDUCED BONE PAIN

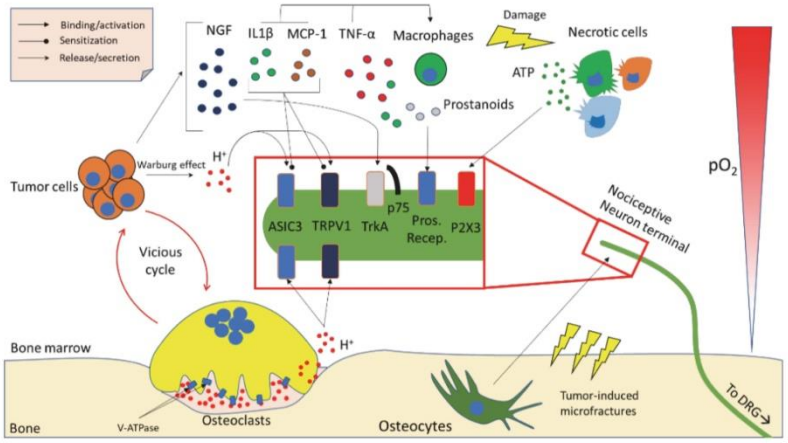

Figure 2. Cartoon representing the main cellular and molecular players in cancer-induced bone pain (CIBP).

Int. J. Mol. Sci. **2019**, *20*, 280

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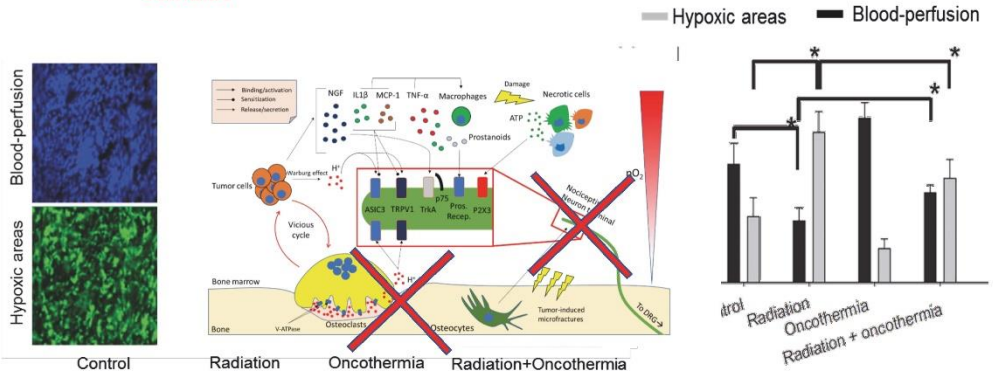
MODULATED ELECTRO-HYPERTHERMIA (mEHT) + RT

Heat → vasodilatation → decrease hypoxia → decrease H+ release and nociceptive stimulus



Five fields in each of the three tissue sections per tumor were studied and the % positive area calculated. Means of five tumors ±1 SE are shown. _indicates p<0.05.

Wonwoo Kim, Mi-Sook Kim, Hee-jong Kim, Eunjin Lee, Jae-hoon Jeong, Inhwan Park, Youn Kyoung Jeong & Won Il Jang (2017): Role of HIF-1α in response of tumors to a combination of hyperthermia and radiation in vivo, International Journal of Hyperthermia, DOI: 10.1080/02656736.2017.1335440; https://doi.org/10.1080/02656736.2017.1335440

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mEHT FOR PAINFUL BONE METASTASES

- We **prospectively** included **10 patients** with different types of primary active tumors with PBM and tested mEHT as an "analgesic" treatment for PBM.
- **All patients had pain which was not responding** to systemic and/or analgesic treatment. (No new treatments besides mEHT which could impact on PBM relief).
- All patients were under **high dose of opioids** and other analgesics.
- **All treatments at PBM sites were prescribed for pain relief as main objective** (not for tumor control).

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PATIENT FEATURES

	*Sex	Primary Tumor
1	F	GYN
2	F	BREAST
3	M	MYELOMA
4	F	BREAST
5	F	BREAST
6	F	BREAST
7	F	LUNG
8	F	SARCOMA
9	F	BREAST
10	F	BREAST

**SEX: F: Female, M: Male.*

- **9 patients had solid tumors** and **1 had a multiple myeloma** with only one vertebral body affected.
- All patients with solid tumors had stage IV (AJCC) and the patient with myeloma had stage III (ISS).

PATIENT FEATURES

	*Sex	Primary Tumor	Systemic Treatment
1	F	GYN	YES
2	F	BREAST	YES
3	M	MYELOMA	NO
4	F	BREAST	YES
5	F	BREAST	YES
6	F	BREAST	NO
7	F	LUNG	YES
8	F	SARCOMA	YES
9	F	BREAST	NO
10	F	BREAST	YES

7 patients were under systemic treatment.

PATIENT FEATURES

- **Unable to walk because of pain: 3 (Myeloma, sarcoma and breast)**
- **Able to walk with help: 1**

- **Able to move on his/her own but limited by pain: 6**

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PATIENT FEATURES

	*Sex	Primary Tumor	Systemic Treatment	**mEHT NO bone
1	F	GYN	YES	UTEROUS
2	F	BREAST	YES	BREAST
3	M	MYELOMA	NO	NO
4	F	BREAST	YES	LIVER
5	F	BREAST	YES	BRAIN
6	F	BREAST	NO	NO
7	F	LUNG	YES	NO
8	F	SARCOMA	YES	NO
9	F	BREAST	NO	NO
10	F	BREAST	YES	NO

- ***4 patients*** *received* ***mEHT*** *treatment at other* ***no bone sites*** *(cervix, breast, liver, brain).*

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PATIENT FEATURES

	*Sex	Primary Tumor	Systemic Treatment	**mEHT NO bone	mEHT Bone
1	F	GYN	YES	UTEROUS	FEMUR
2	F	BREAST	YES	BREAST	VERTEBRAE
3	M	MYELOMA	NO	NO	VERTEBRAE
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5	F	BREAST	YES	BRAIN	VERTEBRAE
6	F	BREAST	NO	NO	VERTEBRAE
7	F	LUNG	YES	NO	RIBS
8	F	SARCOMA	YES	NO	HIP
9	F	BREAST	NO	NO	HIP
10	F	BREAST	YES	NO	VERTEBRAE

- *5 patients vertebrae*
- *1 patient femur*
- *3 patients hip*
- *1 patient rib*

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RESULTS:

- All patients received **between 5 and 12 mEHT treatments** at painful bone metastases (PBM) sites.
- **80% of the patients had significant pain response** to mEHT treatment.

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8	F	SARCOMA	YES	NO	-	HIP	YES
9	F	BREAST	NO	NO	-	HIP	YES
10	F	BREAST	YES	NO	-	VERTEBRA	YES

- All patients with good response **felt improvement since de first mEHT** treatment.

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RESULTS:

	*Sex	Primary Tumor	Systemic Treatment	**mEHT NO bone	mEHT Bone
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- **3 patients had radiotherapy scheduled** and after mEHT treatment, **did not need to receive it**.

Unable to walk because of pain: 3 (Myeloma, sarcoma and breast)

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RESULTS:

- **4 patients were treated with mETH at other no bone sites**. All these 4 were receiving systemic treatment.
  - **1 mEHT at cervix (cervical cancer) –> progression**
    - Bone mets femur → significant pain response with mEHT
  - **1 mEHT at breast (breast cancer) –> tumor response**
    - Bone mets vertebrae → significant pain response with mEHT
  - **1 mEHT at liver (breast cancer) –> progression**
    - Hip mets → significant pain response with mEHT
  - **1 mEHT at brain (breast cancer) –> progression**
    - Vertebral mets → NO pain response with mEHT

- **Despite tumor progression** at other sites treated with mEHT, mEHT **was very effective on pain control for treated PBM in 2 patients.**

- **mEHT can relief pain despite tumor progression**

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INTERESTING...

- **The patient with the no solid tumor (myeloma), had a significant pain response after mEHT treatment in monotherapy.**

FACTS about Oncothermia

Oncothermia is active in all solid tumors.

No side effects, rare contraindications.

Combined energy absorption with modulated electric field.

Oncologists or other medical specialists treat with the method worldwide.

Tumour tissue is selectively treated, the malignance is destroyed.

Healthy tissue is unaffected.

Efficacy of chemotherapy and radiotherapy is improved by the treatment.

Reestablishes the intercellular junctions, supresses the dissemination.

Modulated electro-hyperthermia induces immunogenic cell-death.

Improves the quality of life, reduces the side-effects of other treatments.

A proven method since 30 years with more than 200.000 treatments yearly.

Myeloma is cancer of the plasma cells → Is considered a hematologic tumor...

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MYELOMA CASE

- Male 59 year old.
- Dx: **Multiple myeloma** IgG kappa IIA, **mets and fracture L4** and light hypercalcemia.
  - **VAS (Visual analogic scale): 9 with movement, 3 relaxed.**
  - **Wheel chair → could not stand on his own.**
  - **High dose Opioids**
  - **High dose Corticoids**
- Scheduled for bone marrow transplation after induction chemotherapy.
- **Proposed for vertebroplasty + radiotherapy** before beginning CT.

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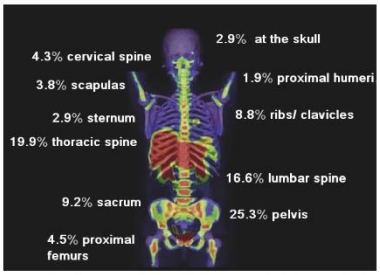
MYELOMA CASE

- **Suggest try with mEHT.**
  - Patient received **6 mEHT treatments** every other day.
    - After 1st treatment → was able to stand on his own.
    - After 3 treatments decreased 50% analgesics and was able to walk with crutches.
    - After 5 treatments stopped opioids, and decrease corticoids 75%.
  - **1 week after 6th treatment**:
    - **No analgesic nor corticoids.**
    - **Able to walk on his own and climbing stairs.**
  - He was treated on february 2020.
    - **Up to date**, he already received bone marrow transplation and **no evidence of disease and no pain.**

WHY?

- **We don't find a pattern related to:**
  - **Histology.**
  - **Tumor systemic or local response.**
  - **Type of bone.**
    - Of course → not enough patients to rise conclusions.



Distribution of Proliferating Bone Marrow in Adult Cancer Patients Determined Using FLT-PET Imaging ijrobp.2009.11.040

HOW LONG?

Length of response

- 1 patient died 1 month after treatment.
- All the other 7 patients still have pain controlled:
  - Follow Up:
    - 4 patients 6 months.
    - 3 patients 9 months.
    - 2 patients 12 months.

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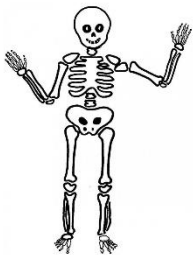
CONCLUSIONS

- **mEHT can be a very safe and effective treatment for PBM as a combined treatment, but also in monotherapy.**
- **Contrary to the common belief that mEHT does not works in hematological tumors, mEHT may have a role also in no solid tumors as multiple myeloma.**
- **These findings open a very interesting path of research.**
  - We need more studies to know:
    - Indications
    - Number of sessions.
    - Length of response.