Current Status of Clinical HYPERThERMIA

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5-J.- Survival

DeVita: Progress in Cancer Therapy, 83
* in Combination with radiation
Hyperthermia

What can I see? Uhuh!
Overview of hyperthermia methods:

I. Active hyperthermia (fever, medical drugs)

II. Passive hyperthermia (device)

A. Whole Body Hyperthermia (WBH)
   - Mild (-39 °C)
   - Moderate (40-41 °C)
   - Extreme (-42.8 °C)

B. „Local“ Hyperthermia“

Invasive:
- RF, LITT, ECT,
- Intracavitary,
- Peritoneal,

Non Invasive:
- Local (surface)
- Regional (deep)

Locoregional (=EHT)
Locoregional Radiowave Electrohypertermia (EHT)

Electromagnetic energy transfer with 13.56 MHz, low-frequency modulation, selective targeting of extracellular fluid of the malignant cells with heat accumulation and over-heating.

**Typical applications of EHT**

- **Solid tumors:** tumour destructive technique without side-effects, during which the treatment of tumours takes place in several sessions

- **Metastasis:** regional treatment of largest tumour region; several treatments by different regions is possible direct after another.
Selected Tumor Entities Treated with Regional Hyperthermia
Hyperthermia in Head & Neck

April 2004 ICHO  Dr. Nagraj G. Huilgol M.D., Nanavati Hospital, Mumbai - India
Initial Response Following HT + RT

N=60

CR: 77.97%
PR: 22.03%

April 2004 ICHO  Dr. Nagraj G. Huilgol M.D., Nanavati Hospital, Mumbai - India
Phase-III-Study (Valdagni and Amichelli in Italy):
Non resectable head-neck-cancer grade IV with metastases in lymphnodes.
Radiotherapy (RT) + Local Hyperthermia (HT)
n= 41 patients

RESULTS:

CR (complete remission):
RT: 41%
RT + HT: 83%

5-Years-Survival:
RT: 0%
RT + HT: 53%
Hyperthermia in Breast Cancer

Before HT and Chemotherapy  17.10.02

Since 17.10.02 to 05.02.03
3x Taxotere + Epirubizin every 3 weeks

After HT and Chemotherapy  06.03.03
Hyperthermia in Breast Cancer

ESHO 2007:

109 Patients with relapsed MAMMA Ca

THERAPY:

• Radiationtherapy + Hyperthermia
• Radiationtherapy alone

RESULTS:

⇒ Hyperthermia-group CR: 68%
⇒ Non hyp.-group CR: 24%

Jones et al., Journal of Clinical Oncology Vol. 23, No 13, May 1, 2005.
Jones et al, June 2007, 24th Annual Meeting of ESHO, Prag,
Patient G.A., 68 years, m.
BC left ul
cT3 cN2 M0 G3 R2
Histology: Plattenepithel-Carzinom

Therapy:
60 Gy,
Cisplatin 1x/Week 5x, 10 HT
8 Weeks post RT-CT-HT,
Lung-resektion R0,

Histology: No Tumor cells
Hyperthermia in Lung Cancer

LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER: RT vs. RT+HT

Result:
HT+RT: 74% after 7 J.
RT: 21% under 4 J.

diffus metast. Pancreatic cancer G3

neoadjuvant Therapy, SIRT-Therapy 07-08.08,
Radiotherapy abd. LK 06.02. – 17.03.2009 PD;
since 02.09 ongoing Chemotherapy,
Since 02.2008 Fatigue + tumoranämia
MRI: 04.09 ➔ PD
Cxt + hyperthermia
MRI: 10.09 ➔ PR
Hyperthermia in Pancreatic Cancer

Temperature monitoring
Hyperthermia in Pancreatic Cancer

3 explorative trials presented at ICHO 2008: Verona, Munich and Kyoto

Takagi et al, Kyoto:  for Gemcitabine plus HT versus for Gemcitabine alone
57 % disease control (CR+PR+SD)  ,, 14 %
49 % 1 year OS  ,, 30 % (p=0.024)

Maluto et al, Verona:  for Chemo + Radiation plus HT versus for Chemo/Radiation alone
68 % 1 year OS  ,, 47 %
no more toxicity observed as in control group

Tschoep et al, Munich:  for Gemcitabine/CIS plus HT as second line therapy!

median progression free survival from start 2nd line therapy:  4.2 months (CI: 2.1-7.7)
median OS:  16.9 months (CI: 11.8-22)

all presented at: ICHO conference, 10th International Congress on Hyperthermic Oncology, Munich, Germany 2008
Pancreatic Cancer

Retrospective Study n=69

One-year survival

% Hyperthermia arm
% Control arm

<table>
<thead>
<tr>
<th>Study</th>
<th>Hyperthermia Arm</th>
<th>Control Arm</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kakolyris et al (1999)</td>
<td>40%</td>
<td>20%</td>
<td>38</td>
</tr>
<tr>
<td>Nat Canc Inst. USA (1999)</td>
<td>30%</td>
<td>15%</td>
<td>4738</td>
</tr>
<tr>
<td>Miller et al (2000)</td>
<td>25%</td>
<td>10%</td>
<td>42</td>
</tr>
<tr>
<td>Gonzalez-Cao et al (2001)</td>
<td>20%</td>
<td>10%</td>
<td>24</td>
</tr>
<tr>
<td>Present, control</td>
<td>15%</td>
<td>5%</td>
<td>34</td>
</tr>
<tr>
<td>Present, hyperthermia</td>
<td>40%</td>
<td>10%</td>
<td>69</td>
</tr>
</tbody>
</table>
Metastatic Colon Cancer

Before HT 03.07.01 with XELODA

During Hyperthermia 22.11.01 + XELODA
## Metastasic Colon Cancer + HT n=80

<table>
<thead>
<tr>
<th>Treatment method</th>
<th>1 year survival</th>
<th>3 years survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td>48 - 58 %</td>
<td>14 - 19 %</td>
</tr>
<tr>
<td>HT + Chemotherapy</td>
<td>91 ± 3 %</td>
<td>31 ± 6 %</td>
</tr>
</tbody>
</table>

D.Hager et.al.: Anticancer Res. 19, 3403-08, 1999
Randomised controlled trials with HT

Statistics based on 44 clinical articles, including 1963 cases

The tumor response according to various tumor sites by the combination treatment with hyperthermia and radiotherapy.

### Randomised controlled trials with HT

<table>
<thead>
<tr>
<th>Tumor site</th>
<th>Experimental</th>
<th>Control</th>
<th>No. of Pts.</th>
<th>OR [%] Control</th>
<th>OR [%] with HT</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervix</td>
<td>RT + HT</td>
<td>RT</td>
<td>65</td>
<td>46</td>
<td>66</td>
<td>57</td>
</tr>
<tr>
<td>Cervix</td>
<td>RT + HT</td>
<td>RT</td>
<td>66</td>
<td>35</td>
<td>72</td>
<td>58</td>
</tr>
<tr>
<td>Cervix</td>
<td>RT + HT</td>
<td>RT</td>
<td>37</td>
<td>53</td>
<td>83</td>
<td>59</td>
</tr>
<tr>
<td>Cervix</td>
<td>RT + HT</td>
<td>RT</td>
<td>40</td>
<td>50</td>
<td>85</td>
<td>60</td>
</tr>
<tr>
<td>Colorectal</td>
<td>RT + HT</td>
<td>RT</td>
<td>24</td>
<td>10</td>
<td>43</td>
<td>26</td>
</tr>
<tr>
<td>Gastric</td>
<td>RT + HT</td>
<td>RT</td>
<td>293</td>
<td>35,5</td>
<td>57,6</td>
<td>33</td>
</tr>
<tr>
<td>Colorectal</td>
<td>RT + HT</td>
<td>HT</td>
<td>71</td>
<td>36</td>
<td>54</td>
<td>61</td>
</tr>
<tr>
<td>Bladder</td>
<td>RT + HT</td>
<td>HT</td>
<td>49</td>
<td>48</td>
<td>83</td>
<td>62</td>
</tr>
</tbody>
</table>

Deep Electro-Hyperthermia in relapsed malignant gliomas treated with Radiofrequency Hyperthermia at 13.56 MHz

University Witten/Herdecke
Department of Radiology
Dr. H. Sahinbas
ASCO 2008
Treatment combination (example)

**WEEK**

- **1**
- **2**
- **3**
- **4**
- **5**
- **6**
- **7**

**RADIATION**

- 5 X 1.8 Gy/W to 50.4 Gy
- 66/72 Gy

**CHEMOTHERAPY**

- Complementary

**HYPERTHERMIA**

- 2 - 3 Sessions / Week
1st diag: 12/99 Astrocytoma, Hydrocephalus occlusus, neurofibromatosis; WHO III, Non-operable
Tu: 4 x 5.6 x 3.6 + edema 2 cm compression of Ventriksels, Hydrocephalus occlusus, left side paralyses, disable of concentration, epileptic attacs KI: 30-40 %
Medication: Fortecotin 4 mg (16.02.00 - 28.03.00.)
Radiation:01/00 bis 02/00 bis 40 Gy + 20 Gy (2 Gy/d)
EHT as MONOTHERAPY:
16.02.– 28.03.00 16 x EHY, 20.04.- 04.05.00 6 x EHY
18.06.– 03.07.00 6 x EHY, 11.12.– 16.02.01 14 x EHY
Results:
shrinking of tumor edema, central tumor necrosis
shrinking of tumormass, shrinking of neur.sympt.
KI: 90-100 % since October 2002,
Follow up till excitus: 20.03.03

University Witten-Herdecke, Gronemayer Institute of Microtherapy, Bochum, Germany, Dr. Sahinbas H.

Before radiation and hyperthermia + 6x radiation
hyperthermia + 6x radiation

ASTROCYTOMA WHO III TREATMENT WITH ELECTRO HYPERTERMIA (EHT)
BRAIN METASTASES FROM BREAST Ca.

25.01.2006 MRC before Radiation + HT

23.08.2007 MRC after Radiation + HT
Glioblastoma multiforme WHO IV

50-year-male. GBM (WHO IV, ED May 2005): surgery, radiation and chemotherapy. Symptoms: cephalgia, epileptic seizures, aphasia, and motor dysfunction. Laboratory evaluation was without relevant pathologic findings.

Recurrent of GBM WHO IV (10.2005): Surgical intervention was not feasible. ➔ PD

Since February 2006: CxT with temozolomide (100 mg/m2/d x 21 days, one week rest) + RF-HT which is ongoing at the time ➔ > 42 month ➔ CR
TEMPERATURE MONITORING BY MRI DURING EHT

Dr. Sahinbas H, Univ. Witten-Herdecke

Grayscale

Area 4
Area 3
Area 1
Area 2

mean shift

Healthy (reference)
Cerebral liquor
Tumor
Eodema

<table>
<thead>
<tr>
<th>Area 1</th>
<th>Area 2</th>
<th>Area 3</th>
<th>Area 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>20.4</td>
<td>14.1</td>
<td>36.9</td>
<td>46.0</td>
</tr>
</tbody>
</table>
# RESULTS

Hyperthermia may increase overall median survival time (MST)

| MST of patients with WHO grade III and IV gliomas (Kaplan-Meier-Estimation) |
|-----------------------------------|------------------|------------------|
| MST from                          | Grade III AA; N = 53 pts months ± se [95%CI] | Grade IV GBM; N = 126 pts months ± se [95%CI] |
| 1st Diagnosis of Disease          | 38.2±3.7 [31.2;45.0] | 20.3±1.7 [15.9;22.1] |
| 1st RF-Hyperthermia               | 10.6±2.0 [6.7;14.4]  | 7.6±0.9 [5.9;9.3] |
| Events / Censored N (%)           | 39 / 14 (26.4%)    | 101 / 25 (19.8%) |

<table>
<thead>
<tr>
<th>Survival Probability (Kaplan-Meier-Estimation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>From newly diagnosed</td>
</tr>
<tr>
<td>AA WHO°III; N=53</td>
</tr>
<tr>
<td>GM WHO°IV; N=126</td>
</tr>
</tbody>
</table>

Censored (AA): 14 (26.4%); events: 39 (73.6%)
Censored (GM): 25 (19.8%); events: 101 (80.2%)
Survival time in brain tumors

Glioblastoma Median Survival (m)

- EORTC RT
- EORTC RT+TMZ
- MRC RT total
- MRC RT+PCV total
- RTOG total
- GIMT + Hyperthermia

SEER (Surveillance, Epidemiology, and End Results) by the National Cancer Institute USA, April 2000

MRC (Medical Research Council, Brain Tumor Working Party)

RTOG (Radiation therapy Oncology Group)

EORTC (European Organisation for Research and Treatment of Cancer)

RT = Radiotherapy, PCV = Procarbazine+CCNU(Lomustine)+Vincristine, TMZ = Temizolomide
Local Hyperthermia
Side effects:

Negative side effects:

A. Short-term (two hours) asthenia after treatment (8-10%)
B. Local redness (rubor) of the skin (8%)
C. Complications: (13%)
  • Subcutaneous fibrosis of fat tissue (1%)
  • Burning of the skin of one cm in diametre stage I-II (2%)
  • After treating brain Tumor: headache and vomiting (12%)
Side Effects:

Right Leg*

* The patient was paraplegic and did not feel the burn, thus did not pushed the pause button.
INTERACTION BETWEEN CHEMOTHERAPY AND HYPERThERMIA

CISPLATIN (CDDP): FIBROSARCOMCELLS IN COMBINATION WITH CDDP, RT, HT

<table>
<thead>
<tr>
<th>THERAPY GROUP</th>
<th>EFFECT (DAYS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDDP (5mg/kg)</td>
<td>4.4 +/- 0.9</td>
</tr>
<tr>
<td>CDDP (10 mg/kg)</td>
<td>8.0 +/- 1.7</td>
</tr>
<tr>
<td>34 °C, 30 min.</td>
<td>1.4 +/- 0.7</td>
</tr>
<tr>
<td>CDDP and HT</td>
<td>5.9 +/- 1.1</td>
</tr>
<tr>
<td>Radiatio (5 X 3 Gy)</td>
<td>6.3 +/- 1.5</td>
</tr>
<tr>
<td>HT and Radiation</td>
<td>8.4 +/- 2.2</td>
</tr>
<tr>
<td>CDDP and Radiation</td>
<td>11.7 +/- 1.8</td>
</tr>
<tr>
<td>Radiation &gt; CDDP &gt; HT</td>
<td>13.9 +/- 2.3</td>
</tr>
<tr>
<td>CDDP &gt; Radiation &gt; HT</td>
<td>19.3 +/- 3.4</td>
</tr>
<tr>
<td>CDDP &gt; HT &gt; Radiation</td>
<td>25.2 +/- 2.8</td>
</tr>
</tbody>
</table>

Source: Towle, L.R., Hyperthermia and drug resistance; Hyperthermia and Oncology, Vol.4 Chemopotentiation by Hyperthermia. 1994; 135 - 160
1. RF Electro-Hyperthermia has the potential to increase overall median survival time (MST) for different tumor entities.

2. Complete and long-term partial remissions or stable diseases could be better achieved, occasionally even with HT alone.

3. Quality of life: increased in most of the cases.

4. Equivalent temperatures measuring is possible.

2. RF Electro-Hyperthermia for **brain tumors**, show a valid treatment potential and can be safely applied.

3. **No toxicity** problem did occur.

⇒ This oncological treatment can be considered a new beneficial method, adjuvant to conventional therapies.
THANK YOU FOR YOUR ATTENTION

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