Multicenter Phase II Study with Weekly Bendamustine and Paclitaxel as First- or Later-Line Therapy in Patients with Metastatic Breast Cancer: RiTa II Trial

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Keywords

Bendamustine · Paclitaxel · Breast cancer, metastatic · Efficacy · Combination therapy · First-line chemotherapy

Summary

The combination of bendamustine (B) and paclitaxel (P) as anthracycline-free treatment option in patients with advanced breast cancer has been evaluated in the previous RiTa I trial. The regimen of weekly B 70 mg/m² and P 90 mg/m² with a pause every 4th week was established as an effective regimen with low toxicity. The aim of the present RiTa II study was to investigate the potential of BP as anthracycline-free combination therapy. The primary objective was to determine the progression-free survival (PFS); secondary endpoints were safety, tolerability, overall response rate (ORR) and overall survival (OS). 26 patients were available, 15 received BP as first-line, 11 as beyond first-line treatment. 27% patients had triple-negative breast cancer (TNBC). Median PFS and OS were 7.3 months (95% confidence interval (CI): 5.5–10.9) and 14.9 months (95% CI: 9.9–22.9), respectively. The 1-year PFS rate was 20.3% and the 1-year OS rate 71.2%. The ORR was 42.3%, including 4 complete and 7 partial remissions. TNBC patients reached an ORR of 71.4%. Anthracycline-pretreated patients showed an ORR of 43.8%, confirming bendamustine's lack of cross-resistance to anthracycline agents. BP represents a favorable option with moderate toxicity in pretreated metastatic breast cancer and offers a possibility for application in anthracycline-pretreated and TNBC patients.

Schlüsselwörter

Bendamustin · Paclitaxel · Mammakarzinom, metastasiertes · Wirksamkeit · Kombinationschemotherapie · Erstlinien-Chemotherapie

Zusammenfassung

Die Kombinationstherapie von Bendamustin (B) mit Paclitaxel (P) bei Patienten mit fortgeschrittener Brustkrebs-erkrankung wurde in der vorausgegangenen RiTa-I-Studie geprüft. B 70 mg/m² und P 90 mg/m² mit einer Behandlungspause jede 4. Woche erwies sich als ein effektives Behandlungsregime mit moderatem Nebenwirkungsprofil. Ziel der RiTa-II-Studie war es, das Potenzial von BP als anthracyclinfreie Kombination zu prüfen. Primäres Zielkriterium war die Bestimmung des progressionsfreien Überlebens (PFS), sekundäre Studienziele waren Sicherheit, Verträglichkeit, Gesamtansprechrate (ORR) und Gesamtüberleben (OS). 26 Patientinnen standen für die Evaluation zur Verfügung, 15 Patientinnen erhielten BP als Erstlinientherapie, 11 in weiterer Behandlungslinie. 7 Patientinnen (27%) hatten ein tripel-negatives Mammakarzinom (TNBC). Das mediane progressionsfreie Überleben (PFS) und das Gesamtüberleben betrugen 7,3 Monate (95% Konfidenzintervall (CI): 5,5–10,9) bzw. 14,9 Monate (95% CI: 9,9–22,9). Die PFS- und OS-Rate nach 1 Jahr betrugen 20,3% bzw. 71,2%. Die ORR lag bei 42,3% (darunter 4 Patientinnen mit kompletter und 7 mit partieller Remission). Tripel-negative Patientinnen erreichten eine ORR von 71,4%. Die ORR bei anthracyclin-vorbehandelten Patientinnen lag bei 43,8%, was eine fehlende Kreuzresistenz von Bendamustin zu anthracyclinhaltigen Substanzen bestätigt. Bei fortgeschrittener Brustkrebs-erkrankung bietet die Kombinationstherapie mit BP bei moderatem Nebenwirkungsprofil die Möglichkeit, eine Tumoresistenz zu überwinden, und stellt eine Therapieoption für anthracyclinvorbehandelte sowie TNBC-Patienten dar.

Introduction

In search for effective treatment schedules with anthracycline-free agents, bendamustine in combination with paclitaxel was investigated as an alternative to cyclophosphamide.

Bendamustine is an anti-neoplastic agent with low toxicity and both alkylating and antimetabolic properties. It combines a bifunctional alkylating nitrogen mustard derivative and a purine-like benzimidazol and 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 monotherapy or in combination with methotrexate/5-fluorouracil as substitute for cyclophosphamide or an anthracycline or vincristine with moderate activity [3–8]. Since taxanes are amongst the most effective agents for the treatment of breast cancer, another anthracycline-free combination chemotherapy in addition to docetaxel/cyclophosphamide or capecitabine/vinorelbine might be of interest [9, 10]. In the adjuvant setting, the combination of docetaxel with cyclophosphamide (TC) demonstrated to be superior to standard doxorubicin and cyclophosphamide (AC), with the possibility to spare cardiotoxicity [11]. In the preceding RiTa I phase I trial with bendamustine at a dose of 70 mg/m² and paclitaxel at 90 mg/m² in a weekly setting, the tolerable toxicity profile was evaluated, resulting in an overall response rate (ORR) of 27.8% [12]. To obtain more information about the efficacy of the established dose, this phase II study was conducted.

Patients and Methods

Inclusion criteria were transferred from the RiTa phase I trial [12]: patients with locally advanced or distant metastasis of confirmed breast cancer and up to 1 prior chemotherapy for metastatic disease, Karnofsky performance status (KI) $\geq$ 60%, measurable or non-measurable lesions according to World Health Organization (WHO) criteria for response, normal left ventricular ejection fraction by echocardiography, and absence of severe organ or hematological dysfunction were eligible. After an amendment, pretreatment with anthracycline-containing chemotherapy was not compulsory. As established in RiTa phase I, the patients received 70 mg/m² bendamustine (Ribomustin®, Mundipharma GmbH, Limburg/Lahn, Germany) applied as intravenous (i.v.) infusion and paclitaxel 90 mg/m² as i.v. infusion, both on days 1, 8, and 15 every 4 weeks, given for 6 cycles unless evidence of disease progression, unacceptable toxicity or patient's wish [12].

Study Design

This was a prospective, multi-center, open label, non-randomized phase II study conducted in compliance with the Good Clinical Practice Guidelines of the International Conference on Harmonization and approved by the competent authorities and the ethical committee. Written informed consent was obtained from each patient before enrolment. The trial registration number is NCT00661739. Investigations during chemotherapy and response evaluation were performed according to the RiTa I trial [12].

Statistical Analysis

The primary objective was to determine the progression-free survival (PFS) defined as the time interval in months from the date of registration

until tumor progression or death due to any cause. Patients who did not experience disease progression or death were censored at the date of the last contact. Secondary objectives were to determine the safety and tolerability of the combination, ORR, overall survival (OS), and duration of response. PFS, duration of response, and OS were analyzed using the Kaplan-Meier product-limit method and are presented graphically. The median time to event and the 1-year event-free rate were reported together with the 95% confidence interval (CI) based on the log-log transformation (SAS® version 9.2) and a two-sided significance level of 0.05.

The primary analysis was performed using the intention-to-treat (ITT) population, which included all patients registered and started with the therapy. Patients treated with the maximum tolerated dose (MTD) in phase I were included in the efficacy evaluation. In addition, a per-protocol analysis was conducted, which excluded those patients who did violate 1 or more inclusion or exclusion criteria. To exclude a progression-free rate of 17.7% at 1 year with $\alpha = 0.05$ and power 80%, 48 patients were required. The null hypothesis of 4.8 months median PFS was rejected since the 95% CI for the median PFS does not include 4.8 months. The study was closed prematurely after 20 patients were enrolled because of slow enrolment.

Results

Patient Characteristics

A total of 26 patients were enrolled in this phase II study, with inclusion of 20 patients from January 2009 to December 2009 and 6 patients from November 2006 to February 2007 who received the MTD in the phase I study. The median age was 63 years (range 43–85 years). At the time of study registration, the majority of the recruited patients had more than 1 site of metastasis (73%). The most frequent localizations were liver (42%), lymph nodes (42%), lung (39%), and bone (35%). The patient characteristics are given in table 1. 69.2% (n = 18) of the patients were pretreated with adjuvant chemotherapy and 11 patients had received first-line chemotherapy (table 2).

Efficacy Results

As demonstrated in figure 1, the median PFS was 7.3 months (95% CI: 5.5–10.9), with a median follow-up of 14 months. The 1-year PFS rate was 20.3%. Median OS was 14.9 months (95% CI: 9.9–22.9) (fig. 2) and the 1-year OS rate was 71.2%. In a post-hoc analysis, PFS and OS were determined in the subgroup of patients with triple-negative breast cancer (TNBC), who showed a median PFS of 6.8 months (95% CI: 1.9–9.4) and a median OS of 9.9 months (95% CI: 6.0–22.9). PFS and OS Kaplan-Meier-plots are given in figures 3 and 4.

For response, 25 patients were evaluable. As shown in table 3, the ORR was 42.3%. 4 patients (15.4%) achieved a complete response and 7 patients (26.9%) a partial response, stable disease was observed in 9 patients (34.6%), in 7 patients lasting for 24 weeks or longer, resulting in a clinical benefit rate of 69.2%. Primary progression was observed in 5 patients (19.2%). In the subgroup of TNBC (n = 7), in 3 patients (42.9%) a complete and in 2 patients (28.6%) a partial response was achieved (ORR of 71.4%), 1 patient had

progressive disease and 1 patient was not evaluable. Regarding the subgroup of anthracycline-pretreated patients (n = 16), the ORR was 43.8% (3 patients with complete, 4 patients with partial response, and 4 patients with stable

disease), summing up to a clinical benefit rate of 56.3%. In 31.3% (5 patients) progressive disease was observed. The response of the subgroups is shown in table 3. The median follow-up was 14 months.

Table 1. Patient characteristics at baseline

Baseline parameter	
Age, years	
Median	63.0
Minimum, maximum	43.0, 85.0
	n (%) ^a
Age, years, categories	
<65	16 (61.5)
65–69	7 (26.9)
≥70	3 (11.5)
Karnofsky index	
50%	1 (3.8)
60–80%	5 (19.2)
90–100%	20 (76.9)
ER/PgR	
ER and/or PgR positive	17 (65.4)
Both ER, PgR negative	9 (34.6)
HER2 status	
Positive	2 (7.7)
Negative	19 (73.1)
Not known	5 (19.2)
Triple negative	7 (26.9)
Metastatic site ^b	
Visceral	22 (84.6)
Non-visceral	11 (42.3)
Pleura	6 (23.0)
Bone	9 (34.6)
Lymph node	11 (42.3)
Other	7 (26.9)
Number of metastatic sites	
Multiple sites	19 (73.1)
Single site	7 (26.9)
Metastatic site, dichotomized	
Low risk ^c	4 (15.4)
High risk	22 (84.6)

^aAll percent values are valid percents.

^bThe sum is not 100% since 1 patient can have lesions with different locations.

^cDefined as no visceral metastasis or lung only.

ER = Estrogen receptor, PgR = progesterone receptor.

Table 2. Cancer pretreatment

Pretreatment	n (%)
Adjuvant chemotherapy	
Anthracycline-containing	3 (11.5)
Taxane- and anthracycline-containing	10 (38.5)
Non-anthracycline and non-taxane: 4 × CMF, 1 × CM	5 (19.2)
None	8 (30.8)
Palliative chemotherapy	
Anthracycline-containing	2 (7.7)
Taxane-containing	1 (3.8)
Taxane- and anthracycline-containing	1 (3.8)
Non-anthracycline and non-taxane (4 × capecitabine, 1 × CMF, 2 × vinorelbine)	7 (26.9)
None	15 (57.7)
Adjuvant endocrine therapy	11 (42.3)
Palliative endocrine therapy	9 (34.6)
Palliative radiotherapy	6 (23.1)

CMF = Cyclophosphamide, methotrexate and 5-fluorouracil, CM = cyclophosphamide, methotrexate.

Fig. 1. PFS in months for all treated patients (n = 26). Events: 17, censored: 9, median time: 7.3 months; 1-year PFS rate: 20.3%.

Fig. 2. OS in months for all treated patients (n = 26). Events: 13, censored: 13, median time: 14.9 months; 1-year OS rate: 71.2%.

Fig. 3. PFS in months for TNBC. Median time: 6.8 months vs. 7.9 months compared with non-TNBC patients.

Fig. 4. OS in months in TNBC. Median time to progression: 9.9 months vs. 15.5 months compared with non-TNBC patients.

Table 3. Response rates (n = 26)

	Response, n (%)					
	CR	PR	CR or PR	NC	PD	Not evaluable
Overall (n = 26)	4 (15.4)	7 (26.9)	11 (42.3)	9 (34.6)	5 (19.2)	1 (3.8)
Anthracycline pretreated (n = 16)	3 (18.8)	4 (25.0)	7 (43.8)	4 (25.0)	5 (31.3)	–
Triple negative (n = 7)	3 (42.9)	2 (28.6)	5 (71.4)	–	1 (14.3)	1 (14.3)

95% exact CI for the overall rate of patients with complete or partial response (23.4%, 63.1%).

CR = Complete response, PR = partial response, NC = no change (stable disease), PD = progressive disease.

Safety Results

A total of 122 cycles of bendamustine and paclitaxel were administered to 26 patients, with a median number of 6 cycles (range 1–6 cycles) per patient, including 16 (61.5%) patients who received all 6 cycles.

During study treatment, 10 patients (38.5%) discontinued therapy, 4 because of progression of disease, 3 patients due to an adverse event (exanthema, reduced general condition, and one patient only missing the last dose of the last cycle, who discontinued due to leukopenia and abdominal pain), and 2 patients died due to tumor progression. 1 discontinuation was due to the patient's wish. A dose delay was reported in 34 (27.9%) of 122 administered cycles, in 22 cycles due to hematological, in 2 cycles due to non-hematological toxicity, in 7 cycles due to administrative reasons, and in 5 cycles because of an adverse event. 2 delays were due to the patient's wish.

In 80.8% (21 patients), the assigned dose was given without reduction, in 4 patients dose reduction was necessary due to hematological toxicity and there was 1 dose reduction due to other reasons. Hematologic toxicities grade 3–4 were observed in 50% (1 case referring to febrile neutropenia, others to leucopenia and/or neutropenia).

The most common grade 3–4 non-hematologic toxicities were infection in a total of 4 patients (16%) and fatigue in 4 patients (16%), cardiac event in 2 patients (8%), dyspnea in 2 patients (8%) and fever in 2 patients (8%), whereas grade 3–4 nausea, loss of appetite, allergic reaction, mucositis, or sensory neuropathy were reported in only 1 patient each (4%).

Discussion

The present study investigated the potential of bendamustine plus paclitaxel. Based on previous phase I results, it could be demonstrated that the combination of bendamustine and paclitaxel is very effective as first- or second-line treatment for patients with metastatic breast cancer. Previous phase II studies have recommended bendamustine as additional agent for palliative treatment in metastatic breast cancer, using bendamustine as monotherapy [4–7]. Bendamustine in metastatic breast cancer showed, in about 17% of the patients, mainly grade 3–4 hematological toxicities, when given at a dose of 120 mg/m² on days 1 and 2 of a 4-weekly cycle [4], whereas with the weekly regimen of 60 mg/m² no grade 3 and 4 hema-

tological toxicities were observed [6]. Paclitaxel as weekly regimen is well established in the therapy for breast cancer in earlier and advanced stages [9, 10, 13–15], and the toxicity profile of each single agent has no dose-limiting interferences. Therefore, in this study, the regimen of weekly bendamustine and paclitaxel with a week of rest after 3 applications was chosen. The results of bendamustine at the dose of 70 mg/m² and paclitaxel at 90 mg/m² showed an efficacious and tolerable combination, without compromising in dose reductions. An American group in Ohio currently investigates the combination of bendamustine with erlotinib [16]. We found a median PFS of 7.3 months (95% CI: 5.5–10.9), which is significantly higher in comparison with the PFS in the studies of Steinbild et al. [7] and Reichmann et al. [4] (median time to progression (TTP) 4.2 months and 3.4 months, respectively). The median OS was 14.9 months in the RiTa study (95% CI: 9.9–22.9), compared to a median OS of 11.3 months with bendamustine monotherapy [7]. In the phase II study of Reichmann et al. [4], bendamustine as single agent was applied at a dose of 120 mg/m² on days 1 + 2 every 4 weeks. A partial response was described in 20% and stable disease for at least 6 months in 28% of the patients. The phase II study of Steinbild et al. [7] with a fixed flat dose of 200 mg on days 1 and 2 in a 4-week cycle in patients pretreated with 2 or 3 cycles of an anthracycline- and/or taxane-containing chemotherapy showed tumor regression in 16% and stabilization of disease in 22%. In the RiTa II trial, disease control for at least 6 months could be observed in 76.9% of the patients (complete remission in 15.4%, partial response in 26.9%, and stable disease in 34.6%). Whereas with bendamustine monotherapy no complete remission was reported. However, the patients in the other studies were heavily pretreated (with 66.7% having received 2 or more previous regimens) [4]. The collective in our study has received up to 1 chemotherapy regimen in the metastatic situation; therefore, the results are not exactly comparable and inter-trial comparisons have to be done with caution. In a post-hoc analysis, we investigated response according to pretreatment with anthracycline-containing chemotherapy. In 43.8% of the anthracycline-pretreated patients, complete remission or partial response was observed, and stable disease in 25%. Reichmann and colleagues presented comparable results with partial response in 21.3% of the patients pretreated with anthracyclines, in 21.6% with taxane pretreatment, and in 21.6% after therapy with anthracyclines and taxanes. There is obviously no significant difference in

response according to the previously given regimens, reflecting bendamustine's lack of cross-resistance with alkylating agents.

In the subgroup of TNBC patients, the clinical benefit rate of 71.4% was higher compared to the rate of 68.4% in non-TNBC patients. Although the validity is limited by the small number of patients, a tendency towards a high responsiveness in this subgroup might be demonstrated. Triple-negative tumors are associated with genetic instability and are therefore more sensitive to DNA-damaging agents. The increased response in this subgroup may be explained by the chemical structure of bendamustine causing longer-lasting DNA damage and being associated with a relatively slower repair of DNA damage in comparison with other alkylating agents.

Conclusions

The present study demonstrated that the combination of bendamustine 70 mg/m² plus paclitaxel 90 mg/m² represents a very effective regimen with a favorable toxicity profile in palliative breast cancer therapy. Bendamustine plus paclitaxel in a weekly setting demonstrates an anthracycline-free treatment option when a polychemotherapy is indicated and might be an option in patients with cardiac comorbidity. TNBC tumors may probably also benefit from a bendamustine-containing setting. To obtain more data regarding this hypothesis, additional studies are warranted.

Disclosure Statement

The authors declare no conflict of interest.

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