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Bendamustine in Metastatic Breast Cancer: An Old Drug in New Design

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Key Words
Bendamustine · First-line chemotherapy · Metastatic breast cancer

Abstract
The goal of treatment for patients with advanced breast cancer is to prolong survival, control symptoms, and reduce disease-related complications. Despite the introduction of many cytotoxic agents during the past decade, only modest improvement in survival in metastatic breast cancer has been achieved. In order to improve this situation, new cytotoxic drugs as well as molecule-targeted agents are now under investigation. Bendamustine is a bifunctional alkylating agent with cytotoxic activity against several types of solid tumors. In the search for new anthracycline-free combinations, taxanes and alkylating agents might be worth investigating, in order to reduce cardiac toxicity. In this article, we reviewed the latest information regarding antitumor activity, toxicity, pharmacokinetics, and clinical application of bendamustine as a cytotoxic agent in metastatic breast cancer.

Schlüsselwörter
Bendamustin · First-line Chemotherapie · Metastasiertes Mammakarzinom

Zusammenfassung
Die Verbesserung des Überlebens ohne Einschränkung der Lebensqualität, das Management der klinischen Beschwerden und die Verminderung der krankheitsbedingten Komplikationen stehen im Fokus der Therapieplanung bei Patientinnen mit metastasiertem Mammakarzinom. Trotz der Einführung neuerer zytotoxischer Medikamente in den letzten Jahrzehnten ist die Verlängerung des Überlebens im metastasierten Stadium bisher nur marginal verbessert worden. Daher werden neue chemotherapeutische, endokrine, vor allem aber zielgerichtete Ansätze im Rahmen zurzeit laufender klinischer Studien untersucht, um die Prognose für diese Zielgruppe weiter zu verbessern. Bendamustin ist ein bifunktionelles alkylierendes Zytostatikum, das neben hämatologischen Erkrankungen auch bei verschiedenen soliden Tumoren Einsatz findet. Der Einsatz von Anthrazyklin-freien Therapiekombinationen mit geringen kardiotoxischen Eigenschaften, wie die Taxane und Alkylantien, soll in weiteren Untersuchungen etabliert werden. In dieser Übersichtsarbeit wurden die wesentlichen aktuelleren Daten bezüglich der antitumoralen Wirkungsmechanismen, des Toxizitätsprofils und der Effektivität von Bendamustin bei Patientinnen mit metastasiertem Mammakarzinom zusammengetragen.

Introduction

Metastatic breast cancer (MBC) is incurable; the median time of survival is 2–3 years [1]. Only a limited number of patients survives more than 10 years after the diagnosis of metastases. Nevertheless, an analysis from Giordano and colleagues [2] suggests that the survival of women with recurrent breast cancer has been overall improved over the past three decades.

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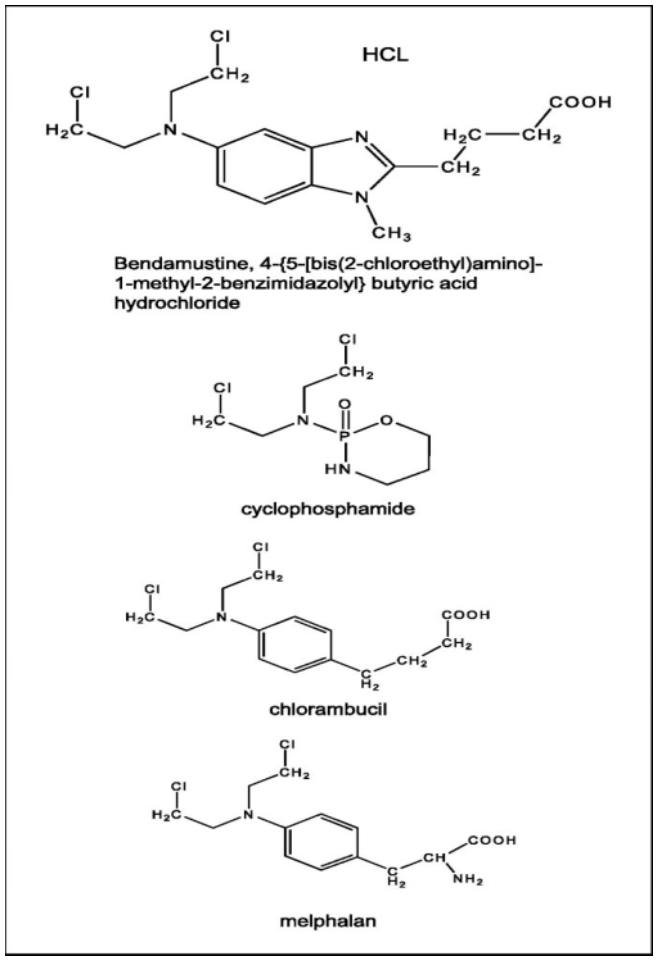

Fig. 1. Chemical structure of bendamustine.

Therefore, the main aim of the treatment is not to cure but palliation, which can be achieved by chemotherapy, endocrine treatment, bisphosphonates, surgery, radiotherapy, and palliative treatment. Since the mid 1990s, a number of new agents have been introduced to the treatment of breast cancer, such as the taxanes, vinca alkaloids, oral formulations of known drugs, and antibodies.

Bendamustine: Pharmacological Profile

Bendamustine hydrochloride (fig. 1) is the active ingredient of Ribomustin® (Mundipharma GmbH, Limburg, Germany). It was originally synthesized in 1963 in Jena, Germany, with the intention of producing an antineoplastic agent with low toxicity and both alkylating and antimetabolic properties, and was first used in multiple myeloma. Bendamustine has 3 active moieties: (i) an alkylating group, in common with the nitrogen mustard family, (ii) a benzimidazole ring, which may act as a purine analogue, and (iii) a butyric acid side chain [3]. However, it has been shown that, at high concentrations, it primarily acts as an alkylating agent. Bendamustine undergoes extensive first-pass metabolism, is rapidly metabolized and eliminated, with a half-life of 30 min [4, 5]. The properties of bendamustine are summarized in table 1.

Table 1. Properties of bendamustine

Mechanism of action	
Alkylating agent	cross-linking of DNA single and double strands
Pharmacokinetics	
Volume of distribution at steady state	19.8–20.51 l
Mean total clearance	31.7–49.6 l/h (renal)
Plasma elimination half-life	32–36 min
Dosage and administration	
Solid tumors	120–150 mg/m^2 d 1+2 q4w
Frequency	once daily
Route	intravenous, 30–60 min infusion
Adverse events	
Most frequent	hematological toxicities gastrointestinal toxicities
Applications	
Hematological malignancies	Hodgkin's, non-Hodgkin's disease multiple myeloma chronic lymphocytic leukemia
Solid tumors	colorectal cancer lung cancer breast cancer

Based on the multiple actions and cell cycle effects (such as activation of DNA damage stress response, apoptosis, inhibition of mitotic checkpoints, and induction of mitotic catastrophe) of this agent, mechanism-based combination strategies have been suggested. Early investigations could demonstrate the same efficacy as for other alkylating agents in hematological diseases [6]. Bendamustine as a single agent or in combination with other anticancer agents has also shown pro-apoptotic activity in several in vitro tumor models [7–10]. Unlike other alkylators, bendamustine activates a base excision DNA repair pathway rather than an alkyl transferase DNA repair mechanism [11]. This issue may contribute to its distinct clinical efficacy profile.

In solid tumors, bendamustine has been a promising alternative to other alkylating agents. The most experiences have been gained in therapy of metastatic breast cancer [12, 13]. Also in lung and gastrointestinal cancer, bendamustine as monotherapy or in combination with cytotoxic drugs induced remissions [14–18].

Currently, there are few proven treatment options available to patients with breast cancer whose disease has rapidly progressed or is not responding to prior treatment with standard chemotherapies such as anthracyclines and taxanes. Given this high unmet need, it is necessary to investigate new drug application strategies, taking into consideration the individual predisposition to well-known toxicities, such as cardiovascular events and myelosuppression.

Bendamustine has an excellent toxicity profile, with neutropenia, nausea, and vomiting as most common side effects [19–21]. This aspect is especially important in metastatic patients, as one of the primary aims is to improve quality of life. Therefore, the conclusion was drawn to test bendamustine in patients with solid tumors, preferably breast cancer. In the 1990s, some clinical trials were conducted with bendamustine as primary therapy and as therapy for recurrent breast cancer. Our objective is to review the evidence of bendamustine-containing chemotherapy regimens and bendamustine as monotherapy in MBC patients.

Methods

The studies analyzed in this report have been identified via systemic computerized search on Medline and the Cochrane Breast Cancer Group Specialized Register back to the 1990s. The codes for 'breast cancer', 'solid tumor' and 'bendamustine' have been used. Details of the search strategy used to create the register are described in the Group's module in *The Cochrane Library*. The reference lists of other related literature reviews and articles were also searched. Data were collected from published trials and congress abstracts. Studies were assessed for eligibility and quality.

Main Results

We identified 16 studies, 9 of these (6 full publications, 3 abstracts only) on breast cancer treatment and 7 studies (4 full publications, 3 abstracts) for other solid tumors. 6 studies were reported as abstracts and provided few details of methodology and complete results. Moreover, information about treatment length and response criteria used was often not completely reported.

Bendamustine as Monotherapy in MBC

Bendamustine has been evaluated not only in combination with other antitumor drugs, but also as monotherapy in pilot, phase I or phase II trials.

Jamitzky conducted a trial in 18 patients with bendamustine as the third-line therapy. Bendamustine was given at a dosage of 150 mg/m^2 on days 1 and 2 of a 3-week cycle for 6 cycles. In 15 evaluable patients, 20% had a partial remission (PR) and 60% stable disease (SD). The median progression-free (PFS) and overall survival (OS) was 6 and 8 months, respectively. Hematological adverse events were the main side effects. There were no grade III/IV gastrointestinal toxicities or alopecia [22].

In a multicenter study in recurrent breast cancer (one or more previous regimens for metastatic cancer), the same dosage was used in a 4-week cycle. The overall remission rate was 25% (1 complete response (CR), 8 PR) with 4 patients having a primary progression. There was no difference between the anthracycline-pretreated and anthracycline-naive patients. The toxicity profile consisted of grade III–IV leukopenia (17%) and thrombocytopenia grade III–IV (6%) [23].

Eichbaum conducted a phase II study with weekly bendamustine in MBC patients with 3 or more previous cytotoxic therapies. Most of the patients had received (88%) anthracyclines and (71%) taxanes. Bendamustine (60 mg/m^2) was given weekly in 3 consecutive weeks followed by a week of rest as the second-line therapy. In case of Her2/neu overexpression, trastuzumab was given concurrently every week if the patients had not received trastuzumab before (10 of the 34 patients). On average, the patients received 3 cycles (range: 1–6); however, only 10 patients received all planned cycles as scheduled. All patients were eligible for toxicity and 27 for response evaluation. 5 patients (19%) reached PR. SD for at least 6 months was reached in 9 patients, resulting in a clinical benefit rate (CBR) of 48%. In a subgroup analysis, CBR increased to 60% for patients treated with the bendamustine/trastuzumab combination. During the follow-up period of 14 months, disease progressed in all patients and 19 (59%) died. No treatment-related deaths occurred. The median PFS and OS were 6 months (range, 1–16) and 15 months (range, 2–28), respectively. The toxicity profile was moderate with only 2 grade III toxicities as a reversible allergic reaction after the end of the infusion. No grade IV toxicities were observed [24].

A multicenter, open-label, nonrandomized phase II trial has investigated the efficacy and tolerability of single-agent bendamustine in 51 multimodally pretreated patients, with a dose of 120 mg/m^2 on days 1 and 2 every 4 weeks [25]. Most patients (92%) had received chemotherapy for metastatic disease, 53% adjuvant chemotherapy, and 47% an adjuvant hormone therapy. All patients were assessable for toxicity; grade III–IV adverse events occurred very rarely; only 2 febrile neutropenias were observed with no treatment-related deaths. 10 of the 50 patients evaluable for response showed PR (20%), and 14 patients (28%) SD. Primary progression was observed in 26 cases (52%). The median time to progression (TTP) was 3.4 months (range, 0.34–51.1); the median duration of response was 6.6 months (range, 1.8–48.7). The response rate was independent of pretreatment.

A summary of the main trials with bendamustine as monotherapy of MBC is presented in table 2.

Combination Therapy with Bendamustine in MBC

Several pilot, phase I, II and III studies have investigated the efficacy of bendamustine in combination with anthracyclines or other agents in MBC (table 3).

In 2 trials, bendamustine was combined with either adriamycin and a vincristine analogue (VAC scheme) in 62 patients with

Table 2. Bendamustine as monotherapy: literature overview

Reference	Trial	Patients, n (overall)	Dose, mg/m^2	Response rate, %	Toxicity	Survival, months (range)
Jamitzky et al., 1996 [22]	pilot, third-line	18	150 mg/m^2 on day 1 and 2 every 3 weeks	overall 20, 3/15 pts, SD 60	thrombocytopenia, leukopenia	PFS 6, OS 8
Höffken et al., 1998 [23]	multicenter, phase II	37	150 mg/m^2 on day 1 and 2 every 4 weeks	overall 25, CR 1 pt, PR 8 pts, PD 4 pts	thrombocytopenia, leukopenia	TTP 2
Eichbaum et al., 2007 [24]	double-center, open-label phase II	34	Her2 negative: 60 mg/m^2 on day 1, 8, 15 every 4 weeks; Her2 positive: 60 mg/m^2 on day 1, 8 and 15 every 4 weeks + trastuzumab 2 mg/kg (loading 4 mg/kg)	overall 48, PR 19 (5 pts), SD 33 (8 pts), PD 48 (13 pts), Her2 negative: overall 41, Her2 positive: overall 60	infection, hypotension, fatigue	PFS 6 (1–16), OS 15 (2–28)
Reichmann et al., 2007 [25]	multicenter, open-label phase II	51	120 mg/m^2 on day 1 and 2 every 4 weeks	overall 48, PR 20 (10 pts), SD 28 (14 pts), PD 52 (26 pts)	nausea, hematological, leukopenia, anemia	TTP 3.4 (0.34–51.1)

pts: Patients.

MBC, and/or 5-fluorouracil (5-FU) plus mitomycin C in 40 patients with colorectal cancer. The overall response rate (ORR) was 50% in breast cancer and 48% in colorectal cancer, which demonstrated the high efficacy of the drug when bendamustine was added to other cytotoxic agents [26, 27]. The combination of bendamustine with mitoxantrone showed a similar efficacy, with 48% ORR in advanced breast cancer [28].

A pilot study investigating the efficacy and tolerability of bendamustine 100 mg/m^2 in combination with gemcitabine 1000 mg/m^2 was conducted in 14 patients with MBC and 5 patients with relapsed ovarian cancer. 2 of 9 patients with breast cancer had PR and 4 SD. Because of the severe myelotoxicity, thrombocytopenia, and leukopenia, this study was preterm discontinued [29].

The first randomized trial with 49 patients compared the classical CMF (cyclophosphamide, methotrexate, and fluorouracil) with BMF (bendamustine 30 mg/m^2, days 1–8; methotrexate and 5-FU) as first-line therapy in MBC [12]. There was no significant difference between the two groups concerning ORR (46 vs. 52%). However, there were more complete remissions in the BMF group (16%) compared to the CMF group (4%). The median duration of response and the median OS were in favor of BMF, with 17.5 vs. 7 months and 12.9 vs. 5.5 months, respectively.

Because of these promising results, a prospective, randomized, multicenter phase III trial was undertaken to compare two combinations (BMF: bendamustine 120 mg/m^2, methotrexate, 5-FU d 1+8 q28; and CMF: cyclophosphamide 500 mg/m^2, methotrexate, 5-FU d 1+8 q28) as first-line therapy of 364 patients with MBC [13]. 175 patients received BMF and 189 CMF. Visceral metastases were present in 63.8% of all patients, and 54.4% had previously received adjuvant chemotherapy. The hematological toxicity was higher in the BMF group (leukopenia 62.7 vs. 40%), with comparable non-hematological toxicities. ORR was not different between the two groups with 44% (BMF) and 40% (CMF). The response rates at the individual end of study were similar in both treatment arms (BMF: CR 9.3%, PR 35.2% and NC (no change) 48.1%; CMF: CR 7.1%, PR 32.8% and NC 55.7%). Considering only the cases with confirmed responses, the response rates for both treatment arms were again very similar, but lower than expected (BMF: CR 2.5%, PR 19.8%; CMF: CR 4.4%, PR 18%). However, TTP was significantly longer with BMF compared to CMF (8.2 vs. 6.7 months). Patients who were free from visceral metastases and who had received prior adjuvant therapy showed an improved TTP of 14.6 months for patients on BMF and 4.9 months on CMF. TTP of patients with a confirmed PR (BMF 19.8% vs. CMF 18%) tended to be longer in the BMF arm compared to the CMF arm (14.8 vs. 10.3 months).

New Design in MBC: Bendamustine and Taxanes

There is a paucity of data on the use of bendamustine in combination with taxanes in MBC. In the adjuvant setting, the anthracycline-free combination docetaxel plus cyclophosphamide has shown the same efficacy and a superior toxicity profile to standard anthracycline plus cyclophosphamide, giving the possibility to spare cardiotoxicity [30]. A prospective

Table 3. Bendamustine in combination with chemotherapeutical agents in breast cancer: literature overview

Reference	Trial	Patients, n (overall)	Dose, mg/m^2	Response rate, %	Main toxicities	Survival,
Brockmann et al., 1991 [26]	pilot	62	bendamustine 125 mgm^2 d1(–3), doxorubicin 20 (40) mg/m^2 d1, vincristine 1 mg/m^2 d1, q2w	overall 50, CR 11.3, PR 38.7	nausea, emesis, hematological for high doses, thrombophlebitis	no data reported
Meyer et al., 1998 [29]	pilot	9	bendamustine 120 mg/m^2 d1+2, gemcitabine 1000 mg/m^2 d1+8; q4w	PR 22.2, SD 44.4	fatigue, myelotoxicity	study stopped
Ruffert et al., 1998 [12]	randomized	49	bendamustine 30 mg/m^2 d1–8, methotrexate 40 mg/m^2 d1+8, 5-FU 500 mg/m^2 d1+8, q3w (BMF), versus CMF	BMF:overall 52, CR 16, CMF: overall 49, CR 4	hematological, no severe toxicities (liver, renal) compared to CMF	TTP 17.5 vs. 7, OS 12.9 vs. 5.5
Schmidt et al., 1999 [28]	pilot, first- and second-line, heterogeneous collective	39	bendamustine 120 mg/m^2 d1+2 ± mitoxantrone 8 mg/m^2 d1+2; q4w	mono: overall 25, CR 0, PR 25; combination: overall 48, CR 10, PR38	hematological, nausea, emesis	TTP 440 days for CR, PR
von Minckwitz et al., 2005 [13]	phase III, randomized, open-label, multicenter, first-line	345	bendamustine 120 mg/m^2 d1–8, methotrexate 40 mg/m^2 d1+8, 5-FU 600 mg/m^2 d1+8, q3w (BMF) versus CMF	BMF: CR 9.3, PR 35.2, NC 48.1; CMF: CR 7.1, PR 32.8, NC 55.7	hematological, gastrointestinal, mucositis, alopecia, cardiac toxicities equal distribution	TTP 14.8 (BMF) vs. 10.3 (CMF) for PR

pts, Patients.

multicenter phase I dose-finding study with bendamustine and paclitaxel (RiTa trial) in a weekly setting for MBC patients was conducted by the German Breast Group between 2005 and 2007 in order to establish another anthracycline-free feasible combination. The first results of this trial were presented at the German Cancer Congress in February, 2008. Altogether 18 patients with MBC were enrolled and treated as follows: 3 patients per dose level (maximum 6 patients) and 6 patients at the last dose level, overall 5 levels. The starting dose of bendamustine was 50 mg/m^2 and was stepwise increased by 10 mg/m^2 up to 70 mg/m^2. The starting dose of paclitaxel was 60 mg/m^2 and was increased up to 90 mg/m^2. No dose-limiting toxicity up to 70 mg/m^2 bendamustine and 90 mg/m^2 paclitaxel occurred during the first cycle. Dose-limiting toxicities were severe neutropenia and thrombocytopenia as well as non-hematological toxicities ≥ National Cancer Institute common toxicity criteria (NCI-CTC) grade 3 (except emesis and alopecia) in the first cycle. The combination of bendamustine with paclitaxel seems to be effective with 1 CR and 3 PR, and to have a good tolerability with only 5 serious adverse events (2 fatigues, 1 anemia, 1 allergic reaction and 1 dehydration). Therefore, a phase II trial is now being conducted to investigate the efficacy and tolerability of the determined doses of bendamustine 70 mg/m^2 in combination with paclitaxel 90 mg/m^2 [31]. The weekly setting of paclitaxel plus bendamustine might be an even more efficacious and tolerable anthracycline-free combination and is therefore worth to be further explored.

Activity of Bendamustine on Central Nervous System Breast Cancer Metastases

Central nervous system (CNS) metastases are present in 10% of MBC and have the worst prognosis of all metastatic sites of breast cancer, despite palliative treatment with radiotherapy. The blood-brain barrier represents a major problem for most drugs because of poor permeability. Nevertheless, bendamustine may be active in CNS metastases, as described by Zukolski in a first case report [32]. A young patient with hormone receptor-negative MBC and advanced liver, bone and CNS metastases showed a promising benefit after 2 courses of bendamustine, with regression of liver metastases and a complete disappearance of 2 of 3 CNS lesions. Moreover, the patient's performance status improved considerably. This finding may suggest an alternative therapeutic option with bendamustine against CNS metastases of breast cancer and needs to be further investigated.

Conclusions

Bendamustine is a substance that has been used for more than 40 years in indications like non-Hodgkin's lymphoma, chronic lymphocytic leukemia, multiple myeloma, Hodgkin's disease, small cell lung cancer, colorectal cancer and breast cancer.

The therapy decision for MBC should take into consideration the patient's expectation, health condition and age, aggressiveness of disease, location of metastasis, and previous treatments. The combination of bendamustine with methotrexate and fluorouracil is recommended in individual situations by the Commission Mamma of the Arbeitsgemeinschaft Gynäkologische Onkologie e.V. (AGO) as an alternative to polychemotherapies, such as the combination of anthracyclines, taxanes and capecitabine, with a level of evidence (LOE) 1b (AGO +/–) [33, 34].

The particular importance of bendamustine as a single agent is clearly proven, as it is mostly used as monotherapy, mainly in a palliative setting, in breast cancer. The advantage compared with other comparable drugs is attributed to the fact that bendamustine causes hardly any alopecia or organ toxicity, resulting in a profit for the patients in terms of quality of life. Moreover, patients with cardiac co-morbidity can benefit from bendamustine as an alternative to vinorelbine and capecitabine therapy.

The main toxicity caused by bendamustine is hematotoxicity, defined as leukopenia, neutropenia and thrombocytopenia. In terms of non-hematologic toxicity, nausea and vomiting are dominant. Toxicity is generally mild, manageable and controllable. Late effects are unknown so far. Secondary malignancies are not documented as late effects, but this might be due to the relatively short follow-up periods and small patient collectives in the recently performed systematic studies.

The standard treatment in MBC has been modified due to the introduction of new drugs like the taxanes; thus, the role of bendamustine would have to be redefined and tested against modern therapy schedules. 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.

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