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CLINICAL TRIAL REPORT

Phase I dose finding study evaluating the combination of bendamustine with weekly paclitaxel in patients with pre-treated metastatic breast cancer: RiTa trial

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Abstract
Purpose The aim of the RiTa trial is to establish a feasible combination of bendamustine and paclitaxel in a weekly schedule in anthracycline pre-treated metastatic breast cancer patients.
Methods Starting dose of bendamustine was 50 mg/m² and was stepwise increased by 10 mg/m² up to 70 mg/m². The starting dose of paclitaxel was 60 mg/m² and was increased up to 90 mg/m². There are five pre-defined dose levels with three patients per dose level (maximum six patients) and six patients in the last dose level according to the Goodman design. Dose-limiting toxicities were defined as severe neutropenia and thrombocytopenia as well as non-haematological toxicities ≥NCI-CTC grade 3 in the first cycle.
Results No dose-limiting toxicity up to 70 mg/m² bendamustine and 90 mg/m^2 paclitaxel occurred during the first cycle. Over all cycles, the following severe haematological toxicities (grade 3 and 4) were documented: neutropenia five patients and anaemia one patient. Relevant grade 3 and 4 non-haematological toxicities over all cycles were fatigue two patients, dyspnoea one patient, infection four patients and bone pain in one patient. Five serious adverse events, but no therapy related death occurred. Five patients showed a complete or partial remission, six patients stable disease and six progressed during treatment. The median progression-free survival was 8 months.
Conclusion Treatment with weekly bendamustine and paclitaxel is a feasible and effective regimen in patients with metastatic breast cancer. The recommended dose for forthcoming phase II study is 70 mg/m^2 bendamustine and 90 mg/m^2 paclitaxel.

Keywords Bendamustine · Paclitaxel · Breast cancer · Anthracycline free · Phase I

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Introduction

Bendamustine is an anti-neoplastic agent with low toxicity and both alkylating and antimetabolic properties. It is a bifunctional alkylating agent containing a heterocyclic nucleus that induces more long lasting DNA double-strand breaks compared to other alkylating agents [1, 2]. So far, bendamustine has been used in metastatic breast cancer either as single agent or in combination with methotrexate/5-fluorouracil as substitute for cyclophosphamide, anthracycline or vincristine with moderate activity [3, 4]. Since taxanes are among the most effective agents for the treatment of metastatic breast cancer, it might be an interesting combination.

Bendamustine as monotherapy has been evaluated using the following regimens: regimen with bendamustine 120 or 150 mg/m² [4–6] given on day 1 and 2 of a 4-week cycle; regimen where bendamustine was given on day 1 and 8 of a 4-week cycle [7, 8]; regimen with weekly bendamustine 60 mg/m². Efficacy did not differ between the treatments but haematotoxicity was less prominent with the regimen used by Eichbaum and colleagues. Weekly regimen of paclitaxel in metastatic breast cancer has become quite popular because of its better toxicity profile and effectivity [9].

In search for new anthracycline-free combinations, paclitaxel as an alternative to docetaxel and bendamustine as an alternative to cyclophosphamide might be worth to investigate. However, both the drugs are used with a variety of schedules and doses, therefore this phase I study was conducted to evaluate the appropriate dose of weekly bendamustine and paclitaxel as first or second line therapy in patients with metastatic breast cancer after anthracycline pre-treatment.

Methods

Patients aged 18 years or older with histologically confirmed breast cancer with locally advanced or distant metastases and up to one prior chemotherapy for metastatic disease were eligible. Pre-treatment with anthracycline, but not with taxane, was allowed. Hormone therapy in the adjuvant or metastatic setting was permitted provided it was discontinued at least 4 weeks prior to study entry. Patients were required to have a Karnofsky performance status of ≥60%, measurable or non-measurable disease according to WHO and absence of severe organ and haematological dysfunction (serum creatinine ≤2 mg/dl, GPT, bilirubin ≤1.5 × ULN, in the presence of liver metastases ≤5 × ULN, WBC ≥1,500/mm³, haemoglobin ≥9 g/dl, platelets ≥100,000/mm³) and life expectancy ≥3 months.

All patients gave written informed consent that was approved by the local ethical authorities. The study was conducted according to the Helsinki Declaration.

Baseline evaluation included patient history, physical evaluation, haematology, biochemistry, cardiac function (by echocardiogram and ECG), bone scan and evaluation of indicator lesion (preferably by CT scan, alternatively by X-ray or ultrasound). During therapy haematology was performed weekly and biochemistry before each cycle. ECG or echocardiography was performed as clinically indicated. Tumour response was evaluated every other cycle and at the end of the study.

Treatment was given on an outpatient basis and was planned for up to six cycles unless there was evidence of disease progression, unacceptable toxicity, or patient refusal.

Bendamustin (Ribomustin™) was supplied by Ribosepharm and applied as infusion in 500 ml normal saline over 30–60 min on days 1, 8, and 15 of every 4-week cycle.

Paclitaxel was given as infusion over 30 min on days 1, 8, and 15 every 4 weeks (Table 1).

A prophylactic treatment with steroids, 5HT3-agonists, and H1and H2 blocker was recommended to prevent nausea, emesis and hypersensitivity reactions. In case of hypersensitivity, a guideline for re-challenge of paclitaxel after hypersensitivity reaction was provided.

Toxicity was assessed according to National Cancer Institute Common Toxicity Criteria Version 2.0 (NCI-CTC v2).

Dose escalation was carried out according to Table 1 with doses being assigned at study entry, starting at level 1. No intra-patient dose-escalation was allowed. The decision for dose escalation was based on toxicity observed in cycle one.

The classical phase I design is chosen according to Goodman et al. [10]. The doses of both the drugs were escalated in five dose levels with at least three patients per dose level (six patients in the last dose level). If the dose cannot be escalated to the maximum dose level, the trial had to be terminated earlier. When a dose-limiting toxicity (DLT) is observed during the first cycle, the level is enlarged to six patients. If a DLT is observed during the first cycle in only one of the six patients, the next dose level is started. If two DLTs are observed in six patients, the previous dose level is filled up to six patients. The maximal tolerated dose (MTD) is established with a maximum of one DLT in six patients. It is estimated that this part of the trial will require 6–18 patients.

According to general conventions for phase I trials, that define treatment related non-haematological toxicitiy ≥grade 3 and/or treatment related haematological toxicities ≥grade 4 as dose limiting, the dose-limiting toxicities have been defined as follows: ANC < 0.5 × 10^9/l > 7 days, ANC < 0.1 × 10^9/l > 3 days, ANC < 1.5 × 10^9/l on day 42, febrile neutropenia (e.g. fever > 38.2°C and ANC < 0.5 × 10^9/l) and/or antibiotics and/or hospitalisation are necessary,

Table 1 Flowchart of the trial from levels 1–5

Level	Treatment	Dose (mg/m^2)	Application	Number of patients
Level I	Bendamustine Paclitaxel	50 60	Day 1, 8,15 q28	3–6
Level II	Bendamustine Paclitaxel	60 60	Day 1, 8,15 q28	3–6
Level III	Bendamustine Paclitaxel	60 80	Day 1, 8,15 q28	3–6
Level IV	Bendamustine Paclitaxel	70 80	Day 1, 8,15 q28	3–6
Level V	Bendamustine Paclitaxel	70 90	Day 1, 8,15 q28	6

thrombocytopenia >25 × 10^9/l or <100 × 10^9/l on day 42, and non-hematological toxicities ≥NCI-CTC grade 3 (except nausea/emesis and alopecia).

The sample size of at least three patients per dose level was chosen according to the classical 3 + 3 design which has been approved in many phase I designs. The possibility to miss a severe toxicity with a 75% probability is only 1.6%. A toxicity which is actually occurring in every second patient could be missed with a probability of 12.5% [11]. The need for six patients in the level of the MTD refers to a probability of a type I and type II error of <0.1% and 1.6%, respectively.

Response was defined according to WHO criteria. Osteolytic lesions documented by X-ray were considered evaluable but not measurable.

The progression-free survival (PFS) was calculated from the date of registration until tumour progression or death had occurred. Patients with no event were censored at the time of the last contact.

Trial Registration Number is NCT00661739 (clinicaltrials.gov).

Results

In the study period, from February 2005 to January 2006, a total of 18 patients were treated with bendamustine and paclitaxel as first or second line for metastatic breast cancer.

The median age was 62 years (range 38–77). The majority of patients had a performance status of ≥90%. Visceral disease was present in all but one patient, liver metastases in 15 (83.3%) of the 18 patients. Ten of the 18 patients had anthracycline pre-treatment either as an adjuvant or a metastatic treatment (Table 2).

Treatment

In total, 95 cycles of 108 planned cycles have been applied to the 18 patients. The median number of cycles per patient is six. In dose level 5, five patients received all planned six cycles and one patient stopped after four cycles. Overall seven patients discontinued the trial prematurely, one patient had a complete remission after the fourth cycle which was confirmed after the fifth cycle and she refused to receive the sixth cycle. Four patients stopped due to progressive disease, one patient due to side effects and one due to other reasons.

Toxicity

All 18 patients were fully evaluable for toxicity analysis. There were no dose-limiting toxicities observed, neither in the first nor in the second cycle as defined in the protocol.

Table 2 Patients characteristics

Age (years)		
mean	58.5	
median	62	
Minimum, Maximum	38, 77	
Age not known (number of patients)	0	
	N	%
Age categories		
<65 years	14	70.0
65 to <70 years	4	20.0
≥70 years	2	10.0
Karnofsky index		
100%	10	55.6
90%	4	22.2
80%	4	22.2
ER/PgR		
ER and/or PgR positive	14	77.8
ER and PgR negative	4	22.2
Her2 status		
Her2 positive	1	6.7
Her2 negative	14	93.3
Not known	3	
Pretreatment		
Adjuvant anthracycline-containing chemotherapy[a]		
Yes	6	40.0
No	9	60.0
Not known	3	
Palliative chemotherapy		
Anthracycline-containing	4	26.7
Non-athracycline	4	26.7
None	7	46.7
Not known	3	
Anthracycline-containing chemotherapy, adjuvant or/and palliative		
Yes	7	46.7
No	8	53.3
Not known	3	
Palliative endocrine therapy[a]		
Tamoxifen	3	20.0
AI	8	53.3
GnRH-analoga	1	6.7
Others[b]	2	13.3
None	6	40.0
Not known	3	
Palliative radiotherapy		
Yes	5	33.3
No	10	66.7
Not known	3	
Metastatic site[a]		
Primary tumour	1	5.6

Table 2 continued

Liver	15	83.3
Lung	4	22.2
Pleura	1	5.6
Bone	10	55.6
Lymphatic nodes	9	50.0
Others	1[c]	5.6
Number of metastatic sites		
Multiple sites	15	83.3
Single site	3	16.7
Metastatic site, dichotomised		
Low risk[d]	2	11.1
High risk	16	88.9

[a] The sum is exceeding 100% since one patient could have more than one metastatic site or palliative endocrine treatment

[b] Fulvestrant

[c] Chest wall

[d] No visceral metastases or lung metastasis only

All percents are valid percents

Toxicities per patient or per cycle were not different between the dose levels. Haematological toxicities seen in the different dose levels are outlined in Table 3. Leucopenia and neutropenia were the most common toxicities. Grade 3–4 leucopenia and neutropenia was observed in 5/18 and 6/18 patients, respectively, but none of the patients developed febrile neutropenia and no G-CSF use was necessary. Anaemia and thrombopenia were generally mild (Figs. 1, 2).

Non-haematological toxicities were generally mild and infrequent and not dose-level dependent. One patient with liver metastases developed hyperbilirubinemia, and three patients with liver metastases increased liver enzymes grade 3. Fatigue grades 3–4 (one patient grade 4) was observed in two patients in level one and two in a later cycle. One patient developed hypocalcaemia grade 4 in dose level 5. Alopecia grade 1 or 2 was observed in 13 of the 18 patients (Fig. 3).

Table 3 Toxcity over all cycles and dose levels

	DL1	DL2	DL3	DL4	DL5	Overall
Leucopenia 1–4	3	3	3	3	6	18
Leucopenia 3–4	1	0	3	1	1	6
Neutropenia 1–4	1	0	3	1	6	11
Neutropenia 3–4	0	0	2	1	2	5
Febrile neutropenia 3–4	0	0	0	0	0	0
Thrombopenia 1–4	1	1	2	0	0	4
Thrombopenia 3–4	0	0	0	0	0	0
Anaemia 1–4	3	3	3	3	6	18
Anaemia 3–4	0	1	0	0	0	1

DL dose level

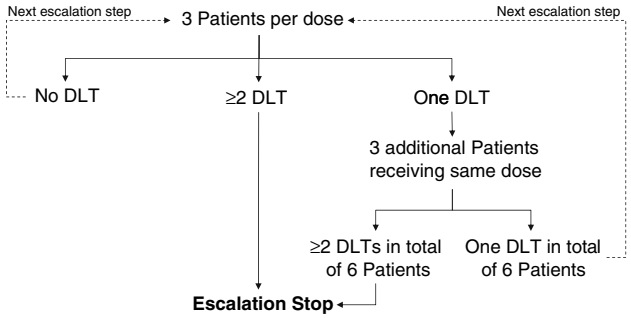

Fig. 1 Dose escalation schedule

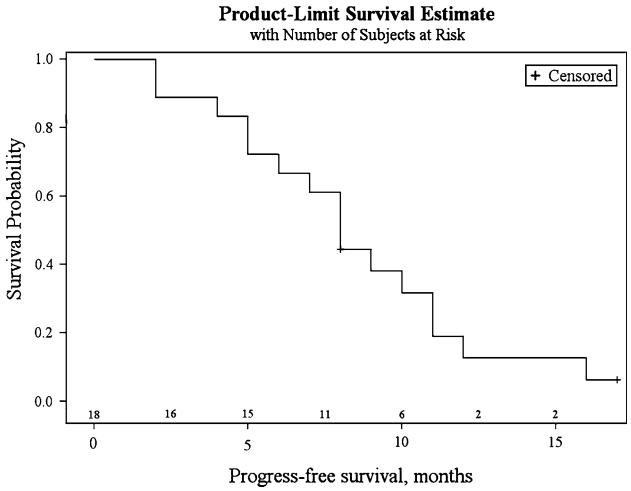

Fig. 2 Kaplan–Meier plot depicting progression-free survival

Efficacy

Seventeen of the 18 patients were evaluable for response. Responses were seen at all dose levels. Five of the 17 evaluable patients (27.8%) showed partial or complete response. Partial responses ($n = 4$) were observed in dose level one, two and five; the complete ($n = 1$) remission in dose level three. Six patients had stable disease at the end of therapy lasting for more than 24 weeks and six patients progressed during therapy. The median progression-free survival was 8 months [95% CI: 6.0–11.0] with a median follow-up of 13 months (range 4–29 months). The median overall survival has not been reached yet.

Discussion

The present study with bendamustine and paclitaxel is the first, combining the two cytotoxic drugs with different modes of action. The previous phase II trials with bendamustine as monotherapy in metastatic breast cancer reported mainly haematological toxicities grade 3–4 in

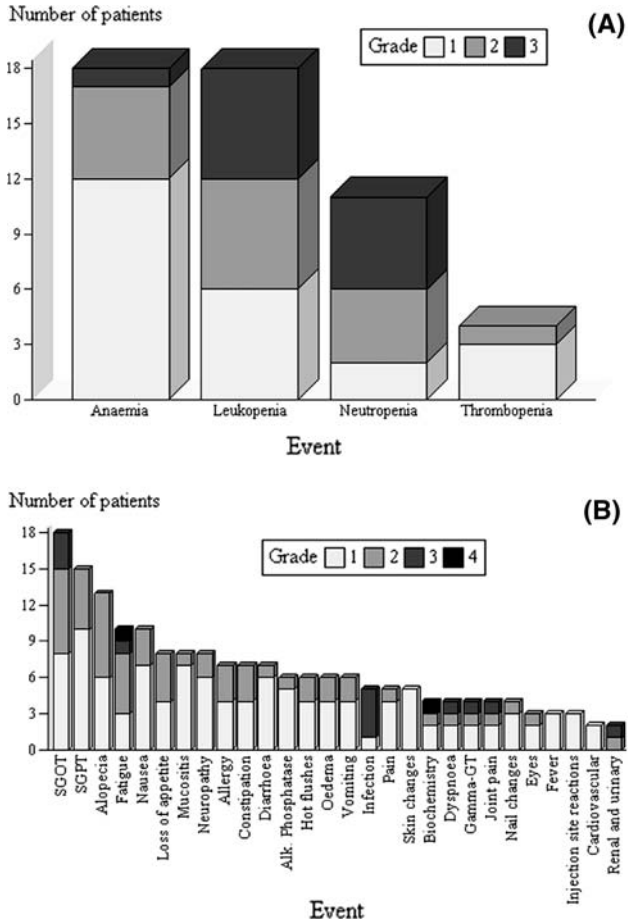

Fig. 3 Haematological (**a**) and non-haematological (**b**) toxicities per patient over all dose levels

about 17% of the patients, when given on day 1 and 2, whereas with the weekly regimen of 60 mg/m² no grades 3 and 4 hematological toxicities could be observed. Paclitaxel as weekly regimen is well established in the therapy of breast cancer because of its efficacy and feasibility especially in metastatic breast cancer [12]. Therefore, for the combination of bendamustine with paclitaxel, the weekly regimen with a week of rest after three applications has been chosen.

The combination is feasible with no dose-limiting toxicities as those defined in the protocol in the first and second cycle of the treatment. Haematological toxicities, especially neutropenia were common but not complicated and did not need the use of G-CSF. Non-haematological toxicities were generally mild. None of the toxicities was dose-level dependent. All planned cycles that could be applied were 88%. Responses were seen at all dose levels leading to a progression-free survival of 8 months.

The strength of the trial is that the combination partners have been chosen according to their toxicity profile of the single agent. Paclitaxel causes few haematological toxicities and different non-haematological side effects compared to bendamustine and is therefore the preferred taxane in this setting. Docetaxel is used with 100 mg/m² as monotherapy but in combination with other agents like capecitabine, carboplatin or gemcitabine the dosage has to be reduced to 75 mg/m². Some trials could therefore not demonstrate superiority in terms of efficacy for the combination with docetaxel compared to the monotherapy [13, 14]. There are several different studies combining paclitaxel with cyclophosphamide using a 3-week schedule and G-CSF support. Febrile neutropenia and severe thrombocytopenia defined the maximum tolerated dose of paclitaxel 200 mg/m² and cyclophosphamide 2,000 mg/m² every 3 weeks, but the response rate is comparable with those observed in our phase I study [15]. However, for a combination regimen it is the optimum if the agents can be combined without compromise on the doses due to toxicity. Bendamustine at the dose of 70 mg/m² and paclitaxel at the dose of 90 mg/m² are exceeding the established doses of both the drugs used for monotherapy. The combination of bendamustine and paclitaxel might be an option for elderly patients as well. Six (33%) of the 18 patients in this study were 65 years of age or older. The weekly schedule of paclitaxel was evaluated in elderly patients demonstrating no difference in terms of efficacy and tolerability between patients above or below the age of 65 years [16]. A Dutch study evaluated the activity and toxicity of weekly paclitaxel as first-line chemotherapy in elderly patients (>70 years of age) with hormone-refractory metastatic breast cancer. Paclitaxel (80 mg/m²) was administered weekly on days 1, 8 and 15 of a 28-day cycle. A dose increase to 90 mg/m² was allowed in the absence of toxicity. Overall treatment was relatively well tolerated; eight patients (32%) had to prematurely discontinue treatment because of fatigue [17]. Nevertheless bendamustine in combination with paclitaxel might be an option for elderly patients and should be further evaluated.

The trial has several limitations. One can argue that the chosen design for phase 1 studies is not sufficient because it only evaluates toxicities seen in the first cycle. The classical 3 + 3 design would take into account the toxicities of at least a minimum of two cycles. However, retrospectively there are no additional DLTs in the second cycle, but leucopenia grades 3–4 have occurred in the cycles 2–5. Therefore, we did not further increase the doses after the fifth level as set in the protocol.

The combination of bendamustine and paclitaxel has a tolerable toxicity profile and seems to be an effective treatment for metastatic breast cancer patients. A response rate of 25% is sufficient to start a phase II study to obtain more information about the efficacy of the combination in this setting. Per definition the MTD has not been reached and the toxicity profile does not differ between the dose levels 3–5. Therefore, the forthcoming phase II study for Her-2 negative patients will be conducted using bendamustine

70 mg/m² and paclitaxel 90 mg/m² as the recommended dose found in this phase I study.

In the adjuvant setting, the anthracycline free combination docetaxel in combination with cyclophosphamide (TC) could demonstrate to be superior to standard AC with the possibility to spare cardiotoxicity. Paclitaxel plus bendamustine in a weekly setting might be an even more efficacious and tolerable anthracycline free combination and is therefore worth to be further explored [18].

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