Weekly administration of bendamustine as salvage therapy in metastatic breast cancer: final results of a phase II study

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Single-agent bendamustine has shown promise in the treatment of metastatic breast cancer. As toxicity was low after weekly administration of this drug in other solid tumors, the present double-center phase II trial was conducted to evaluate the efficacy and toxicity of weekly bendamustine as salvage treatment in metastatic breast cancer. A total of 34 patients with anthracycline (88%) and/or taxane (71%) pretreated for metastatic breast cancer received 60 mg/m^2 bendamustine on day 1, 8 and 15 every 28 days for six cycles. In addition, 10 patients with HER2/*neu*-overexpressing tumors either continued (five patients) or started treatment with 2 mg/kg trastuzumab weekly (loading dose 4 mg/kg) at study entry. Patients had predominantly visceral disease and had received one (88%) or two chemotherapy regimens for metastatic breast cancer. All patients were eligible for toxicity and 27 for response evaluation. No grade 3 or 4 hematologic toxicity occurred. Only three patients experienced grade 3 nonhematologic toxicity. Five patients (19%) reached a partial response. Stable disease for at least 6 months was achieved in eight patients, for a clinical benefit rate of 48%. The median progression-free survival and median overall survival were 6 months (range, 1–16) and 15 months (range, 2–28), respectively. We conclude that weekly bendamustine is a valid treatment option in patients with anthracycline-pretreated and/or taxanepretreated metastatic breast cancer; in particular, due to its low toxicity profile. Future trials should evaluate higher single doses of bendamustine in a weekly schedule. *Anti-Cancer Drugs* 18:963–968 © 2007 Lippincott Williams & Wilkins.

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Introduction

Treatment of metastatic breast cancer (MBC) is basically palliative, although long-term remission could be achieved in upto 30% of patients with limited disease [1]. Chemotherapy is indicated if the disease does not respond to hormone treatment or there is a marked demand for remission, for example, owing to severe symptoms or disseminated visceral metastases. The most effective cytotoxic drugs for the treatment of MBC are the anthracyclines and taxanes [2]. In most trials, combined treatment regimens, in particular those containing anthracyclines and taxanes, usually induced higher response rates, but the toxicity was more severe than for single-agent therapies without improving survival [3–6]. In anthracycline-pretreated MBC patients, however, the combined treatment with docetaxel and capecitabine or paclitaxel and gemcitabine, respectively, improved response rate, quality of life and survival as compared with single-agent taxane [7–9]. If anthracyclines and taxanes fail, outcome is poor, with a median overall survival of about 1 year despite further cytotoxic therapy [10,11]. For these patients new and efficacious treatment options with low-grade toxicity are needed.

The nitrogen mustard derivative bendamustine is an active antineoplastic agent, which has shown cytotoxic efficacy against breast cancer cell lines mainly via alkylating mechanisms [12]. Its exact mode of action, however, is not yet completely understood, because an additional function, such as purine antimetabolism, is presumably involved [13]. Finally, a unique role may be attributed to this drug as a result of its proven activity against anthracycline-resistant breast cancer cell lines and as it shows less cross-resistance than other alkylating agents [14].

Bendamustine has shown promise as a single-agent therapy in MBC patients [15–18]. Furthermore, weekly administration of this drug to treat advanced solid tumors, e.g. colorectal carcinomas, resulted in low hematotoxicity [19–21]. The maximum-tolerated dose of weekly infusions within phase I studies was found to be 80 mg/m^2, as indicated by dose-limiting mouth dryness, fatigue and fever. Thus, 60 mg/m^2 was recommended as the ideal dose for weekly administration of bendamustine in phase II trials [21].

We conducted this single-center phase II trial to evaluate the efficacy and toxicity of bendamustine given weekly

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for 3 consecutive weeks following 1 week off as salvage treatment in anthracycline-pretreated and/or taxane-pretreated MBC patients.

Patients and methods

Patient selection

For study enrollment patients had to be suffering from progressive MBC with at least one measurable tumor lesion and have received at least one systemic cytotoxic pretreatment for metastatic disease. Further inclusion criteria were age ≥ 18 years, an Eastern Cooperative Oncology Group performance status ≤ 2 and a life expectancy ≥ 3 months. Adequate hematologic function criteria had to be met: a white blood cell count $\geq 3 \times 10^9$/l and a platelet count $\geq 100 \times 10^9$/l, adequate liver function with serum levels of bilirubin, aspartate aminotransferase and alanine aminotransferase $\leq 1.5 \times$ upper normal limit, and adequate kidney function with serum levels of creatinine $\leq 1.5 \times$ upper normal limit. Patients with brain metastases, pretreatment with bendamustine, hypersensitivity to bendamustine or trastuzumab, or a history of another malignancy except successfully treated basal cell carcinoma or preinvasive cervical cancer were excluded. Further exclusion criteria were acute infections or other major concomitant diseases, which could increase the risk for participating patients, such as chronic heart failure, history of thromboembolic accidents or severe metabolic disorders. Previous radiotherapy was permitted, provided that at least one measurable tumor lesion existed outside the radiation field. patients in whom disease progressed for the first time while under treatment with trastuzumab were included in the study according to current recommendations [22]. Before study entry all patients gave their written informed consent according to the recommendations of the responsible ethics committee.

Study design

The trial was planned as an open, double-center phase II study. The design was based on procedures described by Fleming [23].

Treatment

Patients in whom human epidermal growth factor receptor 2/*neu* (HER2/*neu*) was not overexpressed received single-agent bendamustine at a dose of 60 mg/m^2 administered as an intravenous infusion over 30 min on days 1, 8 and 15 of a 28-day cycle. In patients with tumors overexpressing HER2/*neu* (score 3+ as assessed by immunohistochemistry), bendamustine was combined with trastuzumab at weekly doses of 2 mg/kg intravenous infused over 30 min (loading dose 4 mg/kg intravenous infused over 90 min). Trastuzumab was continued until there was clear evidence of tumor progression. A maximum of six cycles of chemotherapy were planned and the tumor status was to be reevaluated after every cycle. If complete remission (CR) was achieved, the application of one further cycle was planned if the maximum number of six cycles had not yet been reached. Patients showing a partial remission (PR) or stable disease (SD) were meant to receive the full six cycles.

As a concomitant treatment 4 mg dexamethasone and 8 mg ondansetrone were administered as antiemetic prophylaxis before chemotherapy and also 50 mg ranitidine to prevent gastritis. On days 2, 9 and 16 patients received 4 mg dexamethasone twice a day as prophylactic antiemetic treatment and metoclopramide, if needed.

Baseline, toxicity, and response assessment

Before trial entry patients received a physical examination. A complete blood count (CBC), differential count and blood chemistry tests were taken. ECG, echocardiogram, liver ultrasound, chest radiograph, bone scan, and, if indicated, computed tomography or magnetic resonance imaging examinations were carried out.

During cytotoxic treatment the CBC was monitored weekly or, in cases of grade 3/4 neutropenia, thrombopenia and febrile neutropenia, at shorter intervals until hematologic recovery. Side effects were documented according to World Health Organization (WHO) criteria for drug toxicity. In patients receiving trastuzumab, ECG and echocardiogram were repeated every 3 months.

Primary efficacy endpoint was the overall response rate (ORR), defined as CR or PR. Treatment response was evaluated every two cycles according to the standard WHO criteria. Only patients who completed at least two cycles were eligible for response evaluation. Secondary endpoints were clinical benefit rate (CBR), defined as CR, PR or SD for at least 6 months; toxicity; time to progression (TTP), measured from the start of study treatment until progression; and overall survival (OS), measured from the start of study treatment until death. Survival curves were estimated using the Kaplan–Meier product limit method [24].

Results

Between March 2001 and September 2002, 34 patients were enrolled in the study. Patient and tumor characteristics are presented in Table 1. Median age was 53 years (range, 29–76 years), 25 patients (74%) presented with two or more metastatic sites, and in 88%, visceral metastases were the predominant site of the disease. HER2/*neu* receptor antigen was overexpressed in 10 patients (29%). Eighteen patients (53%) had received adjuvant chemotherapy; 30 patients (88%) had received one and four had received two chemotherapeutic regimens for metastatic disease. In 88% of patients, cytotoxic pretreatment included anthracyclines and in 71% taxanes. Table 2 provides an overview of all cytotoxic pretreatment, stratified according to neoadjuvant setting, adjuvant setting or palliative treatment. Of the patients,

Table 1 Pretreatment, patient and tumor characteristics

	N	%
Number of patients enrolled	34	100
Eligible for response evaluation	27	79
Age, years, median (range)	53 (29–76)	
Disease-free interval, months, median (range)	26 (0–216)	
Dominant disease site, bone/soft tissue/viscera/NA	0/3/30/1	0/9/88/3
Number of metastatic sites, 1/2/>2/NA	9/18/6/1	26/53/18/3
ER, positive/negative/NA	21/5/8	62/15/24
PgR, positive/negative/NA	14/12/8	41/35/24
ER or PgR positive/ER and PgR negative/NA	21/5/8	62/15/24
Her2/*neu*, 0–2+/3+/NA	20/10/4	59/29/12
Endocrine pretreatment adjuvant, yes/no	12/22	35/65
Cytotoxic pretreatment adjuvant, yes/no	18/16	53/47
Number of endocrine pretreatments for MBC, 1/2/3	13/5/3	38/15/9
Number of cytotoxic pretreatments for MBC, 1/2	30/4	88/12
Pretreated with anthracyclines, yes/no	30/4	88/12
Pretreated with taxanes, yes/no	24/10	71/29
Pretreated with trastuzumab, yes/no	5/29	15/85
Pretreated with radiotherapy, yes/no	24/10	71/29

ER, estrogen receptor; MBC, metastatic breast cancer; NA, data not available; PgR, progesterone receptor.

Table 2 Cytotoxic pretreatment

Chemotherapy regimen	*N*/Responders	%
Neoadjuvant setting		
Anthracyclines	3	9
Taxanes	1	3
Adjuvant setting		
Anthracyclines	4	12
Taxanes	0	0
High-dose chemotherapy	2	6
CMF	13	38
Palliative setting		
Anthracyclines	22/15	65
Taxanes	25/16	74
High-dose chemotherapy	4/4	12
Gemcitabine	2/0	6
CMF	5/2	15
Vinorelbine	1/0	3

CMF, cyclophosphamide, methotrexate and fluorouracil.

71% had received radiotherapy in the earlier course of their disease. All patients were eligible for toxicity and 27 for response evaluation. Seven patients were not eligible for response evaluation for the following reasons: one was lost to follow-up after the first cycle; one developed an allergic reaction after the first cycle; one received intercurrent radiotherapy after the first cycle; in three performance status deterioriated after the first cycle; and one was lost to follow-up after the second cycle.

Ten patients received all six cycles as scheduled. The reasons for discontinuing the study treatment in the remaining 24 patients were: lost to follow-up, allergic reaction or intercurrent radiotherapy (each in one patient) after the first cycle; deterioration of performance status (three patients), lost to follow-up (one patient) or progressive disease (PD) (seven patients) after the second cycle; allergic reaction (one patient) or PD (five patients) after the third cycle; refusal to proceed (one patient) after the fourth cycle; and fatigue (one patient) or PD (two patients) after the fifth cycle. A total of 119 cycles were administered with a median of three cycles per patient (range, 1–6). The median relative dose intensity for bendamustine was 98% (range, 82–100). Ten patients (29%) with overexpression of Her2/*neu* received an additional treatment with trastuzumab. Half of the patients with HER2/*neu*-overexpressing tumors started trastuzumab before study entry.

No CR was achieved. Five patients (19%) reached a PR and SD was achieved in nine patients (33%), for a CBR of 48%. In a subgroup analysis, a CBR of 41 and 60% were found, respectively, for patients treated with a bendamustine single-agent and for patients who received a bendamustin/trastuzumab combination therapy. Patients pretreated with anthracyclines and taxanes showed a CBR of 48%. Finally, all response data were analyzed additionally on an intent-to-treat basis (Table 3).

With a median follow-up period of 14 months (range, 2–28), disease progressed in all patients and 19 (59%) died. The median PFS and OS were 6 months (range, 1–16) and 15 months (range, 2–28), respectively (Figs 1 and 2).

Table 3 Response and survival

Response	*n*	%
Eligible for response evaluation	27 (34)[a]	100
PR	5	19 (15)[a]
SD	9	33 (26)[a]
CR+PR+SD ≥ 6 months	13	48 (41)[a]
PD	13	48 (41)[a]
Subgroup analysis Bendamustine single-agent treatment		
Eligible for response evaluation	17 (24)[a]	100
PR	3	18 (13)[a]
SD	4	24 (17)[a]
CR+PR+SD ≥ 6 months	7	41 (29)[a]
PD	10	59 (42)[a]
Bendamustine/trastuzumab combination therapy	10 (10)[a]	100
Eligible for response evaluation		
PR	2	20 (20)[a]
SD	5	50 (50)[a]
CR+PR+SD ≥ 6 months	6	60 (60)[a]
PD	3	30 (30)[a]
Subgroup analysis Anthracycline and taxane refractory patients	21 (24)[a]	100
Eligible for response evaluation		
PR	5	24 (21)[a]
SD	5	24 (21)[a]
CR+PR+SD ≥ 6 months	10	48 (42)[a]
PD	11	52 (46)[a]
Survival	*n*	Months
Eligible for survival	34	
Follow-up all patients, median (range)		14 (2–28)
Follow-up patients alive, median (range)		22 (5–28)
PFS, median (range), all patients progressed		6 (1–16)
OS, median (range), 19 patients (59%) died		15 (2–28)

CR, complete remission; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial remission; SD, stable disease.
[a]Data based on an intent-to-treat analysis, referring to $n=34$ patients.

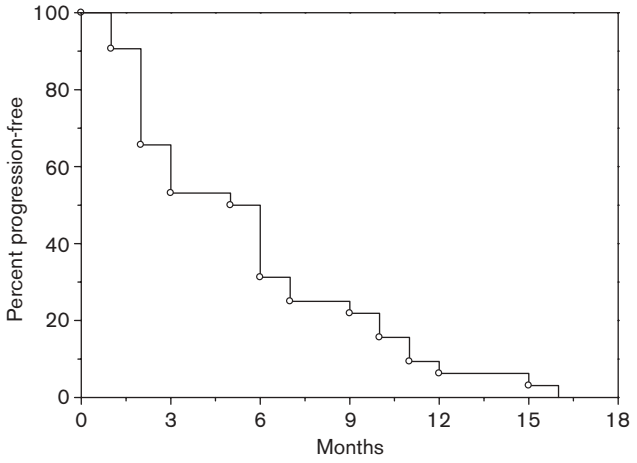
No treatment-related deaths occurred. The overall toxicity was mild to moderate. In particular, no grade 3 or grade 4 hematologic toxicity was observed. The severe kinds of nonhematologic toxicity were infection, hypotension and fatigue, which occurred each in one patient (Table 4).

For the entire study population ($n = 34$) only two grade 3 allergic reactions were seen in total: in one patient within the first cycle of treatment and in another patient after three cycles of therapy. In both cases, the allergic reaction occurred after the end of the infusion, presenting with fever, flush, palpitations and dyspnea due to bronchiospasm. Symptoms could be relieved rapidly after intravenous administration of prednisolone and antihistaminic drugs. Both patients could be discharged from the hospital after 24 h of observation without any sequelae.

Table 4 Overview of most severe toxicity

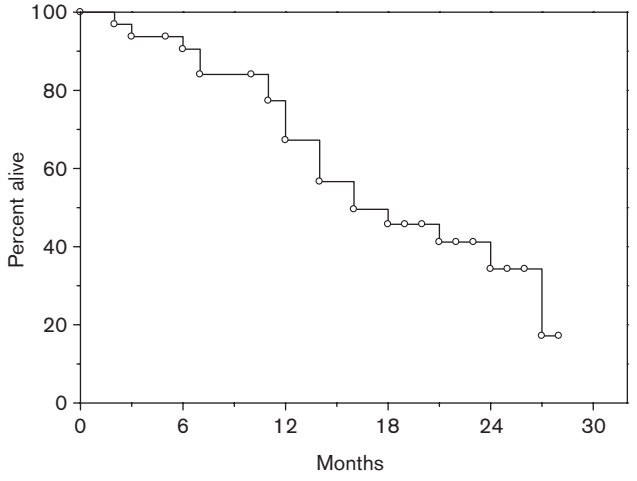
	Grade I		Grade II		Grade III		Grade IV	
Toxicity	*n*	%	*n*	%	*n*	%	*n*	%
Nonhematologic toxicity								
Allergic reaction	0	0	0	0	2	5.9	0	0
Fatigue	9	26.5	6	17.6	1	2.9	0	0
Nausea/vomiting	9	26.5	7	20.6	0	0	0	0
Diarrhea	1	2.9	1	2.9	0	0	0	0
Constipation	1	2.9	3	8.8	0	0	0	0
Stomatitis	5	14.7	1	2.9	0	0	0	0
Paresthesia	3	8.8	0	0	0	0	0	0
Pain	9	26.4	3	8.8	0	0	0	0
Infection	0	0	0	0	1	2.9	0	0
Hypotension	0	0	0	0	1	2.9	0	0
Skin toxicity	0	0	3	8.8	0	0	0	0
Hematologic toxicity								
Anemia	1	2.9	1	2.9	0	0	0	0
Leukocytopenia	5	14.7	1	2.9	0	0	0	0
Thrombopenia	3	8.8	1	2.9	0	0	0	0

Fig. 1



Kaplan–Meier curve of progression-free survival of 27 eligible patients.

Fig. 2



Kaplan–Meier curve of overall survival of 27 eligible patients.

Discussion

This is the first study of MBC in which single-agent bendamustine was administered weekly for 3 consecutive weeks after 1 week off. In 27 evaluable patients, mainly pretreated with anthracyclines (88%) and taxanes (71%), single-agent bendamustine achieved an ORR and CBR of 19 and 48%, respectively. Median PFS and median OS amounted to 6 months (range, 1–16) and 15 months (range, 2–28), respectively. In this high-risk group of patients, according to pretreatment, the dominant site of metastases (88% visceral) and tumor load (71% two or more metastatic sites), and response and survival rates are similar to those achieved with other single-agent chemotherapy protocols, e.g. capecitabine or liposomal doxorubicin [10,11].

Remarkably, 48% of these patients showed a clinical benefit from this regimen even after pretreatment with anthracycline and taxane had failed. Furthermore, bendamustine was active even though altogether 82% of patients had received alkylating agents (mainly cyclophosphamide) as part of adjuvant or palliative first-line treatment. Of particular importance is the fact that as many as 60% of the patients who received bendamustine/trastuzumab combination therapy demonstrated a clinical benefit, suggesting that bendamustine and trastuzumab may be therapeutically synergistic. This subgroup of patients in our trial is, however, small ($n = 10$), so that further, larger investigations are needed to clarify this hypothesis.

As no grade 3 or 4 hematologic toxicity occurred and the most severe nonhematologic toxic events were only one

grade 3 allergic reaction, infection, hypotension or fatigue, respectively, these response and survival rates were achieved with doses lower than those reported so far as the maximum tolerated dose of weekly single-agent bendamustine [21].

From MBC trials that used higher doses of single-agent bendamustine, partly better results were reported. In 15 eligible patients single-agent bendamustine (150 mg/m^2) administered on days 1 and 2 of a 3-week cycle achieved an ORR and CBR of 20 and 80%, respectively, as third-line treatment. Median PFS and OS were 6 and 8 months, respectively [15]. In another study including 36 MBC patients, 150 mg/m^2 bendamustine given on days 1 and 2 of a 4-week cycle achieved an ORR of 25%. Only four cases (11%) of primary PD were observed, but the median PFS was short. Furthermore, the efficacy of bendamustine in this trial seemed to be independent of previous treatment with anthracyclines. The ORR was 23% in the subgroup of patients who had already received anthracyclines [16]. The ORR and CBR were 23 and 57%, respectively, in a trial including 35 eligible MBC patients treated with 120 mg/m^2 bendamustine on days 1 and 2 of a 4-week cycle. Again the efficacy of bendamustine seemed to be independent of taxane and/or anthracycline pretreatment [17]. A further trial showed a 25% ORR after 60–100 mg/m^2 bendamustine administered on days 1, 2 and 3 every 4 weeks [18]. The overall toxicity in all these trials was mild to moderate, with predominantly hematologic side effects (e.g. 17% grade 3–4 leukocytopenia and 6% grade 3–4 thrombocytopenia [16]). No cases of severe gastrointestinal toxicity or alopecia occurred.

Thus, the low dose of bendamustine used in our trial (180 mg/m^2 per 4-week cycle) as compared with the doses administered in other single-agent studies with bendamustine (240–300 mg/m^2 per 3–4-week cycle) might have been less efficacious. This is underlined by efficacy data for bendamustine-containing combination chemotherapy regimens in MBC. The doses of bendamustine used in those combination regimens were generally higher. Substituting 240 mg/m^2 bendamustine for cyclophosphamide in the cyclophosphamide, methotrexate and fluorouracil (CMF) regimen in 25 patients with MBC, for example, resulted in a longer median duration of remission (15.2 versus 6.2 months) for patients treated with bendamustine, methotrexate, and fluorouracil [25]. In 40 patients in whom disease had progressed on CMF, an ORR of 48% (18% CR, 30% PR) was achieved with 240 mg/m^2 bendamustine per cycle in combination with doxorubicin and vincristine. Data from a recently published randomized multicenter phase III trial confirm that the use of bendamustine instead of cyclophosphamide in a CMF regimen as first-line therapy significantly prolonged the progression-free survival in MBC patients [26].

Furthermore, bendamustine-containing protocols that were effective in other solid tumors mostly used higher doses per cycle as well. Bendamustine at 120 mg/m^2 on 2 consecutive days every 3 weeks as first-line treatment in 26 patients with small-cell lung cancer resulted in an ORR of 45% [27]. In the same setting, 70 mg/m^2 bendamustine on 4 consecutive days every 4 weeks achieved an ORR of 41% [28]. For head and neck cancer relapse, 100–150 mg/m^2 bendamustine on 2 consecutive days combined with radiotherapy (3 Gy per day) over 5 days led to an ORR of 73% [29].

Conclusion

In conclusion, single-agent weekly bendamustine is a promising, active and well-tolerated treatment option in patients with anthracycline-pretreated and/or taxane-pretreated MBC. Future trials should use higher doses of bendamustine of at least 240 mg/m^2 per 4-week cycle.

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