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ORIGINAL ARTICLE

Effect of bevacizumab combined with docetaxel in the treatment of HER-2-negative recurrent metastatic breast cancer

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Summary

Purpose: *To explore the efficacy and safety of bevacizumab combined with docetaxel in the treatment of human epidermal growth factor receptor-2 (HER-2)-negative recurrent metastatic breast cancer.*

Methods: *The clinical data of 128 patients with HER-2-negative recurrent metastatic breast cancer treated in our hospital from January 2015 to December 2016 were retrospectively analyzed. Sixty-four patients were treated with bevacizumab combined with docetaxel (Bevacizumab group), while the remaining 64 patients were treated with docetaxel alone (Docetaxel group). The clinical efficacy and adverse reactions were compared between the two groups, and the expressions of Ki-67, p53, matrix metalloproteinase-2 (MMP-2) and MMP-9 in breast cancer tissues were compared in both groups before and after treatment. The patient survival status and progression of disease were recorded through follow-up.*

Results: *In Bevacizumab group and Docetaxel group, the objective response rate (ORR) was 57.8% and 39.1%, and the clinical benefit rate (CBR) was 90.6% and 81.3%, respectively. The ORR was significantly better in Bevacizumab group than that in Docetaxel group. There was no statistically significant difference in the incidence rate of adverse reactions between the two groups. After treatment, the positive expression rates of Ki-67, p53, MMP-2 and MMP-9 obviously declined in both groups compared with those before treatment, showing statistically significant differences between the two groups. In Bevacizumab group and Docetaxel group, the mean overall survival (OS) was 13.3±5.5 months and 11.7±5.0 months, and the mean progression-free survival (PFS) was 7.1±2.6 months and 6.6±2.3 months, respectively. According to log-rank test, the OS rate was remarkably superior in Bevacizumab group to that in Docetaxel group (p=0.041), while the PFS rate had no statistically significant difference between the two groups (p=0.095).*

Conclusions: *Bevacizumab combined with docetaxel has more excellent efficacy than docetaxel alone in the treatment of HER-2-negative recurrent metastatic breast cancer, and it prolongs the survival of patients, with tolerable adverse reactions, which is worthy of further clinical application.*

Key words: *bevacizumab, docetaxel, human epidermal growth factor receptor-2, breast cancer, recurrence and metastasis*

Introduction

There are many chemotherapy regimens for breast cancer, mainly anthracyclines and taxanes, and fluorouracil is used as a second-line drug. However, it is recommended by the 2010 NCCN guidelines that metastatic breast cancer should be treated with anthracyclines, taxanes or antimetabolites alone, because combined chemotherapy does not have better efficacy than mono-chemotherapy, but has more obvious toxic and side effects according to related studies [1,2]. Bevacizumab can inhibit the activity of vascular endothelial growth factor and reduce angiogenesis, thereby exerting a therapeutic effect on metastatic malignant tumors. It also provides a new opportunity of targeted therapy for

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human epidermal growth factor receptor-2 (HER-2)-negative breast cancer patients who cannot undergo anti-HER-2 targeted therapy [3-5]. There are studies showing that first-line chemotherapy combined with bevacizumab can effectively improve the progression-free survival (PFS) and overall response rate of patients with HER2-negative breast cancer, which has been approved by the European Union for the treatment of breast cancer [6-8].

In this study, the clinical data of 128 patients with HER-2-negative recurrent metastatic breast cancer treated in our hospital from January 2015 to December 2016 were retrospectively analyzed, and the efficacy and safety of bevacizumab combined with docetaxel in the treatment of HER-2-negative recurrent metastatic breast cancer were explored, so as to provide a basis for developing clinical therapeutic strategies for such patients.

Methods

General data

The clinical data of 128 patients with HER-2-negative recurrent metastatic breast cancer treated in our hospital from January 2015 to December 2016 were collected. Inclusion criteria: 1) patients aged ≥18 years old; 2) those diagnosed with recurrent metastatic breast cancer via surgery or pathological biopsy; 3) those in HER-2 negative status confirmed by immunohistochemistry; 4) those with measurable or evaluable lesions; 5) those with an Eastern Cooperative Oncology Group (ECOG) score of 0-2; and 6) those with an estimated survival time ≥3 months. Exclusion criteria: 1) patients with severe dysfunction of liver, kidney or other organs; 2) those complicated with hyperthyroidism, diabetes or other endocrine system diseases; 3) those with abnormalities in electrocardiogram and blood routines; 4) those who used to take bevacizumab; or 5) those with an estimated survival time <3 months. All patients were divided into the Bevacizumab group (n=64, treated with bevacizumab combined with docetaxel) and the Docetaxel group (n=64, treated with docetaxel alone) according to different therapeutic regimens. The patients were 25-73 years old with an average of 55.3±9.9 years. The general clinical baseline data (age, pathological type, metastatic site, number of metastatic lesions, etc.) had no statistically significant differences between the two groups (p>0.05), and they were comparable (Table 1). All patients enrolled abided by the *Declaration of Helsinki*, and signed the informed consent. This study was approved by the ethics committee of Tinglin Hospital of Jinshan District. Signed written informed consents were obtained from all participants before the study entry.

Table 1. Baseline demographic and clinical characteristics of the studied patients

Parameters	*Bevacizumab group (n=64) n (%)*	*Docetaxel group (n=64) n (%)*	*p value*
Age (years)	54.37±9.72	56.13±9.91	0.312
Pathological type			0.866
Invasive ductal carcinoma	45 (70.3)	42 (65.6)	
Invasive lobular carcinoma	10 (15.6)	13 (20.3)	
Invasive poorly differentiated adenocarcinoma	4 (6.3)	3 (4.7)	
Medullary carcinoma	5 (7.8)	6 (9.4)	
Menstrual status			0.291
Menopause	17 (26.6)	12 (18.8)	
Premenopause	47 (73.4)	52 (81.2)	
Hormone receptor			0.372
ER or PR +	34 (53.1)	39 (60.9)	
ER and PR -	30 (46.9)	25 (39.1)	
Number of metastatic lesions			0.367
1	28 (43.8)	23 (35.9)	
>1	36 (56.2)	41 (64.1)	
Previous chemotherapy			0.386
Anthracycline or Taxane	29 (45.3)	27 (42.2)	
Anthracycline and Taxane	26 (40.6)	22 (34.4)	
No Anthracycline or Taxane	9 (14.1)	15 (23.4)	
ECOG			0.853
0	18 (28.1)	23 (35.9)	
1	29 (45.3)	28 (43.8)	
2	17 (26.6)	13 (20.3)	

ER: Eastrogen receptor, PR: Progesterone receptor, ECOG: Eastern Cooperative Oncology Group

Treatment methods

Before chemotherapy, various examinations and symptomatic treatment (nutritional support and increase of leucocytes) were performed, and dexamethasone and 5-HT_3 receptor blockers were used to prevent vomiting. In the Bevacizumab group, bevacizumab (15 mg/kg, intravenously injected on days 1 and 2) combined with docetaxel (75 mg/m^2, intravenously injected for 1 h on day 1) was applied for 3 weeks as one treatment cycle. In the Docetaxel group, docetaxel alone (75 mg/m^2, intravenously injected for 1 h on day 1) was applied for 3 weeks as one treatment cycle. The patients in both groups were treated for 4 cycles. At 3, 7 and 10 day after chemotherapy, the hepatic-renal function and blood routine examinations were performed, and symptomatic treatment was given in the case of abnormalities. During chemotherapy, the adverse reactions were observed and registered.

Observation indexes

The short-term efficacy of therapy was evaluated according to the Response Evaluation Criteria In Solid Tumors (RECIST). Complete response (CR): All target lesions disappear for at least 4 weeks; partial response (PR): the sum of long diameter of baseline lesions declines by ≥30% for at least 4 weeks; progressive disease (PD): the sum of long diameter of baseline lesions increases by at least ≥20% or there are new lesions; and stable disease (SD): the sum of long diameter of baseline lesions declines less than PR or increases less than PD. The objective response rate (ORR =CR + PR) and clinical benefit rate (CBR=CR + PR + SD) were calculated.

Adverse reactions were evaluated according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTC 4.0), and graded (I-IV) based on the severity. Before and after treatment, the breast cancer tissue samples were collected in both groups, in which the expressions of Ki-67, p53, matrix metalloproteinase-2 (MMP-2) and MMP-9 were detected via immunohistochemistry. Clear brown color in the nucleus indicated positive Ki-67 and p53, and red color in the cytoplasm indicated positive MMP-2 and MMP-9.

The patients were followed up at 1, 2, 3, 6, 9 and 12 months after treatment, and every 3-6 months thereafter till December 2019, while their survival and progression of disease were recorded. PFS refers to the duration from treatment initiation to first PD or death of any cause, and overall survival (OS) refers to the duration from treatment initiation to death or last to follow-up.

Statistics

SPSS 22.0 software (IBM, Armonk, NY, USA) was used for statistical analyses. Measurement data were expressed as mean ± standard deviation (x±s), and t-test was performed for intergroup comparison. Enumeration data were expressed as rate (%), and x^2 test was performed for intergroup comparison. The survival curves were plotted using the Kaplan-Meier method, and log-rank test was used for intergroup survival differences. P<0.05 suggested statistically significant difference.

Results

Comparison of short-term efficacy between the two groups

The efficacy in all patients was evaluated after treatment. In the Bevacizumab group, there were 7 cases (10.9%) of CR, 30 cases (46.9%) of PR, 21 cases (32.8%) of SD, and 6 cases (9.4%) of PD. The ORR and CBR were 57.8 % (37 cases) and 90.6% (58 cases), respectively. In the Docetaxel group, there were 5 cases (7.8%) of CR, 19 cases (29.7%) of PR, 28 cases (43.8%) of SD, and 12 cases (18.8%) of PD. The ORR and CBR were 39.1% (24 cases) and 81.3% (52 cases), respectively. The ORR was significantly better in the Bevacizumab group than in the Docetaxel group, but the CBR had no statistically significant difference between the two groups (p=0.021, p=0.127) (Table 2).

In the Bevacizumab group, 29 patients were taking anthracyclines in adjuvant chemotherapy, 26 patients were taking anthracyclines or taxanes in adjuvant chemotherapy, and the remaining 9 patients did not take taxanes or anthracyclines before. The patients were stratified according to whether they received anthracyclines or taxanes during adjuvant therapy, and then the efficacy of bevacizumab combined with docetaxel was compared. It was found that the efficiency of bevacizumab combined with docetaxel was higher in patients who did not take taxanes or anthracyclines before (77.8%, 7/9) than in patients who used to take paclitaxel (54.5%, 30/55), but the difference was not statistically significant (p=0.282).

Table 2. Clinical effective rates of the two studied groups

	Bevacizumab group (n=64) n (%)	*Docetaxel group (n=64) n (%)*	*p value*
CR	7 (10.9)	5 (7.8)	
PR	30 (46.9)	19 (29.7)	
SD	21 (32.8)	28 (43.8)	
PD	6 (9.4)	12 (18.8)	
ORR	37 (57.8)	24 (39.1)	0.021
CBR	58 (90.6)	52 (81.3)	0.127

CR: Complete Response, PR: Partial Response, SD: Stable Disease, PD: Progressive Disease, ORR: Overall response rate, CBR: Clinical benefit rate

Comparison of adverse reactions between the two groups

The non-hematological adverse reactions related to chemotherapy mainly included fatigue, nausea and vomiting, diarrhea, joint and muscle pain, neurotoxicity and mucositis, and they were all in grade I-II and improved after symptomatic treatment. The most common grade III-IV adverse reaction related to chemotherapy was bone marrow suppression, manifested as follows: 7 cases (10.9%) and 3 cases (4.7%) of anemia, 12 cases (18.8%) and 14 cases (21.9%) of neutropenia (including 2 cases of febrile neutropenia in each group), and 5 cases (7.8%) and 2 cases (3.1%) of thrombocytopenia, respectively, in the Bevacizumab group and Docetaxel group. In terms of specific adverse reactions possibly related to bevacizumab, there were 29 cases (45.3%) and 17 cases (26.6%) of epistaxis, respectively, in the Bevacizumab group and the Docetaxel group, and the difference was not statistically significant (p=0.057). Proteinuria occurred in 18 cases (28.1%) and 14 cases (21.9%), respectively, in the Bevacizumab group and the Docetaxel group, without a statistically significant difference (p=0.541), and the renal function returned to normal without special treatment. There were 6 cases (9.4%) and 4 cases (6.3%) of hypertension of grade I-II in the two groups, and it was well controlled after treatment

Table 3. Comparison of adverse reactions of patients in the two studied groups

Parameters	*Bevacizumab group (n=64)*		*Docetaxel group (n=64)*		*p value*
	Grade I-II n (%)	*Grade III-IV n (%)*	*Grade I-II n (%)*	*Grade III-IV n (%)*	
Fatigue	30 (46.9)	0 (0)	25 (39.1)	0 (0)	0.475
Nausea / Vomiting	26 (40.6)	0 (0)	22 (34.4)	0 (0)	0.584
Diarrhea	17 (26.6)	0 (0)	14 (21.9)	0 (0)	0.680
Joint/ muscle pain	28 (43.8)	0 (0)	23 (35.9)	0 (0)	0.470
Neurotoxicity	11 (17.2)	0 (0)	8 (12.5)	0 (0)	0.620
Mucositis	21 (32.8)	0 (0)	15 (23.4)	0 (0)	0.326
Epistaxis	29 (45.3)	0 (0)	17 (26.6)	0 (0)	0.057
Anemia	23 (35.9)	7 (10.9)	16 (25.0)	3 (4.7)	0.069
Neutropenia	29 (45.3)	12 (18.8)	24 (37.5)	14 (21.9)	0.716
Thrombocytopenia	24 (37.5)	5 (7.8)	17 (26.6)	2 (3.1)	0.100
Hypertension	6 (9.4)	0 (0)	4 (6.3)	0 (0)	0.744
Proteinuria	18 (28.1)	0 (0)	14 (21.9)	0 (0)	0.541
Elevated ALT/AST	16 (25.0%)	0 (0%)	19 (29.7%)	0 (0%)	0.692

ALT: Alanine transaminase, AST: Aspartate Aminotransferase

Table 4. Comparison of positive expression rates of Ki-67, p53, MMP-2, MMP-9 of patients in the two studied groups

	Bevacizumab group (n=64) n (%)	*Docetaxel group (n=64) n (%)*	*p value*
Ki-67 +			
Pretreatment	41 (64.1)	38 (59.4)	0.616
Posttreatment	30 (46.9)	20 (31.3)	0.041
p53 +			
Pretreatment	50 (78.1)	47 (73.4)	0.680
Posttreatment	39 (60.9)	29 (45.3)	0.036
MMP-2 +			
Pretreatment	42 (65.6)	40 (62.5)	0.654
Posttreatment	31 (48.4)	19 (29.7)	0.031
MMP-9 +			
Pretreatment	45 (70.3)	41 (64.1)	0.573
Posttreatment	41 (64.1)	22 (34.4)	0.002

MMP: Matrix metalloproteinase

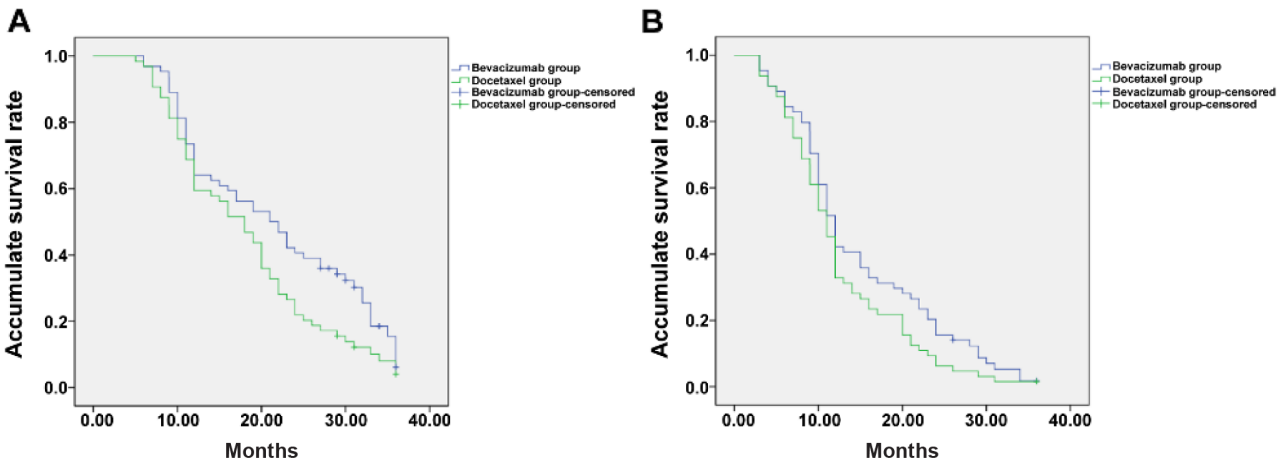

Figure 1. Kaplan-Meier survival curves of patients in the Bevacizumab and the Docetaxel. **A:** The overall survival rate of patients in Bevacizumab group was significantly higher than that of Docetaxel group (p=0.041). **B:** The difference between progression-free survival rate of patients in the Bevacizumab and the Docetaxel group had no statistical significance (p=0.095).

with angiotensin-converting enzyme inhibitors, calcium ion antagonists and other antihypertensive drugs. No severe adverse reactions, such as congestive heart failure, gastrointestinal perforation and poor wound healing, were observed, and no deaths related to adverse drug reactions occurred. There was no statistically significant difference in the incidence rate of adverse reactions between the two groups (p>0.05) (Table 3).

Changes in expressions of p53, Ki -67, MMP-2 and MMP -9 in both groups

The positive expression rates of Ki-67, p53, MMP-2 and MMP-9 had no statistically significant differences between the two groups before treatment (p>0.05). After treatment, the positive expression rates of Ki-67, p53, MMP-2 and MMP-9 obviously declined in both groups compared with those before treatment (p<0.05), and they had statistically significant differences between the two groups (p<0.05) (Table 4).

Follow-up results of patient survival status

As of December 2019, the mean follow-up time was 22.1±5.7 months and 21.0±5.1 months, respectively, in the two groups. In the Bevacizumab group and the Docetaxel group, the mean OS was 13.3±5.5 months and 11.7±5.0 months, and the mean PFS was 7.1±2.6 months and 6.6±2.3 months, respectively. In the Bevacizumab group and the Docetaxel group, the 1-year OS rate and PFS rate were 64.1% (41/64) *vs.* 59.4% (38/64), and 42.2% (27/64) *vs.* 32.8% (21/64). The 2-year OS rate and PFS rate were 40.6% (26/64) *vs.* 21.9% (14/64), and 15.9% (10/64) *vs.* 7.8% (5/64). The 3-year OS rate and PFS rate were 17.2% (11/64) *vs.* 6.3% (4/64), and 0% *vs.* 0%. The survival curves were plotted in both groups using the Kaplan-Meier method. According to log-rank test, the OS rate was remarkably superior in the Bevacizumab group than in the Docetaxel group (p=0.041), while the PFS rate had no statistically significant difference between the two groups (p=0.095) (Figure 1).

Discussion

At present, classified therapy is recommended for breast cancer. Anti-HER-2 targeted therapy based on trastuzumab has achieved encouraging results in the salvage therapy of recurrent metastatic breast cancer, and postoperative adjuvant therapy and preoperative neoadjuvant therapy of early breast cancer, which has become the standard treatment for HER-2-positive breast cancer patients. It is necessary to explore the biological targeted therapy of HER-2-negative patients based on the successful experience of anti-HER-2 targeted therapy. Anti-angiogenesis targeted therapy has become another important targeted therapy after anti-HER-2 targeted therapy [9-12]. Bevacizumab is the most mature anti-angiogenesis targeted drug currently used in the clinic, and it is theoretically not restricted by HER-2 status in the treatment of breast cancer, which provides a new opportunity of targeted therapy for HER-2-negative patients who cannot undergo anti-HER-2 targeted therapy.

In the treatment of advanced breast cancer, bevacizumab is often used in combination with chemotherapy as first-line or second-line treatment of HER-2-negative recurrent metastatic breast cancer. According to most clinical studies, bevacizumab combined with chemotherapy can delay the time of disease progression, and

raise the ORR [13-16]. In E2100, an ECOG-initiated phase III clinical trial, a total of 722 patients with advanced breast cancer were enrolled and randomly divided into combination group (paclitaxel combined with avastin) and paclitaxel group (paclitaxel alone). It was found that PFS was significantly prolonged (11.8 months *vs.* 5.9 months, HR=0.60, p<0.001), the ORR raised (36.9% *vs.* 21.2%, p<0.001), but OS had no significant improvement (26.7 months *vs.* 25.2 months, HR=0.88, p=0.16) in the combination group compared with those in the paclitaxel group [17]. In the RIBBON-1 phase III clinical trial, the efficacy and safety of first-line chemotherapy based on anthracyclines, taxanes and capecitabine were evaluated in the case of bevacizumab combined or not. Then, PD patients in RIBBON-1 were enrolled into the RIBBON-2 phase III clinical trial, and the efficacy and safety of bevacizumab combined with anthracycline-free chemotherapy were compared [18]. According to the midterm follow-up results, bevacizumab combined with anthracyclines or capecitabine could prolong PFS of patients compared with chemotherapy alone, and bevacizumab combined with capecitabine could also prolong PFS by 2.9 months compared with docetaxel alone.

In this study, the ORR was 57.8% (37 cases) and 39.1% (24 cases), and the CBR was 90.6% (58 cases) and 81.3% (52 cases), respectively, in the bevacizumab group and the docetaxel group. It can be seen that the ORR was significantly better in the bevacizumab group than in the docetaxel group, but the CBR had no statistically significant difference between the two groups (p=0.021, p=0.127). According to follow-up results, the OS rate was remarkably superior in the bevacizumab group to that in the docetaxel group (p=0.041), while the PFS rate had no statistically significant difference between the two groups (p=0.095). The analysis of adverse reactions revealed that the most common non-hematological toxicities related to bevacizumab were bleeding and proteinuria usually of grade I-II, and bleeding was mostly manifested as epistaxis, which was relieved spontaneously after drug withdrawal without special treatment. No severe visceral bleeding was observed. The occurrence of proteinuria might be related to the damage to glomerular vascular endothelial cells, mostly of grade I-II. The patients had no obvious symptoms, and urine protein returned to normal in most patients after drug withdrawal. Hypertension is also one of the common adverse reactions of bevacizumab [19]. Hypertension occurred in 10 cases, all of grade I-II, and the blood pressure could be controlled within the normal range after oral administration of antihypertensive drugs. Besides, hematological toxicities included neutropenia, and decrease in hemoglobin and thrombocytopenia, dominated by neutropenia in 12 cases (18.8%) and 14 cases (21.9%), respectively, in the two groups, which was improved after supportive treatment with granulocyte colony-stimulating factors. The decrease in hemoglobin and thrombocytopenia were mostly of grade I-II, and they could restore spontaneously without special treatment.

There are studies showing that tumor markers can reflect the efficacy of chemotherapy and biotherapy from multiple aspects. As a tumor cell apoptosis factor, p53 can monitor the cancerization of cells. As a proliferating cell nuclear antigen, Ki-67 can objectively reflect the cell proliferation activity, and its positive expression corresponds to poor prognosis. Moreover, extracellular matrix and basement membrane are degraded due to the invasion and metastasis of malignant tumor cells, thus stimulating the expressions of MMP-2 and MMP-9 [20,21]. In this study, the results manifested that bevacizumab combined with neoadjuvant chemotherapy had definite clinical efficacy on breast cancer, and it could greatly lower the expressions of Ki-67, p53, MMP-2 and MMP-9 in patients, without increasing the incidence rate of adverse drug reactions.

There were limitations in this study. For example, the sample size was limited, the follow-up period was short, and the follow-up content was not comprehensive enough. In the future, the conclusion made in this study needs to be confirmed by rigorous and highly-reliable large-sample prospective clinical research.

Conclusions

Bevacizumab combined with docetaxel has more excellent efficacy than docetaxel alone in the treatment of HER-2-negative recurrent metastatic breast cancer, and it prolongs the survival of patients, with tolerable adverse reactions, which is worthy of further clinical application.

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Conflict of interests

The authors declare no conflict of interests.

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