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ORIGINAL ARTICLE

Analysis of the activity and safety of weekly low-dose bevacizumab-based regimens in heavily pretreated patients with metastatic breast cancer

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Keywords
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Abstract

Background: Currently, there are no standard regimens for metastatic breast cancer patients (MBC) who have failed ≥ 3 chemotherapy treatments. The aim of this study was to assess whether weekly low-dose bevacizumab-based regimens were well tolerated and would improve efficacy in MBC patients who had failed numerous therapies.

Methods: Seventeen patients with MBC who were heavily pretreated with a median of five regimens of therapy (range 1–10) between 2012 and 2016 were included in the analysis. Bevacizumab was administered at a dose of 100 mg intravenously once a week combined with one or two types of chemotherapeutic drugs until confirmed disease progression or an intolerable adverse event was observed. Patient characteristics, objective response rate, clinical benefit rate, progression-free survival, and toxicity were assessed.

Results: All 17 patients had been pretreated with taxane-based and anthracycline-based chemotherapy. Weekly low-dose bevacizumab combined with one or two types of chemotherapeutic drugs, which had usually not been previously used (e.g. etoposide, irinotecan, pemetrexed, methotrexate, and nab-paclitaxel), was administered. Three patients achieved a partial response, while one had stable disease for > 24 weeks, and the clinical benefit rate was 23.5%. Median progression-free survival was 3.4 months (95% confidence interval 2.0–4.8). The most common hematological adverse events were neutropenia, anemia, and thrombocytopenia. Bevacizumab-related adverse events included grade 1 bleeding (17.6%) and grade 2 hypertension (5.9%).

Conclusions: Weekly low-dose bevacizumab combined with chemotherapy shows a relatively favorable clinical response and tolerable toxicity, providing a feasible option for heavily pretreated MBC patients.

Introduction

Although breast cancer treatment has greatly improved over the last several decades, metastatic breast cancer (MBC) is still incurable with a median survival of two to three years.[1] Anthracyclines and taxanes are the preferred agents for the treatment of MBC.[2] Other drugs (e.g. capecitabine, gemcitabine, and vinorelbine) are also options for metastatic breast cancer patients pretreated with anthracyclines and taxanes. However, there are no standard regimens for patients who have failed ≥ 3 chemotherapy treatments, and most guidelines usually recommend supportive care or participation in clinical trials. New options are needed for patients with heavily pretreated resistant or refractory breast cancer.

Extensive data has shown that angiogenesis plays an essential role in breast cancer development, invasion, and metastasis.[3] As a result, anti-angiogenesis has become a new treatment strategy for breast cancer.[4–6] VEGF is the major regulator of angiogenesis, and the inhibition of VEGF and its receptors has become the focus of anti-angiogenic tumor therapy.[7]

Bevacizumab is a humanized monoclonal antibody that induces the inhibition of new tumor angiogenesis against VEGF-A.[8] The results of the E2100, RIBBON-1, and AVADO clinical trials established an important foundation for bevacizumab as a first-line treatment for MBC.[9–11] In the E2100 trial, the addition of bevacizumab to paclitaxel as first-line treatment in patients with MBC significantly improved progression-free survival (PFS; median 11.8 vs. 5.9 months; $P < 0.001$, alongside the objective response rate [ORR]; 36.9% vs. 21.2%; $P < 0.001$, except for overall survival [OS]; median 26.7 vs. 25.2 months; $P = 0.16$).[12] In a phase III trial by Miller *et al.*, capecitabine plus bevacizumab significantly increased the ORR (9.1% vs. 19.8%, $P = 0.001$) in patients with MBC previously treated with anthracyclines and taxanes. This effect did not lead to longer PFS (4.2 vs. 4.9 months; hazard ratio = 0.98), but OS rates were comparable in both treatment groups (15.1 vs. 14.5 months).[13] Subsequently, the United States Food and Drug Administration revoked approval of bevacizumab for MBC in 2011, as data indicated that the risk of using bevacizumab outweighed any benefit gained. High-dose bevacizumab-based treatment has commonly been associated with increases in adverse effects (overall and grade ≥ 3), such as all-grade bleeding (primarily epistaxis: placebo 19.5%, bevacizumab$_{7.5}$ 48.4%, bevacizumab$_{15}$ 49.4%) and hypertension (placebo 10.0%, bevacizumab$_{7.5}$ 14.3%, bevacizumab$_{15}$ 21.9%).[14]

However, the clinical benefits of anti-angiogenic drugs often only last for several months before tumors become refractory to therapy.[7] This phenomenon can be attributed to hypoxia inducible factor-1 (HIF-1), which is an important transcription factor of oxygen balance in tumor cells. in vitro studies have demonstrated that high-dose bevacizumab could increase the cancer stem cell population by generating hypoxia, which would induce HIF-1 upregulation and promote the transformation of tumor cells into stem cells and epithelial-to-mesenchymal transition, all of which would result in a decrease in intercellular adhesion, thereby promoting tumor invasion and metastasis.[15–17] Furthermore, tumor angiogenesis and abnormalities in the microenvironment result from an interruption to the balance between angiogenic factors and angiogenic inhibitory factors.[18] When the balance of both factors is restored, the abnormal microvasculature in the tumor gradually undergoes apoptosis, and the new blood vessel can achieve normalization.[19] The increase in oxygen supply to tumor cells, however, results in a limited period to enhance therapeutic sensitivity.[20]

Thus, the optimal effective dose of antiangiogenic agents with chemotherapy remains unclear. In this study, we assessed the clinical efficacy and safety of modified weekly low-dose bevacizumab-based treatment in heavily pretreated patients with MBC.

Methods

Patients

The medical records of patients diagnosed with MBC who received weekly palliative low-dose bevacizumab-based chemotherapy at the National Cancer Center/Cancer Hospital, China between 2012 and 2016 were reviewed. Seventeen patients with MBC who had been heavily pretreated with a median of five regimens of therapy (range 1–10) were included in the analysis. Bevacizumab was intravenously administered at a dose of 100 mg once a week combined with one or two kinds of chemotherapeutic drug regimens that had usually not been previously used (e.g. etoposide, irinotecan, pemetrexed, methotrexate, and nab-paclitaxel), until confirmed disease progression or an intolerable adverse event (AE) was observed. Exclusion criteria were diagnosis of another cancer ($n = 1$), diagnosis that was not evaluable for response to bevacizumab-based treatment ($n = 1$), or lost to follow-up after the first cycle ($n = 3$) (Fig 1). All patients had at least one extracranial measurable disease according to Response Evaluation Criteria in Solid Tumors version 1.1 and received two or more cycles of bevacizumab-based treatment.[21]

Statistical analysis

Patient characteristics were assessed prior to adjuvant chemotherapy and palliative therapy. ORR, clinical benefit rate (CBR), toxicity, and PFS were evaluated. The primary endpoint of the study was the relation rate (RR), which included ORR and CBR. The ORR was defined as complete response (CR) plus partial response (PR). CBR was defined as CR + PR + SD ≥ 24 weeks. The secondary endpoints were PFS, defined as the duration from the start of the treatment to disease progression, and clinical toxicity in all enrolled patients. Follow-up evaluations were conducted by telephone, clinical record evaluation, and outpatient visits, including physical examinations, chest, and abdominal computed tomography/magnetic resonance imaging. National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 was used to evaluate, grade, and record AEs. Data of patients lost to follow-up were censored on the date of their last visit. Survival curves were generated using Kaplan–Meier

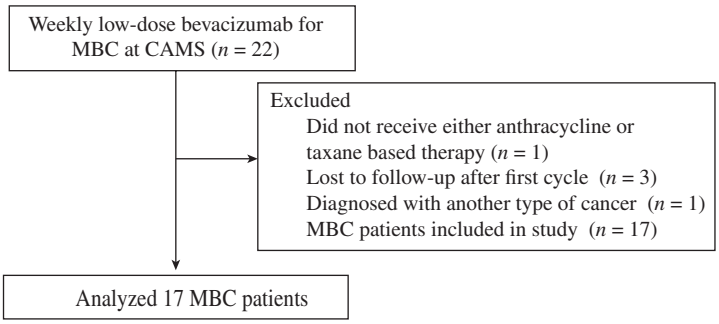

Figure 1 CONSORT form. CAMS, Cancer Academy of Medical Sciences; MBC, metastatic breast cancer.

methods and were compared with the results of log-rank tests. Multivariable analysis was also performed based on Cox's proportional hazard regression model. All statistical tests were two-tailed, with $P < 0.05$ set as significant. Survival curves were presented using GraphPad Prism 5.0 (La Jolla, CA, USA). All statistical analyses were performed using SPSS version 19 (IBM Corp., Armonk, NY, USA).

Results

Patient characteristics

Seventeen patients were eligible for analysis. The median age was 47 years (range 24–75). All patients were pretreated with taxanes and anthracyclines as either adjuvant or palliative treatment. Approximately 88% of patients received more than one chemotherapy scheme for the treatment of advanced breast cancer. Patient characteristics are shown in Table 1. At the last follow-up on 14 April 2017, the patients had received a median of three treatment cycles (range 2–14). Thirteen patients (76.5%) received bevacizumab-based treatment as third-line or further therapy. More than half of the patients had triple negative tumors, 35.3% had hormone receptor-positive disease, and 11.8% had HER2+ tumors. Patients with HER2 (+++) or those tested by florescence in situ hybridization (+) all received trastuzumab as adjuvant chemotherapy for a year. After developing metastases one patient was administered lapatinib and one patient pyrotinib, until disease progression. Approximately 70.6% of the patients had lymph node, 47% liver, 58.8% lung, and 47.1% had bone metastases.

Efficacy

As shown in Figure 2, the median PFS after bevacizumab-based treatment was 3.4 months (95% confidence interval [CI] 2.0–4.8). Three of the 17 patients (17.6%) achieved PR, and 10 (58.8%) SD. Among those patients, an ORR was achieved in three patients (17.6%), and CBR in 4 (23.5%). Of the three patients who achieved a PR, one patient with HER-2+ was treated previously with vinorelbine, gemcitabine, capecitabine, lapatinib, apatinib, and etoposide for MBC and had chest wall recurrence, contralateral breast, brain, and extensive skin metastasis (Fig 3a, b), while bevacizumab combined with pemetrexed was used as the ninth-line treatment. This patient achieved a PR after seven cycles, an obvious reduction of the red swollen and subcutaneous nodules was observed, and the skin itch was markedly relieved (Fig 3c,d). The other two patients were treated with bevacizumab combined with abraxane and the molecular types were luminal and triple negative breast cancer, respectively. Half of the patients who achieved SD had triple negative tumors, while the other half had luminal type tumors.

Survival outcome

According to practical clinical significance and published literature, we analyzed age, disease-free interval, molecular subtype, tumor grade, metastasis site, objective response status (ORR vs. non-ORR), and number of prior chemotherapies.[22,23] According to the results of univariate and multivariate analysis, no factor was predictive for PFS (Table 2). Triple negative tumors were not associated with the clinical efficacy of treatment in terms of PFS ($P = 0.95$) (Fig 4).

Clinical toxicity

Hematological and non-hematological toxicities are summarized in Table 3. The most common hematologic AEs were neutropenia, anemia, and thrombocytopenia. Grade 3 or 4 toxicities primarily included leukopenia (5/17, 29.4%) and neutropenia (1/17, 5.9%). The AEs, which according to previous reports might be related to bevacizumab, consisted of grade 1 bleeding (3/17, 17.6%) and grade 2 hypertension (1/17, 5.9%).[24,25] Hypertension led to the discontinuation of treatment in one case, and this patient received seven cycles before therapy was discontinued. The

Table 1 Patient demographic characteristics

Characteristic	No.	%
No. of patients	17	
Age, median (range)	47 (24–75)	
< 50	10	58.8%
≥ 50	7	41.2%
Progression-free interval, median (range)	3.4 (2.0–4.8)	
Receptor status		
ER or PR(+)/HER2(–)	6	35.3%
ER or PR(±)/HER2(+)	2	11.8%
Triple-negative	9	52.9%
Number of metastatic sites		
< 3	4	23.5%
≥ 3	13	76.5%
Distant metastases		
Lymph nodes	11	64.7%
Chest wall recurrence	4	23.5%
Brain	6	35.3%
Lung	10	58.8%
Liver	8	47.1%
Bone	8	47.1%
Contralateral breast	2	11.8%
Visceral metastasis		
Yes	13	76.5%
No	4	23.5%
Prior adjuvant chemotherapy		
Anthracyclines	13	76.5%
Taxanes	14	82.4%
Disease-free interval†		
>12 months	13	76.5%
≤ 12 months	3	17.6%
Prior chemotherapy regimens for MBC, median (range)	5 (1–10)	
≥ 3	13	76.5%
2	2	11.76%
1	2	11.76%
Prior chemotherapy drug		
Taxanes	17	100%
Anthracyclines	17	100%
Gemcitabine	11	64.7%
Capecitabine	13	76.5%
Vinorelbine	13	76.5%
Bevacizumab cycles, median (range)	4 (2–14)	
< 4	9	52.9%
≥ 4	8	47.1%
Drug co-administered with bevacizumab		
Methotrexate	1	5.9%
Etoposide	2	11.8%
Irinotecan	1	5.9%
Vinorelbine	2	11.8%
Gemcitabine	1	5.9%
Abraxane	3	17.6%
Capecitabine	3	17.6%
Pemetrexed	3	17.6%
Paclitaxel liposome	2	11.8%
ECOG performance status		
1	17	100%

†There was no disease-free interval data for one patient with primary advanced breast cancer who did not receive radical surgery. ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; MBC, metastatic breast cancer; PR, progesterone receptor.

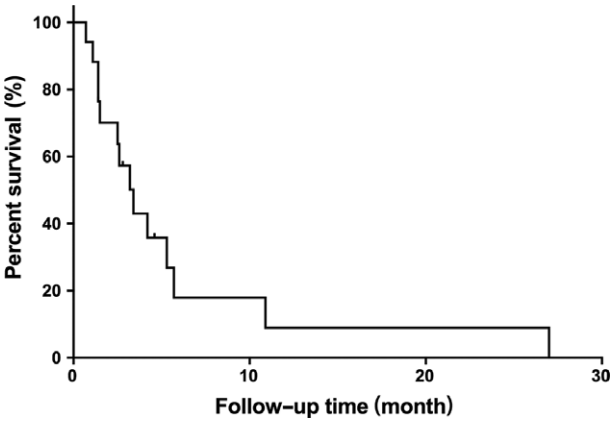

Figure 2 Kaplan–Meier curves of progression-free survival.

bleeding was mainly mild mucosal bleeding, weakly positive occult tests, and prolonged menstrual periods, and clinical intervention was not required.

One of the 17 patients who initially received 15 mg/kg bevacizumab every three weeks developed grade 3 proteinuria (24 hour urinary protein qualification of 3.51 g) after 20 cycles. Considering that the adverse effect was related to bevacizumab,[26] the treatment was adjusted to weekly treatments of 100 mg bevacizumab, which resulted in the relief and eventual elimination of proteinuria symptoms.

Discussion

In this retrospective study, the medical records of 17 MBC patients pretreated with taxane-based and/or anthracycline-based regimens and received a low-dose weekly bevacizumab-based regimen were reviewed. The results showed that the regimen had extensive activity in previously treated MBC patients. Even in patients who had previously received heavy treatment, weekly low-dose bevacizumab-based regimens exhibited efficacy and were well tolerated. The median PFS was 3.4 months, and the ORR and CBR were 17.6% and 23.5%, respectively. We also analyzed 10 MBC patients who received 15 mg/kg bevacizumab every three weeks during the same time period. All high-dose patients achieved SD and the CBR was 40%, but patients who received first-line bevacizumab-based treatment and had good Eastern Cooperative Oncology Group performance status achieved longer remission. PFS was not significantly different between low-dose weekly and high-dose groups ($P = 0.64$).

Bevacizumab, an anti-angiogenesis VEGF inhibitor, has been widely studied in breast cancer. A phase I/II study on a single bevacizumab regimen was conducted in patients previously treated for MBC, and the results showed clinical safety and efficacy with an ORR of 9.3% and a median duration of confirmed response of 5.5 months.[27] In

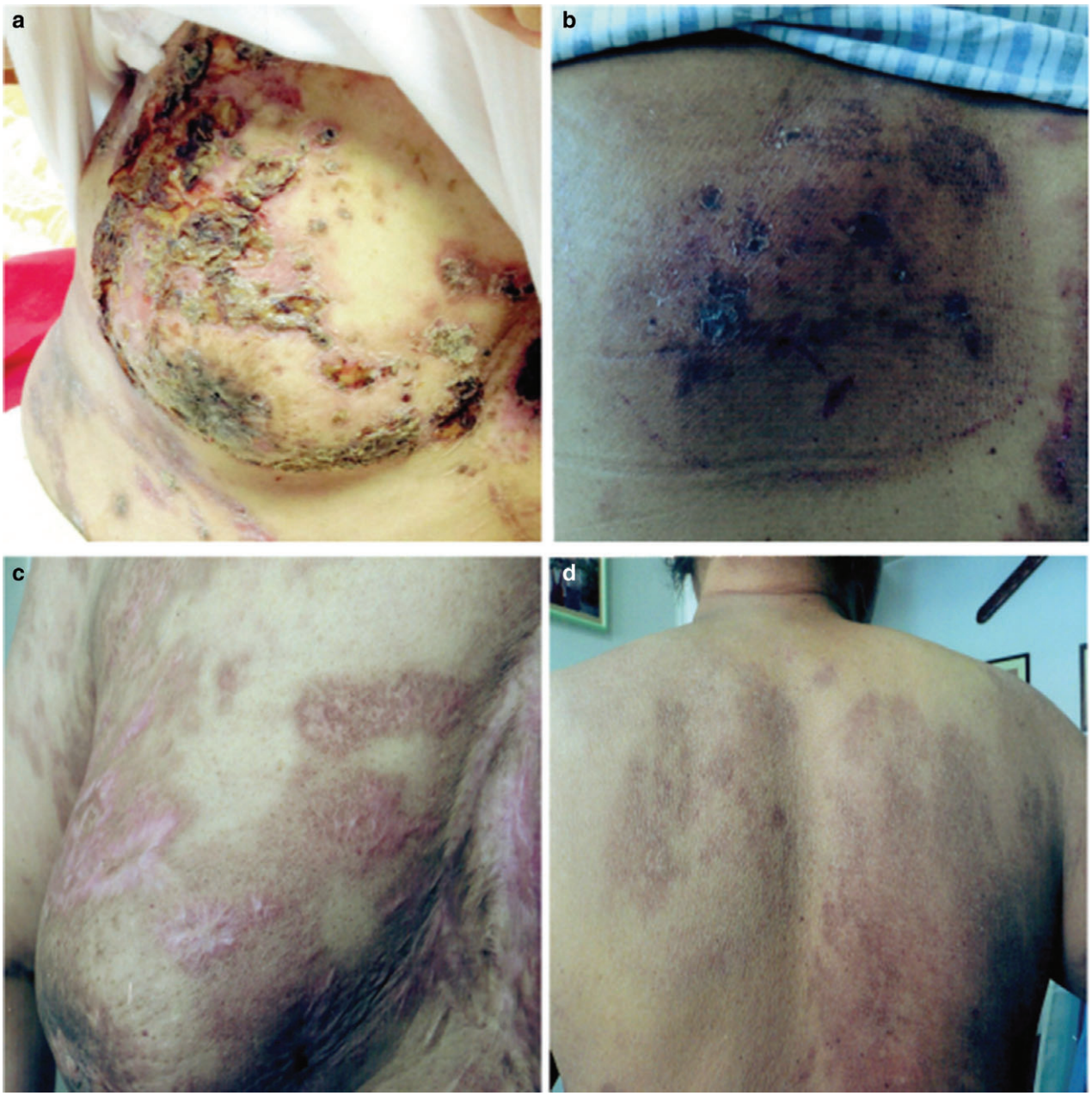

Figure 3 Patient treated with weekly low-dose bevacizumab combined with pemetrexed. (**a,b**) Chest wall recurrence, contralateral breast, brain, and extensive skin metastasis. (**c,d**) The red swollen, subcutaneous nodules and itchy skin were markedly relieved.

addition, bevacizumab combined with other chemotherapeutic agents showed a synergistic antiangiogenic effect with an increase in the response rate. In a phase III trial, 462 patients pretreated for MBC received capecitabine alone or in combination with bevacizumab as second or third-line therapy, which revealed an increased ORR of 19.8%.[13] Polyzos *et al.* combined bevacizumab with paclitaxel and showed an ORR of 30% and median PFS of 4.8 months.[28]

In comparison to other heavy pretreatment regimens for MBC, a comparable or slightly better result can be achieved using the present regimen. In a phase II trial that evaluated ixabepilone in MBC patients pretreated with anthracycline, taxane, and capecitabine, the weekly low-dose bevacizumab-based regimen demonstrated a potentially better result (ORR by independent review 14.1%, CBR 19.7%, median PFS 3.1 months).[29] Compared with another phase II study of eribulin, a standard drug treatment in advanced

Table 2 Univariate Cox proportional hazards model of progression-free survival

Variable	Univariate	
	HR (95%CI)	*P*
Age (≥ 50 vs.< 50 years)	1.15 (0.37–3.55)	0.81
Disease free interval (>12 vs. ≤ 12 months)	1.47 (0.43–5.05)	0.54
Molecular subtype		
ER or PR(+)/HER2(–)	1.0	
ER or PR(±)/HER2(+)	0.69 (0.12–3.87)	0.67
Triple-negative	0.86 (0.26–2.89)	0.81
Tumor grade		
II	1.0	
III	0.52 (0.14–1.97)	0.32
Unknown	1.05 (0.20–5.64)	0.95
Number of metastasis sites (<3 vs. ≥ 3)	2.75 (0.71–10.57)	0.14
Metastasis sites		
Bone	0.83 (0.28–2.50)	0.74
Brain	0.48 (0.14–1.57)	0.22
Visceral	1.71 (0.38–8.17)	0.47
Objective response status (ORR vs. non-ORR)	0.89 (0.24–3.38)	0.87
No. of prior chemotherapies (≥ 3 vs. < 3)	1.70 (0.46–6.27)	0.43

CI, confidence interval; ER, estrogen receptor; HR, hazard ratio; ORR, objective response rate; PR, progesterone receptor.

stage, the present regimen had a better antitumor activity (ORR 14.1%, median PFS, 2.6 months).[30,31] Notably, it should be emphasized that 61.1% of the patients in this study had more than three metastatic sites, 72.2% had undergone fourth-line therapy, and 100% had been exposed to taxanes and 94.4% to anthracyclines.

Regarding safety, the addition of bevacizumab into the chemotherapy regimen was tolerable and acceptable. Grade 3–4 chemotherapy-related toxicities were primarily

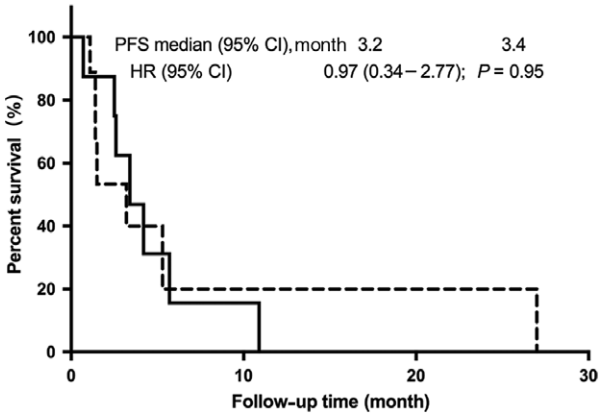

Figure 4 Progression-free survival (PFS) according to triple negative tumor. (------) Triple-negative, and (——) non-triple- negative. CI, confidence interval; HR, hazard ratio.

Table 3 Hematological and non-hematological adverse events

Adverse event	Grade				Total	
	1 or 2		3 or 4			
	No.	%	No.	%	No.	%
Non-hematologic						
Nausea	2	11.8	0	0	2	11.8
Liver dysfunction	1	5.9	0	0	1	5.9
Sensory neuropathy	1	5.9	0	0	1	5.9
Hypertension	1	5.9	0	0	1	5.9
Petechia	1	5.9	0	0	1	5.9
Bleeding	3	17.6	0	0	3	17.6
Hematologic						
Leukopenia	5	29.4	5	29.4%	10	58.8
Neutropenia	7	41.2	1	5.9%	8	47.1
Thrombocytopenia	2	11.1	0	0	3	17.6
Anemia	4	23.5	0	0	4	23.5

restricted to leukopenia, and no dose discontinuation was required as a result of hematological toxicity. In contrast to conventional bevacizumab trials, the bevacizumab-associated toxicity profile of the low-dose bevacizumab-based regimen used in this study was slightly better and rarely limited therapy.[27,32] Hypertension was observed in one patient (grade 2) who received seven cycles of therapy prior to discontinuation. The resulting bleeding was primarily mild mucosal bleeding, with weak positivity in the occult test, and a prolonged menstrual period, but medical intervention was not required. Severe hemorrhage did not occur in any of the patients. One patient initially received 10 mg/kg bevacizumab every three weeks. However, because of grade 3 proteinuria, the therapy was adjusted to 100 mg weekly, and the symptoms eventually disappeared. The regimen was continued for more than two years until disease progression. This finding demonstrates that a low-dose bevacizumab-based regimen has an acceptable and manageable safety profile.

There were several limitations to the present study. First, considering the retrospective nature of the analysis, disparities in both the known and unknown prognostic factors may affect the results. Second, because of the history of heavily pretreated and visceral metastasis, many patients could not bear chemotherapy because of poor tolerance. Additionally, the sample size of our study was small. However, this treatment seems to be effective with manageable toxicity and might provide an alternative option for salvage therapy for patients with heavily pretreated MBC.

To the best of our knowledge, the present analysis is the first real world study to explore and evaluate weekly low-dose bevacizumab-based regimens in late-stage, heavily pretreated MBC patients who had exhausted their treatment options. A low-dose bevacizumab-based therapy regimen may be effective for the treatment of patients with a general

performance status, with potentially promising ORR and PFS, and safety. Studies with larger samples are warranted to verify if this treatment can achieve long-term survival.

Disclosure

No authors report any conflict of interest.

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