Oncothermia Journal 4:12-13 (2011)

Locoregional hyperthermia combined with chemotherapy for metastatic breast cancer patients – preliminary results oft he Mammatherm-trial

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Background:
Treatment options for patients with metastatic breast cancer should be as effective and preferably as little toxic as possible. To date there is no standard therapy available and treatment regimens for metastatic breast cancer vary largely. Locoregional hyperthermia might show additive effects to chemotherapy due to an increased perfusion and a simultaneous occurrence of interstitial acidosis in tumor tissue. In randomized clinical trials the addition of hyperthermia to radiation in advanced breast cancer was associated with improved outcome. [1; 2] To our knowledge so far there are no randomized clinical trials evaluating the effect of a combination of hyperthermia and chemotherapy in breast cancer patients.

Patients and Methods:
Phase I of the multicenter German Mammatherm-trial was a dose-finding-study for liposomal doxorubicin administered in combination with cisplatin (20mg/m^2) and locoregional hyperthermia. Patients received 6 cycles of therapy according to the following regimen:
liposomal doxorubicin 40 or 50mg/m^2 i.v. d1 q22d and cisplatin 20 mg/m^2 i.v. d1, 8, 15 q22d in combination with locoregional hyperthermia administered at d1, 4, 8, 11, 15, 18 q22d. Dosage escalation levels for liposomal doxorubicin were at 40/50mg/m^2; an escalation up to 60mg/m^2 was planned but not effected due to dose limiting toxicities (DLTs).
DLTs were defined as non-hematological toxicities > grade 2 NCI CTCAE (National Cancer Institute Common Terminology Criteria of Adverse Events), - except of nausea and vomiting -, or hematological side effects grade 3 or 4 NCI CTCAE leading to treatment postponement of more than 7 days, if those adverse events were at least possibly associated with the study therapy.
Here first results of the trial concerning the observed DLTs are presented.

Results:
A total number of 10 patients were recruited into the trial between August 2007 and May 2011.
The therapy was prematurely stopped in 6 patients. Therapy was discontinued in only one patient due to toxicity (adiponecrosis); all other discontinuations were required because of tumor progression.
Dose limiting toxicities (DLTs) were observed in 2 patients and comprised liver toxicity (elevated Gamma-glutamyl transferase) in a patient with liver metastases, and, probably, but not proven, tumor-associated bone pain. A causal link to the administered chemotherapy could not be ruled out but appeared to be rather unlikely in both cases. None of these adverse events required treatment discontinuation.
Either of the DLTs occurred in the second dosage escalation level (50mg/m^2). Thus, the dose of liposomal doxorubicin will be at the next lower dosage level, i.e. 40mg/m^2 for the phase II of the trial.
There were neither hematological nor hyperthermia related DLTs seen.

Conclusion:
The combination of locoregional hyperthermia and chemotherapy in pretreated metastatic breast cancer patients showed a tolerable toxicity profile. Data concerning the final toxicity analysis are pending.

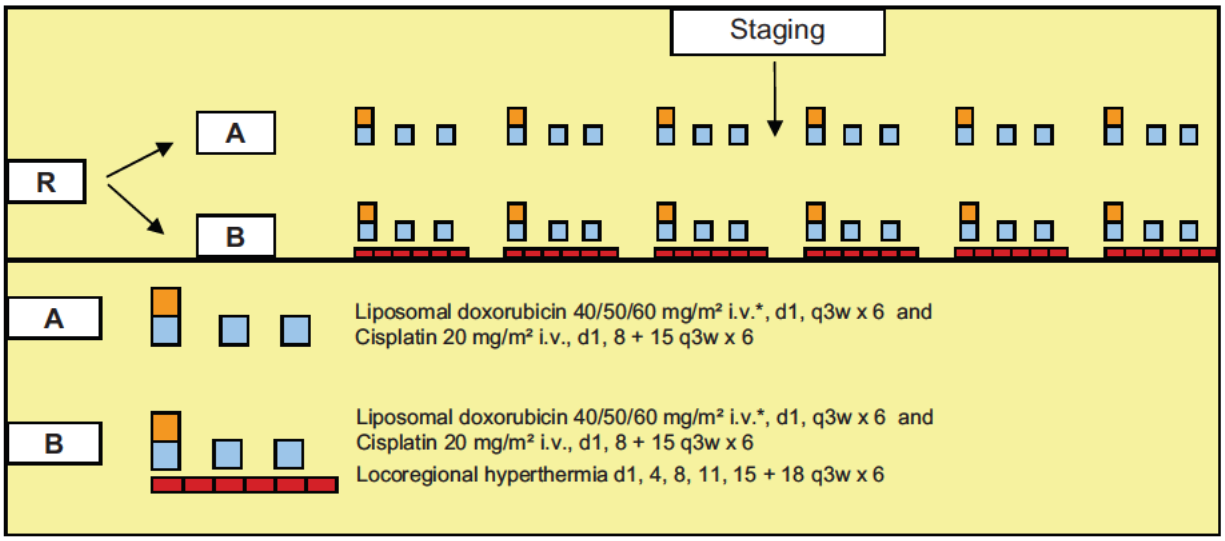

Figure 1: Design of the Mammatherm-trial, (phase I non randomized, pts. treated according to arm B)

References:

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2. Wust P, Hildebrandt B, Sreenivasa G, Rau B, Gellermann J, Riess H, Felix R, Schlag PM. Hyperthermia in combined treatment of cancer. Lancet Oncol. 2002 Aug;3(8):487 97.

Sunday, November 13th, 2011
09:55-10:35

The role and measurement of temperature in oncothermia

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Temperature is always a critical issue in the hyperthermia treatment in oncology. There are intensive discussions about its role in the treatment, looking for controlling parameters and well defined treatment goals of clinical oncologic hyperthermia. The doubts about temperature have multiple origins.
Oncothermia is a hyperthermia method, using heat to reach the desired curative effect. The heat-induced processes are the basic of Oncotherm technologies [1], and oncothermia is definitely a kind of hyperthermia. The improvement is basically in the distribution of the heat: oncothermia applies the heat selectively in cellular level, reaching high temperature microscopically at the malignant cell membrane to destroy it.
Compare the different methods is not a simple task. The energy delivery does various changes in the complex living system, which makes the methods incomparable by an only single parameter. The identical energy exposition does not mean same heating efficacy. The heating efficacy depends on the actual conditions [2], [3], and on the organ to be heated [4] as well as the chosen frequency. The temperature is used in most of the cases as a "success parameter" in hyperthermia, trying to equalize it and declare as a measurement of the energy absorption. The temperature shows only the average kinetic energy of the particles and units in the measured target, but it tells nothing about the chemical and structural changes there. However, the aim of the therapy is to reach structural and chemical changes to stop the malignant processes. Nevertheless, the temperature and energy distribution is very different [5], it is not possible to fit the specific