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

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

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Background:
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.

Patients and Methods:
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 is a dose-finding-study for liposomal doxorubicin administered in combination with locoregional hyperthermia. Dose-escalation-levels are at 40/50/60 mg/m^2 and in each level 3 patients have to be treated without showing severe toxicity.

Results:
The first eligible patient (i.e. metastatic lesions accessible to locoregional hyperthermia) entered the study in August 2007. 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 40/50/60 mg/m^2 (final dose to be defined after phase I) i.v. d1 q22d x 6 and cisplatin 20 mg/m2 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.

Conclusions:
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. First results for phase I are expected by the end of 2011.

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

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 - 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 20th 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 µm). 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 - 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 cisplatinum, ifosfamide, doxorubicin and bleomycin is increased.[13-15]
- The uptake of cisplatinum into the intracellular space can be improved under hyperthemic conditions.[16]
- Sensibilisation of previously cisplatinum-resistent cells under hyperthermic conditions was shown.[17]
- Under hyperthermia significantly higher concentrations of tumor necrosis factor and interleucins were observed.[18]

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 is preponed: At each dosage escalation level (Myocet 40, 50 and 60 mg/m^2) 3 patients have to be treated and complete 4 treatment cycles according to the protocol arm B without any severe side effect or limiting toxicity, (see Figure 1.).

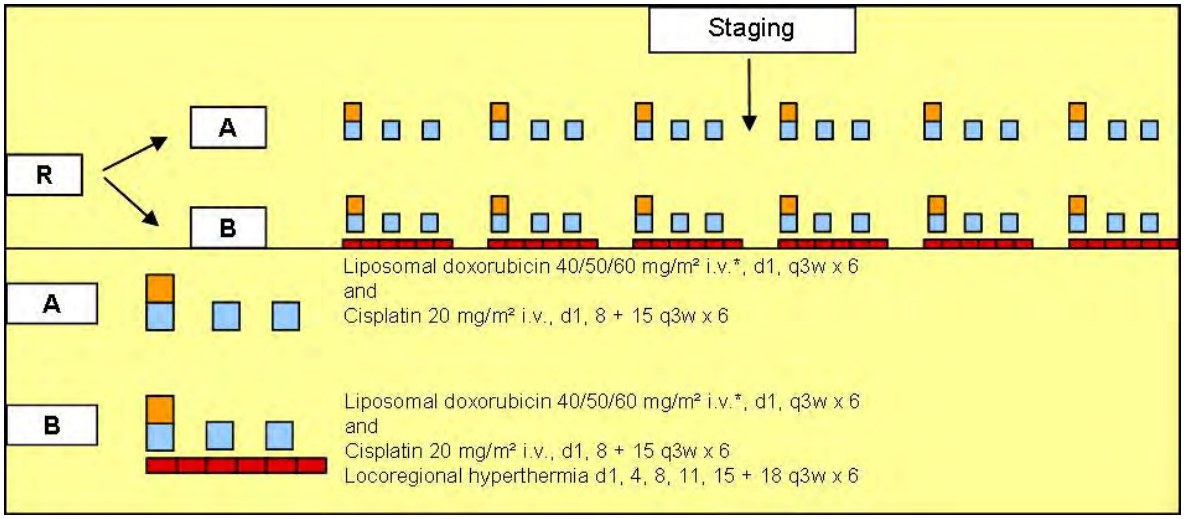

Figure 1. Design of the Mammatherm-trial

Primary objective of the study is 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 and a total of 10 patients will have to be treated without showing severe toxicity until the study can 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 40/50/60 mg/m² i.v. body surface area administered on day 1, repeated on day 22 and Cisplatin 20mg/ m² 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.).

Results

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. First results for phase I are expected by the end of 2011.

Conclusions

The Mammatherm-trial will show if metastatic breast cancer patients have a prolonged progression free survival by adding locoregional hyperthermia to a chemotherapy regimen.

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