

## **Locoregional hyperthermia in combination with chemotherapy for metastatic breast cancer patients: The Mammatherm- trial**

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## *Abstract*

Treatment options for patients with metastatic breast cancer should be both as effective and preferably as little toxic as possible. However to date there is no standard therapy available but treatment regimens for metastatic breast cancer vary much. Locoregional hyperthermia might show additive effects to chemotherapy due to an increased perfusion and a simultaneous occurring of interstitial acidosis in tumor tissue. Primary objective of the multicenter prospectively randomized phase I/II German Mammatherm-trial is to evaluate if metastatic breast cancer patients regarding progression free survival benefit from locoregional hyperthermia given additionally to a chemotherapy regimen. Phase I of this study was a dose-finding-study for liposomal doxorubicin administered in combination with locoregional hyperthermia. Dose-escalation-levels were at 40/50mg/m<sup>2</sup> and in each level 3 patients had to be treated without showing severe toxicity. The first eligible patient (i.e. metastatic lesions accessible to locoregional hyperthermia) entered the study in August 2007, the last patient was recruited in May 2011. Phase II (recruitment of 300 patients planned) will compare 2 different treatment regimens in a randomized setting: Arm A comprises 6 cycles of liposomal doxorubicin 40mg/m<sup>2</sup> i.v. d1 q22d x 6 and cisplatin 20 mg/m<sup>2</sup> i.v. d1, 8, 15 q22d x 6 in combination with locoregional hyperthermia administered at d1, 4, 8, 11, 15, 18 q22d x 6. In arm B patients are treated according to the same chemotherapy regimen but without adding the hyperthermic treatment. Intentions of the study are that patients in the experimental arm will benefit from locoregional hyperthermia administered additionally to chemotherapy, i.e. that progression free survival as well as overall survival (as secondary study objective) can be prolonged significantly without being accompanied by increased toxicity or reduced quality of life. Final results for phase I are expected by the end of 2012.

**Keywords**— hyperthermia, breast cancer, metastatic treatment, chemotherapy

## *I. Introduction*

Breast Cancer is the most common malignancy of females, responsible for 18% of cancer deaths in women. [1].

Unfortunately, a large proportion of patients develop metastatic disease and require chemotherapy to palliate symptoms and improve quality of life [2]. The median survival in this stage has been reported to be 18 to 24 months for most patients. The treatment is palliative in intent and the goals of treatment include improving quality of life and if possible prolongation of life. Treatment in metastatic cancer will usually involve hormone therapy and/or chemotherapy.

Anthracyclines are among the most active agents used in the treatment of advanced breast cancer, and doxorubicin and epirubicin can achieve response rates of around 20% to 40% (when used as single agents) and up to 60% (as part of combination regimens in the first-line setting) [3].

Various analogues and derivatives of doxorubicin were investigated, with the aim of finding chemotherapeutics with less cardiotoxic characteristics while providing the same, or better, cytostatic efficacy. An alternative approach besides the chemical variation of the agent is the variation of formulation.

Until now, non-pegylated liposomal doxorubicin has been investigated in five phase III studies for the treatment of metastatic breast cancer all showing less cardiotoxicity compared to conventional doxorubicin and equal efficacy. [4], [5], [6], [7], [8], [9].

Concerning combination of liposomal encapsulated doxorubicin and hyperthermia Merlin showed already in 1993 that Thermosensitive liposome-encapsulated doxorubicin (TLED) yielded additive effects in the resistant cells while potentiation was observed in the sensitive cells, proclaiming that the possibility of obtaining additive cytotoxicity using TLED combined with hyperthermia may represent an alternative way of intensification of doxorubicin cytotoxicity [9].

The origin of hyperthermia dates back to experiences in ancient days, when it was observed that endogenous fever had an antiproliferative effect on tumor growth. Since the second half of the 20<sup>th</sup> century, the methods of inducing hyperthermia are mainly based on the administration of exogenous energy. Since the 1930's, the hyperthermic water bath has been used as a source of energy (two-chamber hyperthermic tub).

Later, short wave radiation was applied with quartz lamps or various other sources of infra-red radiation. Since the 1980's adverse effects (mainly skin burns) have been decreased and tolerance rates have been improved by filtering the applied radiation either by water or gold-alloyed metal reflectors (wave length 0.75 - 1.40  $\mu\text{m}$ ). This type of filtered infra-red-A radiation is highly equivalent to natural sun-rays under the earth's atmosphere and is therefore better tolerated. Various in-vitro and in-vivo experiments have shown that tumor circulation and oxygenation are increased by higher temperatures while an interstitial acidosis occurs [10], [11], [12].

Several conditions might contribute to a potentially improved antiproliferative efficacy of cytostatic drugs combined with hyperthermia:

- Higher concentrations of the cytostatic drugs can be found in the regions of tumor, even in case of decreased perfusion.
- Cytostatic potency of various cytostatic drugs such as cisplatin, ifosfamide, doxorubicin and bleomycin is increased [13], [14], [15].
- The uptake of cisplatin into the intracellular space can be improved under hyperthermic conditions [16].
- Sensibilisation of previously cisplatin-resistant cells under hyperthermic conditions was shown [17].
- Under hyperthermia significantly higher concentrations of tumor necrosis factor and interleukins were observed [18].

In randomized clinical trials the addition of hyperthermia to radiation in advanced breast cancer was associated with improved outcome [19], [20]. To our knowledge so far there are no randomized clinical trials evaluating the effect of a combination of hyperthermia and chemotherapy in breast cancer.

## ***II. Patients and methods***

In this open-label, multicenter phase I / II study a total of 310 patients with metastatic breast cancer will be randomized into the experimental treatment group receiving chemotherapy in combination with locoregional hyperthermia or the control group receiving the same chemotherapeutic regimen but without hyperthermic treatment.

In order to assure adequate toxicity assessment, a phase-I-trial was preplanned: At each dosage escalation level (Myocet 40 or 50  $\text{mg}/\text{m}^2$ ) 3 patients had to be treated and complete 4 treatment

cycles according to the protocol arm B without any severe side effect or dose limiting toxicity (DLT).

Primary objective of the study was to compare the time to progressive disease (TTPD) in a target volume amenable to locoregional hyperthermia in patients treated with liposomal-encapsulated Doxorubicin (Myocet®) and Cisplatin (MC) chemotherapy versus MC-chemotherapy combined with locoregional hyperthermia.

Secondary objectives of the study are to compare the following items in the two regimen arms:

- Response rate
- Survival time after randomisation
- Toxicity
- Changes in quality of life over time as defined by EORTC QLQ-C30 and QLQ-BR23 questionnaire

The first patient was recruited in August 2007, the last patient entered the study in May 2011. After final analysis of the phase I the study will proceed into phase II.

In phase II 300 patients will be randomized into two treatment groups: The experimental arm will comprise a regimen of 6 cycles of liposomal-encapsulated Doxorubicin 40mg/m<sup>2</sup> i.v. body surface area administered on day 1, repeated on day 22 and Cisplatin 20mg/ m<sup>2</sup> i.v. administered on day 1, 8 and 15, repeated on day 22 combined with locoregional hyperthermia d1, 4, 8, 11, 15, 18, repeated on day 22. In the control group patients will receive the same chemotherapy regimen without hyperthermia.

Application of locoregional hyperthermia will be performed either by capacitive hyperthermia (Oncotherm®) or by Radiofrequency hyperthermia (BSD 2000® by the BSD Medical Corp.)

### III. Results

Intentions of the study were to show in phase I that metastatic breast cancer patients can be treated with a combination therapy of chemotherapy and locoregional hyperthermia without severe toxicities. Phase II will evaluate if patients in the experimental arm benefitted from locoregional hyperthermia administered additionally to chemotherapy, i.e. that progression free survival as well as overall survival (as secondary study objective) can be prolonged significantly without being accompanied by increased toxicity or reduced quality of life. Final results for phase I are expected by the end of 2012.

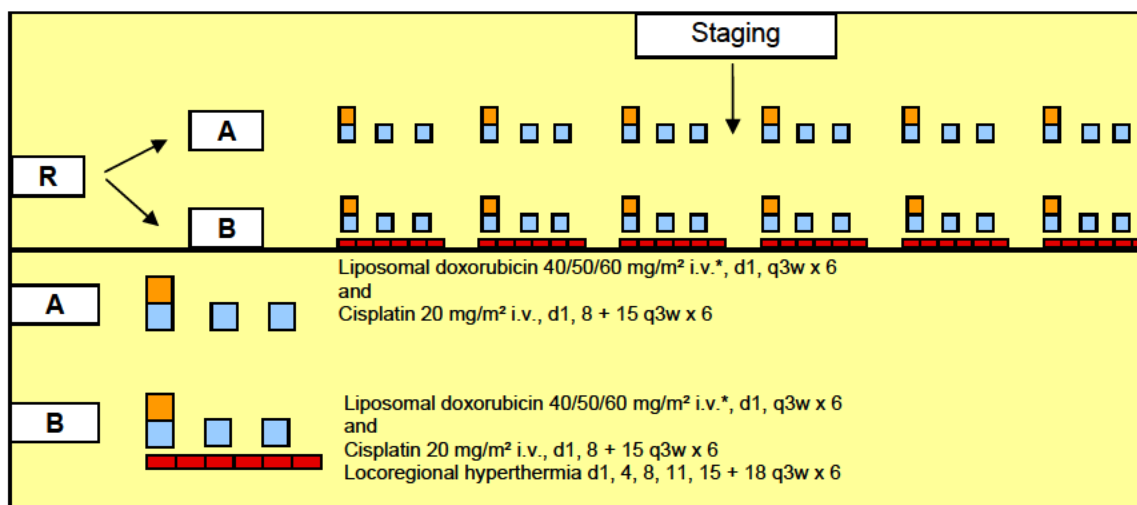


Figure 1. Design of the Mammatherm-trial

## ***IV. Conclusions***

Phase I of the Mammatherm-trial will show if a combination treatment of chemotherapy and locoregional hyperthermia is feasible and shows a tolerable toxicity profile in metastatic breast cancer patients. Phase II of the trial will evaluate if those patients have a prolonged progression free survival by adding locoregional hyperthermia to a chemotherapy regimen.

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