Journal of BUON **16:** 215-218, 2011

ORIGINAL ARTICLE

Metronomic vinorelbine plus bevacizumab as salvage therapy for patients with metastatic breast cancer

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Summary

Purpose: *Continuous administration of oral vinorelbine, given 3 times a week (metronomic), is feasible and exceptionally well tolerated at doses up to 50 mg with clinical activity against refractory tumors. In this phase II study oral metronomic vinorelbine and bevacizumab were evaluated as salvage therapy in women with pretreated metastatic breast cancer (MBC).*

Methods: *Patients received oral vinorelbine (50 mg 3 times a week) and bevacizumab (10 mg/kg) biweekly in cycles of 28 days. The primary endpoint was objective response rate (ORR). A preplanned analysis was performed when the first 13 patients were evaluated for tumor response.*

Results: *One patient (7.7%) achieved partial response (PR) and 6 (46.1%) stable disease (SD). The combination was very well tolerated but, as per protocol, the study was closed prematurely due to lack of efficacy.*

Conclusion: *The combination of oral metronomic vinorelbine and bevacizumab has good tolerance but minimal activity in terms of objective responses in pretreated patients with MBC.*

Key words: bevacizumab, breast cancer, metronomic, salvage, vinorelbine

Introduction

Though an expanding array of active agents has become available for the treatment of MBC, overall survival has changed little in the last half of the century [1]. While initial response rates ≥30% are routinely achieved in previously untreated patients, response rates decrease significantly in patients previously exposed to chemotherapy [2].

Angiogenesis and formation of new blood vessels that nourish the tumor are essential for breast cancer invasion and metastasis [3]. Bevacizumab, an anti-VEGF monoclonal antibody, is well tolerated in heavily pretreated MBC patients [4] and in combination with capecitabine produced a significant improvement in response rates [5]. Oral vinorelbine administered at doses up to 50 mg thrice a week (metronomic) has proven to have sustainable antitumor activity without overt toxicity, probably through anti-angiogenic mechanism [6].

Given that chemotherapy plus bevacizumab results in higher response rates [5,7,8] and may prolong time to disease progression [7,8], this study was initiated to evaluate the feasibility and efficacy of metronomic vinorelbine plus bevacizumab in patients with previously treated MBC.

Methods

Patients

Women with histologically or cytologically confirmed MBC were eligible if they had received prior therapy with both an anthracycline and a taxane and at least one prior chemotherapy regimen for metastatic disease. If relapse had occurred within 12 months of completing adjuvant anthracycline and taxane therapy, patients were eligible without intervening first-line chemotherapy. Patients with HER2-positive disease (3+ protein expression by immunohistochemistry or gene amplification by fluorescence *in situ* hybridization/

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Received 26-10-2010; Accepted 20-11-2010

FISH) must have progressed following trastuzumab treatment. Additional criteria included bidimensionally measurable disease with at least one lesion measuring ≥2 cm; Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1; and adequate renal, hepatic, and hematologic function.

Patients with untreated or symptomatic CNS disease or under therapeutic anticoagulation, regular nonsteroidal anti-inflammatory medication, and aspirin (> 325 mg/d) were excluded.

Treatment

All patients received vinorelbine 50 mg orally 3 times per week (preferably on Monday-Wednesday-Friday). Vinorelbine was interrupted for grade 2 or 3 hematologic or non hematologic toxicity and resumed at a reduced dose (75% of the starting dose for first occurrence, 50% at second occurrence) on resolution to less than grade 2. Vinorelbine was discontinued in case of ≥ grade 2 hematologic or non hematologic toxicity that recurred after two dose reductions, and for grade 4 toxicity of any kind.

Bevacizumab (10 mg/kg) was administered intravenously every 2 weeks. Initially, it was infused over 90 min and if no infusion-related reactions occurred, subsequent infusions were reduced to 60, then to 30 min. Bevacizumab treatment was interrupted for proteinuria ≥2.000 mg/24 h and resumed on resolution to < 2.000 mg/24 h. Blood pressure was monitored before and immediately after each bevacizumab infusion; antihypertensive therapy was given at the investigator's discretion. One cycle of treatment was considered 28 days of vinorelbine-bevacizumab administration. The vinorelbine-bevacizumab combination therapy was continued until disease progression or appearance of unacceptable toxicity.

In accordance with ASCO recommendations for patients treated with agents of low emetic risk, no antiemetics were routinely administered before chemotherapy or prophylactically for delayed emesis [9]. For patients with plain radiographic evidence of bone destruction, zoledronic acid 4 mg over 15 min every 3-4 weeks was administered intravenously [10].

Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 3.0. Disease status was assessed at baseline, and then every 8 weeks until disease progression. Contrast-enhanced spiral computed tomography or magnetic resonance imaging of the chest and abdomen was required at each evaluation. Response was characterized according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria [11].

Statistics

The primary endpoint was ORR and secondary endpoints were progression-free survival (PFS) defined as the time from randomization to the date of documented disease progression or death, and overall survival (OS). Sample size calculations assumed an ORR of at least 40% but no less than 20%. Based on Simon's two-stage optimal design [12], initial enrolment of 13 patients would allow progression to the second stage of enrolment if at least 3 out of 13 patients had responded without significant toxicities. The protocol was planned to enroll 30 additional patients in the second stage for response assessment. If 12 responses were observed in 43 patients, the probability of early termination was 0.05 for a combination with a response rate of >0.20. On the other hand the probability of rejection in the second stage was 0.20 for a combination with actual response rate of more than 0.40. OS and progression-free survival (PFS) were estimated with the Kaplan-Meier method [13].

Results

Between January 2008 and December 2009, 13 women with MBC were enrolled. A preplanned analysis was performed when 13 patients were evaluable for tumor response. The median patient age was 61 years (range 44-73). All patients had previously received chemotherapy with taxanes and anthracyclines for metastatic disease, with a median of 1.37 months (range 0.47-5.37) interval from previous treatment(s). The median number of administered cycles was 4 (range 2-8). A summary of baseline patient characteristics is shown in Table 1. No patient was withdrawn from the study.

The combination was well tolerated, without any ≥ grade 3 toxicity. Grade 1-2 anemia and neutropenia were observed in 5 (38.5%) and 2 (15.4%) patients, respectively. No severe bevacizumab-related vascular toxicity was noted. Hypertension was seen in one patient while another one developed epistaxis. Proteinuria was not of clinical significance. However, the premature discontinuation of the study does not permit a safe conclusion regarding the safety of the combination.

Out of 13 patients, only one achieved a PR, resulting in an ORR of 7.7% (95% CI: 0-22.18); SD was documented in 6 (46.1%) patients; the tumor growth control rate (CR+PR+SD) was 53.8%. After a median follow-up period of 7.97 months (range 2.8-22.4), the median PFS was 4.1 months (Figure 1). Notably, the

Table 1. Patient characteristics

Characteristics	*Number of patients (N=13)*	*%*
Age		
Median (range)	61 (44-73)	
ECOG PS		
0	7	53.8
1	5	35.8
2	1	7.7
ER/PR		
ER(+)/PR(+)	3	23.1
ER(+)/PR(–)	5	35.8
ER(–)/PR(+)	1	7.7
ER(–)/PR(–)	3	23.1
Unknown	1	7.7
HER2		
+	2	15.4
–	11	84.6
Organs involved		
Local	3	23.1
Nodes	6	46.2
Lung	6	46.2
Liver	8	38.5
CNS	0	–
Pleura	1	7.7
Bones	4	30.8
Line of treatment		
2nd	3	23.1
3rd	7	53.8
4th	3	23.1

ECOG: Eastern Cooperative Oncology Group, PS: performance status, ER: estrogen receptor, PR: progesterone receptor, CNS: central nervous system

patient who responded and 4 patients who achieved SD had a PFS of at least 5 months. The 1-year overall survival rate was 73.8% (Figure 2). The observed low ORR led to a premature discontinuation of the study as per protocol-specified stopping rules.

Discussion

To the best of our knowledge this is the first study of metronomic vinorelbine in MBC. The results presented in this report demonstrate that the combination of metronomic vinorelbine and bevacizumab has minimal activity in terms of ORR as salvage treatment of patients with MBC.

In contrast to our results, a previous study has shown that weekly vinorelbine, administered intravenously in combination with bevacizumab (10 mg/kg every 2 weeks), resulted in an ORR of 34% (95% CI 22-48%) and median PFS of 5.5 months, in pretreated patients with MBC [14]. This performs well with the historic experience of vinorelbine in treatment-refractory breast cancer, suggesting response rates in the order of 15-25%, with PFS between 3 and 6 months [15]. Whether the observed low ORR achieved with metronomic vinorelbine and bevacizumab in our study is due to a real lack of activity or due to the fact that there was no selection of patients is not known. A previous study has shown that patients with low pretreatment levels of circulating interleukin-8, vascular endothelial growth factor, and basic fibroblast growth factor may be better candidates for vinorelbine metronomic therapy [6]. Furthermore, the optimal time to use an anti-angiogenic agent might be earlier in the course of disease than that used in our study [5].

Nonetheless, a clinically interesting prolonged PFS (4.5 months) was observed in almost 50% of the patients, whereas 75% of the patients were alive after 1 year from the enrolment. This might be meaningful for the subgroup of patients without rapidly progressing visceral metastases. Additionally, it was achieved without significant toxicity which might be especially important, given that the effect of therapies on quality of

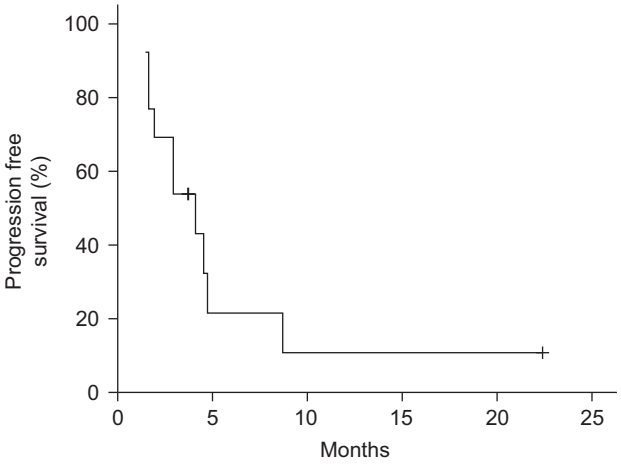

Figure 1. Kaplan-Meier progression free survival.

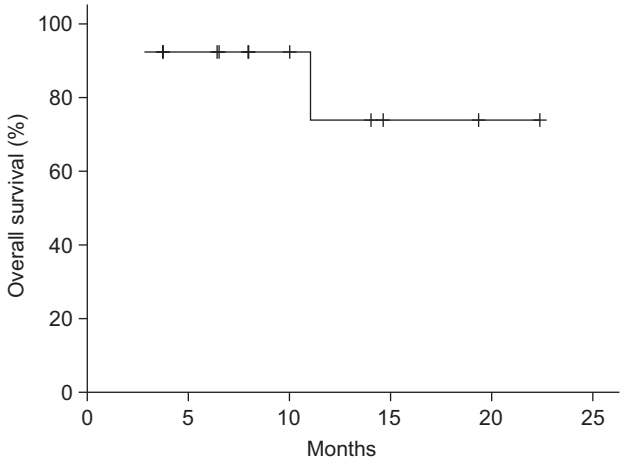

Figure 2. Kaplan-Meier overall survival.

life (QoL) of patients with incurable advanced cancer is fundamentally relevant for planning optimal treatment and supportive care. Unfortunately, baseline and follow up QoL information was not recorded in our study and therefore we can not conclude whether stabilization of disease was accompanied by preservation of QoL.

In conclusion, the combination of oral metronomic vinorelbine and bevacizumab, although well tolerated, did not exhibit a desirable objective activity when measured by tumor shrinkage in patients with MBC who had received prior treatment. Further research should focus on endpoints more sensitive to effects of targeted agents, such as disease stabilization.

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