Clinical proofs of oncothermia

Andras Szasz
Department of Biotechnics, Faculty of Engineering, St. István University, Budaörs, Hungary
biotech@gek.szie.hu

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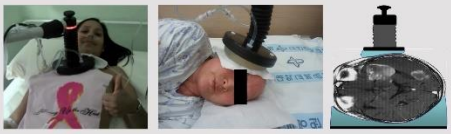
CLINICAL PROOFS OF ONCOTHERMIA

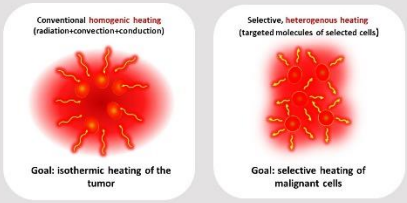
Andras Szasz

Department of Biotechnics, Faculty of Engineering, St. István University, Budaörs, Hungary biotech@gek.szie.hu

SZENT ISTVÁN UNIVERSITY

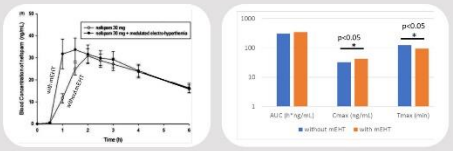
Modulated electro-hyperthermia (mEHT), is a particular kind of hyperthermia in oncology. It considers the heterogeneous structure of the tumor and provides selective thermal actions instead of the homogenous heating. Its advantages are the stable safety, extra low toxicity and systemic effect of the local treatment. The systemic effect is made by the development of the immunogenic cell-death and produces an abscopal effect, excluding the relapse of the same tumor in the system. Our presentation intends to show the clinical studies of mEHT in variously advanced primary and metastatic malignancies.





Some, selected clinical trials

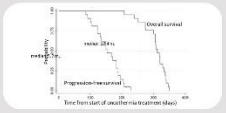
Pharmacokinetics (n=12) Randomized prospective crossover study [Lee SY, Kim M-G (2015); Int J Hyp, 31:869; 2015]



Despite the mild overall heating mEHT significantly increases the maximum of the kinetic curve (C_{max}) and also significantly decreases the time at maximum (T_{max}) parameters. The area under the peak (AUC) was stable, indicating the unchanged systemic adverse effects, despite the increase of the absorption of the drug.

Hepatocellular carcinoma Phase II study (n=21) Gadaleta-Cardarola G. et al.; (2014); Oncology letters 8: 1783-1787

Local control	
Response	n (%)
Complete response	0
Partial response	1 (5)
Stable disease	11 (50)
Progressive disease	9 (45)
Disease control rate	9 (45)

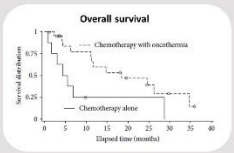


Combination of chemotherapy (sorafenib, 800 mg every other day) and mEHT was applied. Sorafenib treatment interruptions and dose reductions (initially 200 mg twice daily, then reduced to 200 mg once daily) were allowed for drug-related toxicity. The overall response rate was 55%, but no complete response was achieved. The treatment was well tolerated, chemotherapy caused the adverse effects, and it seems that mEHT did not increase these.

Small-cell lung-cancer double arm prospective study (n=31)

Lee DY, et al. (2013) Conference Papers in Medicine, Vol.2013, Article ID 910363, pp.1-7

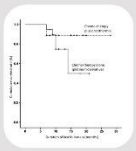
The first line chemotherapy was Irinotecan (60 mg/m2) and Cisplatin (60 mg/m2) three times. In cases of the progression of the malignancy or metastases, the chemotherapy regime changed to Etoposide (110 mg/m2) and Cisplatin (70 mg/m2) in the second line. mEHT was applied in both the chemo-lines in the study group.



Local control		
Year	1	2
Study arm	59.0%	47.0%
Control arm	25.0%	25.0%

Recurrent cervix double arm, randomized study (n=38)

Treatment outcome analysis of chemotherapy combined with modulated electro-hyperthermia compared with chemotherapy alone for recurrent cervical cancer, following irradiation [Lee SY, Lee NR, Cho D-H, Kim JS; Oncology Letters, ttps://doi.org/10.3892/ol.2017.6117, (2017)]

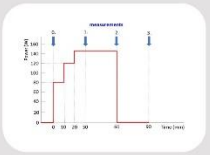


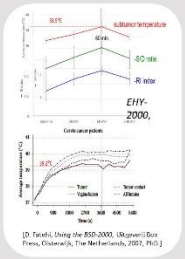
Patients received conventional chemotherapy alone (n=20) compared to the combination to mEHT (n=18). Every patient had chemotherapy [paclitaxel + cisplatin (n=14), paclitaxel + carboplatin (n=10), cisplatin + 5-fluorouracil (n=12), cisplatin alone (n=2)]. Radiotherapy was not possible in this cohort because of the recurrence in the field of previous radiotherapy. The complementary mEHT was applied concomitant with the beginning of the chemotherapy. Every patient had 36 mEHT sessions. The overall response (p=0.0461) and the stable response in the follow-up time (p=0.0218) were measured without any severe adverse effects.

A phase III. cervix clinical trial -Survival of cervical cancer patients with or without associated HIV infection and treated with modulated electro-hyperthermia combined with chemo-radiotherapy-will be presented by Dr. Carrie Minnaar at the conference.

Temperature and blood-flow in cervix carcinoma (n=20)

A Phase II, single arm, single center prospective clinical trial (n=20) of mEHT treated uterus cervix carcinoma ; [Lee SY, Kim JH, Han YH, Cho DH; (2018); Int J Hyperthermia 21:1 8]





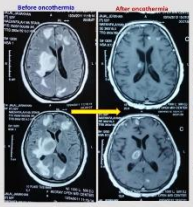
[D. Tatebi, *Using the BSD-2000*, Utrgtverij Box Press, Oisterwijk, The Netherlands, 2007, PhD.]

Studying the blood-flow and temperature increase by mEHT could give relevant information about the complementary applications with chemotherapy (drug-delivery) and radiotherapy (oxygen delivery). The peri-tumor temperature was measured using an internal organ temperature probe. The tumor blood-flow was measured using 3D color Doppler ultrasound. The measured blood-flow values significantly demonstrated the increased tumor blood perfusion by mEHT.

Our common pancreas clinical trial results with Semmelweis University are shown on Dr. Marcell Szász's poster: Modulated Electro-Hyperthermia in Pancreatic Cancer Patients: initial experience and clinicopathologic evaluation.

Some, selected case reports

Brain metastasis from breast cancer

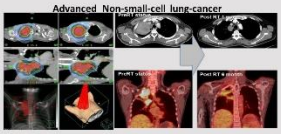


Dr. Marwan Akasheh; **Institute:** Dar Alshefa' Tumor Center, Amman, Jordan; **mEHT, Monotherapy**

Advanced Breast cancer

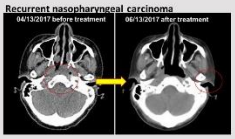
Wang Y-S, Chi K-W, Shih-Kong Hospital, Taipei, Taiwan (11.2017; unpublished yet)

Advanced Non-small-cell lung-cancer



Prof.Dr.Chang Geol Lee; Department of Radiation Oncology, Yonsei University , Seoul, South Korea; RT: 66 Gy/30 fractions; CTx: weekly paclitaxel/cisplatin; Oncothermia: 10 fractions/5 weeks

Recurrent nasopharyngeal carcinoma



Nivolumab 60mg RT: 60Gy/30fx; Oncothermia 6x
Wang Y-S, Chi K-W, Shih-Kong Hospital, Taipei, Taiwan (unpublished)

Conclusion

mEHT has good clinical achievements in the clinical studies making the stable basis of the clinical applications in various advanced primary and metastatic malignancies.