Original Article

Application of apatinib after multifaceted therapies for metastatic breast cancer

Jue Wang, Yangyang Chen, Renwang Chen, Lu Wu, Jing Cheng

Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

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Correspondence to: Jing Cheng; Lu Wu. Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China. Email: chenjin1118@hotmail.com; wulu2781@163.com.

Background: Apatinib is a small molecule tyrosine kinase inhibitor (TKI) that is taken orally and has high specificity for vascular endothelial growth factor receptor 2 (VEGFR-2). This study explored the efficacy and toxicity of apatinib in patients with metastatic breast cancer (MBC) who failed to respond to multifaceted therapy.

Methods: A total of 61 patients with MBC who were unresponsive to previous multifaceted chemotherapy were included in this study. The treatment regimens were either a combination of apatinib and chemotherapy or apatinib administered singly with a dose range of 250 mg every second day to 500 mg per day. Progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), and toxicity were used as outcome measures.

Results: Of the 61 patients, partial response (PR) was observed in 14 patients (23.0%), stable disease (SD) was observed in 30 patients (49.2%), and progressive disease (PD) was observed in 17 patients (27.8%). The DCR was 44/61 (72.1%), and the ORR was 14/61 (23.0%). Of the 44 patients who achieved PR or SD, the median PFS was 4 months and 15 days. Patients with intracranial metastases were found to benefit from apatinib. Furthermore, 11 patients underwent next generation sequencing (NGS) and 5 of these had a P53 mutation. Of those 5 cases, the ORR and DCR were 0% and 20.0%, respectively. Of the 6 cases with wild-type P53, the ORR was 50.0%, and the DCR was 100.0%. Multivariate regression analysis found that hypertension was an independent prognostic factor of better DCR.

Conclusions: Apatinib showed good efficacy and manageable toxicity in patients with MBC that had not responded to multifaceted therapy.

Keywords: Breast cancer; apatinib; vascular endothelial growth factor (VEGF); P53; intracranial metastases

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Introduction

Breast cancer has a higher morbidity than the other malignant tumors prevalent in females (1). Ongoing advances made in radiotherapy, chemotherapy, endocrine therapy, targeted therapy, and immunotherapy have contributed to reducing the breast cancer mortality rate each year (2). However, the majority of patients with metastatic breast cancer (MBC) develop tolerance to treatment and eventually fail to respond to most Food and Drug Administration (FDA)-approved breast cancer drugs. There is therefore a need for the development of more effective drugs to be applied in clinical practice.

Anti-angiogenesis has garnered considerable research attention as an avenue of malignant tumor treatment. Vascular endothelial growth factors (VEGFs) and their

receptor family contribute substantially to tumor growth (3). The VEGF-A monoclonal antibody bevacizumab, combined with chemotherapy, was found to significantly increase the objective response rate (ORR) and progression-free survival (PFS) of patients with metastatic triple-negative breast cancer as a first choice therapy (4-6). Used as second-line treatment, this combination not only improved PFS, but also tended to enhance overall survival (OS) of patients (7). VEGF receptors include VEGFR-1 (Flt1), VEGFR-2 (KDR), VEGFR-3 (Flt4), platelet-derived growth factor receptors (PDGFRs), and c-KIT (8). Sorafenib and sunitinib are small molecule tyrosine kinase inhibitors (TKIs) that inhibit multiple tyrosine kinases, but some studies have shown that neither has a significant effect on MBC (9,10), despite the fact they are thought to react with multiple VEGFRs simultaneously. These TKIs have, in fact, had some success in treating MBC. Due to their toxicity and limited efficacy, however, they are not widely prescribed.

Apatinib is another small molecule oral TKI that is highly specific for VEGFR-2. This TKI is believed to promote cell proliferation and migration, increase vascular permeability, and play a vital role in tumor progression and vasoformation (11). Apatinib administered alone has been shown to inhibit the growth of cholangiocarcinoma cells in preclinical studies (12), and its combination with chemotherapy could reverse multidrug resistance in multiple cancer cell lines. The combination of apatinib and chemotherapy may also result in cytotoxicity by significantly enhancing the cytotoxicity of ABCB1 or ABCG2 substrate drugs in cells where ABCB1 and ABCG2 (wild type) are overexpressed (13). Clinical research on phase II MBC has shown that apatinib administered alone was effective against both triple-negative and non-triple-negative breast cancer with a median PFS (mPFS) of 3.3 and 4 months, respectively, and a median OS (mOS) of 10.6 months and 10 months, respectively (14,15). However, there is limited clinical research investigating the combination treatment of apatinib and chemotherapy or endocrine therapy.

In the present study, apatinib was applied both as a monotherapy and a combination therapy in MBC patients from our cancer center that had not responded to multifaceted therapy. All 61 patients were retrospectively analyzed to investigate the efficacy and toxicity of apatinib. The findings suggest that apatinib can be a viable treatment option for patients with breast cancer, and our research lays a foundation for further clinical studies into the use of this drug in treatment-resistant MBC patients.

We present the following article in accordance with STROBE reporting checklist (available at http://dx.doi.org/10.21037/tcr-19-2588).

Methods

Ethics statement

This research was conducted in line with the Declaration of Helsinki (as revised in 2013) and was ratified by the Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology (IORG No: IORG0003571; No. 2020-S103). All patients provided written informed consent.

Patients

We recruited 61 patients who were treated with apatinib in our department from March 2016 to February 2018 as subjects in our retrospective study. They had all been diagnosed with MBC and had received at least one treatment of anthracycline and taxane chemotherapy. The patients were aged from 30 to 70 years. Hormone receptor-positive (HR+) patients were resistant to endocrine therapy and could not receive other endocrine therapies for financial reasons. Human epidermal growth factor receptor 2 positive (HER-2+) patients had received tastuzumab (Herceptin) treatment and shown drug resistance, but could not receive other anti-HER-2 treatments for financial reasons. These patients were either intolerant to other drugs or rejected the use of other chemotherapeutic agents, and their Eastern Cooperative Oncology Group (ECOG) scores ranged from 0 to 2. Patients elected to receive single-agent or combination therapy with apatinib according to their tolerance and willingness to undergo the treatment.

Exclusion criteria included the following: patients with wounds that did not heal; patients with bone fractures that were traumatic or pathological; patients with urine protein more than 2+ and validated urinary protein/24 h >1.0 g; patients treated by any concomitant antineoplastic therapy; patients with reduced hematologic, hepatic, or renal function; and patients with congestive heart failure or other conditions that increased their risk for toxicity.

Before 2011, ER/PgR negativity was defined as immunohistochemistry (IHC) showing less than 10% positive tumor cells with chromatin. Since 2011, based on the new College of American Pathologists guidelines, ER/PgR negativity has been defined as ER/PgR staining of

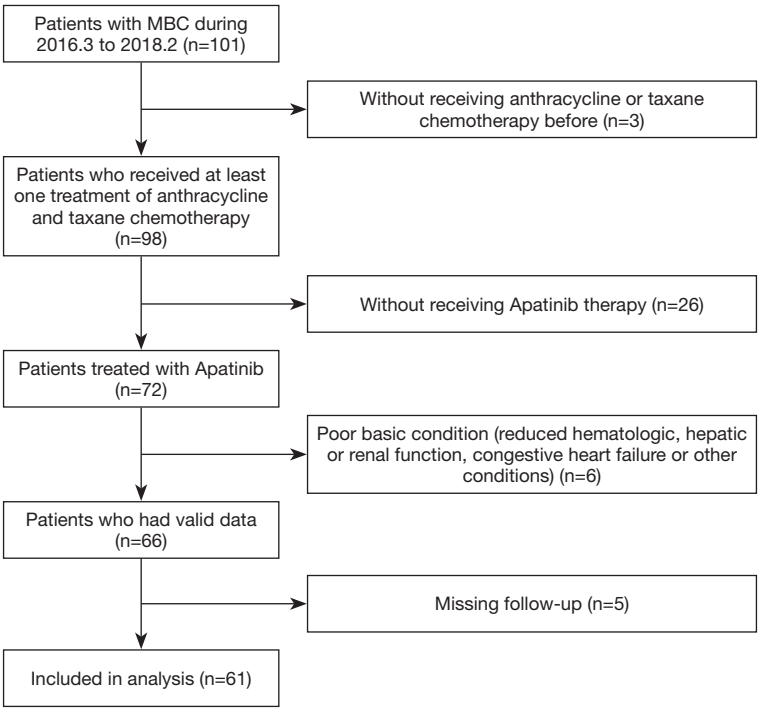

Figure1 Flow diagram of applicable patients. MBC, metastatic breast cancer.

less than 1%. The status of HER2/Neu-negativity in the present study was defined by an IHC score of 0 to 11 or by chromogenic/fluorescent in situ hybridization (CISH/FISH) in line with the guidelines of the American Society of Clinical Oncology (ASCO).

Treatment

Apatinib dose was modified according to toxicity criteria. Therapy continued until a patient's disease deteriorated, drug toxicity was unacceptable, or the patient left the study of their own volition. Patient response was evaluated every 2 months. The gradation of adverse events (AEs) was implemented in line with the Common Terminology Criteria for Adverse Events (CTCAE, Version 4.03) issued by the National Cancer Institute in the United States.

Data collection

The baseline clinical characteristics of patients after enrollment were collected and standardized. The clinical benefit rate (CBR) was considered to be the ratio of assessable patients to achieve a complete response (CR), partial response (PR), or stable disease (SD) for more than 4 weeks and was determined using the RECIST standard 1.1 (16).

Statistical analysis

SPSS 19.0 was used to conduct all the statistical analysis in this study. PFS and OS were calculated by using Log-rank analysis. Single-factor analysis of DCR were performed using Chi-square tests, and variables with P value <0.3 in the single-factor Chi-square tests were evaluated in multivariate regression analysis by using Cox proportional hazards regression models. P value <0.05 was considered statistically significant.

Results

Baseline characteristics

As of February 1, 2018, 61 MBC patients that met our criteria had been observed (*Figure 1*); the general information of these patients is detailed in *Table 1*. Of these patients, 19 had triple-negative breast cancer, 26 had HR+ breast cancer, and 13 had HER-2+ breast cancer. Before receiving apatinib treatment, all patients underwent some

Table 1 Patient characteristics

Variable	Group	Whole population (n=61), n (%)
Age (years)	≥60	12 (19.7)
	<60	49 (80.3)
Menopausal state	Post-menopause	39.3%
	Pre-menopause	60.7%
Pathological type	Invasive ductal carcinoma	58 (95.1)
	Encephaloid carcinoma	3 (4.9)
Subgroup	Triple negative	19 (31.1)
	HER2 positive	13 (21.3)
	Luminal A	15 (24.6)
	Luminal B	11 (18.0)
	Unknown	3 (5.0)
Metastatic sites	Lymph node	24 (39.3)
	Bone	32 (52.5)
	Lung	26 (42.6)
	Liver	23 (37.7)
	Brain	16 (26.2)
	Chest wall	8 (13.1)
	Pleura	5 (8.2)
	Peritoneum	3 (4.9)
	No. of metastatic >3	23 (38.3)
	Visceral	55 (91.7)
Prior chemotherapy regimen	Anthracycline	43 (70.5)
	Taxanes	51 (83.6)
	Capecitabine	43 (70.5)
	Vinorelbine	37 (60.6)
	Gemcitabine	31 (50.8)
Lines of chemotherapy	≤3 cycles	30 (49.2)
	>3 cycles	31 (50.8)
Combination with Apatinib	None	9 (14.8)
	Chemotherapy	49 (80.3)
	Herceptin	1 (1.6)
	Endocrine therapy	2 (3.3)

HER2, human epidermal growth factor receptor-2.

form of chemotherapy, including neoadjuvant, adjuvant, or post-metastasis chemotherapy, and 31 received three or more cycles of chemotherapy post-metastasis. Patients with HR+ breast cancer had all received endocrine therapy that either failed, could not be tolerated, or could not be afforded. Patients with HER-2+ breast cancer had been treated with Herceptin, and disease progression was observed. Of the 61 patients, 16 had brain metastases, and 11 patients had more than 3 intracranial metastases (*Table 1*).

The apatinib regimen for a given patient was developed based on tolerability and current condition; 9 patients received monotherapy with apatinib, and 2 patients received apatinib therapy combined with letrozole; a combination of apatinib and taxane drugs were given to 19 patients, while 5 patients received apatinib combined with vinorelbine, and 12 patients received apatinib combined with capecitabine. For 58 patients, the initial dose of apatinib was 250 mg/day. This was reduced to 250 mg every second day in 8 patients after 1 week due to intolerable AEs, with 2 patients discontinuing apatinib therapy due to AEs. Two patients received an initial dose of 500 mg/day, which was reduced to 250 mg/day in one patient after 2 weeks due to intolerable AEs; one patient received an initial dose of apatinib of 250 mg every 2 days.

Safety

The toxicities encountered in our study are listed in *Table 2*. Due to intolerable AEs, 2 of 61 patients discontinued apatinib treatment. After taking apatinib at a dose of 250 mg/day for 4 days, one patient experienced a small amount of vaginal bleeding that was bright red, intermittent, and persisted approximately 4 days. A reduced dose was recommended, but the patient declined to continue treatment. After 2 weeks of apatinib monotherapy, another patient experienced severe anorexia and fatigue. It was recommended that drug treatment be temporarily suspended to allow time for symptoms to improve, but the patient declined to continue treatment. The chest wall mass in another patient was significantly smaller after 2 weeks of apatinib treatment of 250 mg/day combined with capecitabine, but the remaining metastatic lesions were not evaluated. This patient suffered a gradual onset of gastrointestinal bleeding that mainly manifested as bloody stool. One month after drug treatment ceased, this patient died, with disease progression being considered the cause of death. The remaining 58 patients continued to use apatinib

Table 2 Non-hematologic and hematologic adverse events in patients with apatinib

Adverse event	Total, n (%)	Grade 1, n (%)	Grade, n (%)	Grade 3, n (%)	Grade 4, n (%)
Monotherapy with apatinib					
Hypertension	3 (33.3)	1 (11.1)	1 (11.1)	0 (0.0)	1 (11.1)
Hand-foot syndrome	2 (22.2)	1 (11.1)	1 (11.1)	0 (0.0)	0 (0.0)
Fatigue	1 (11.1)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)
Mucositis	2 (22.2)	2 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)
Bleeding	2 (22.2)	1 (11.1)	1 (11.1)	0 (0.0)	0 (0.0)
Anorexia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	2 (22.2)	1 (11.1)	1 (11.1)	0 (0.0)	0 (0.0)
Proteinuria	1 (11.1)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)
Combintherapy with apatinib					
Hypertension	27 (44.3)	1 (1.6)	12 (19.7)	13 (21.3)	2 (3.3)
hand-foot syndrome	22 (36.0)	6 (9.8)	8 (13.3)	8 (13.1)	0 (0.0)
Fatigue	19 (31.1)	14 (23.0)	5 (8.3)	0 (0.0)	0 (0.0)
Mucositis	11 (18.0)	6 (9.8)	2 (3.3)	5 (8.2)	0 (0.0)
Bleeding	10 (16.4)	6 (9.8)	3 (4.9)	0 (0.0)	1 (1.6)
Anorexia	9 (14.8)	9 (14.8)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	3 (4.9)	3 (4.9)	0 (0.0)	0 (0.0)	0 (0.0)
Neutropenia	29 (47.5)	3 (4.92)	16 (26.2)	9 (14.8)	1 (1.6)
Anemia	23 (37.7)	14 (23.0)	9 (14.8)	0 (0.0)	0 (0.0)
Thrombocytopenia	3 (4.9)	0 (0.0)	1 (1.6)	1 (1.6)	1 (1.6)
Transaminase increased	34 (55.7)	29 (47.6)	5 (8.2)	0 (0.0)	0 (0.0)
Bilirubin increased	24 (39.3)	14 (23.0)	8 (13.1)	1 (1.6)	1 (1.6)
Proteinuria	5 (8.2)	0 (0.0)	5 (8.2)	0 (0.0)	0 (0.0)

until disease progression occurred. One patient received monotherapy with apatinib at a dose of 500 mg/day until disease progression occurred. For the remainder of the patients, regardless of initial dose and whether apatinib treatment was combined with other drugs or used alone, the dose was reduced to 250 mg/day or 250 mg every second day so it could be tolerated.

Of the 61 patients, 37 experienced grade 3 AEs, including hypertension, hand-foot syndrome, oral mucositis, and neutropenia. The most frequently occurring grade 2 AEs were neutropenia, hypertension, hand-foot syndrome, and elevated bilirubin. The most frequently occurring grade 1 AEs were elevated transaminase, anemia, elevated bilirubin, fatigue, anorexia, and hand-foot syndrome. Approximately half of the patients experienced hypertension. In addition, 39.3% of the patients experienced hand-foot syndrome, which was self-mitigated by most patients. Oral mucositis was also a common AE, but this was alleviated by gargling with mouthwash containing vitamin B12, dexamethasone, and gentamicin.

Efficacy

Overall efficacy

Of the 61 patients, PR was observed in 14 patients (23.0%), SD in 30 patients (49.2%), and progressive disease (PD) in 17 patients (27.8%). CR was not observed in any patients. The disease control rate (DCR) was 44/61 (72.1%), and the

Table 3 Treatment plan and clinical effect of patients with brain metastases

No.	Brain radiotherapy with apatinib simultaneously	CNS end
1	Yes	PR
6	No	PR
9	Yes	SD
10	No	PR
11	No	PR
28	Yes	PD
38	No	PR
41	No	SD
42	Yes	SD
43	No	PD
46	No	PR
51	Yes	PD
53	No	SD
56	Yes	PR
58	Yes	PR
60	No	SD

CNS, central nervous system; PR, partial response; SD, stable disease; PD, progressive disease.

ORR was 14/61 (23.0%). The two patients who declined to continue apatinib treatment showed a reduction in size of their chest wall nodules after 1 week of treatment, but drug efficacy could not be evaluated due to the treatment being discontinued. Of the 44 patients who achieved PR or SD, the PFS was 3 to 6 months and the mPFS was 4.5 months.

Clinical efficacy of apatinib alone and apatinib combined with chemotherapy

Of the 61 patients in the study, 49 were treated with apatinib combined with chemotherapy. Of these patients, 19 (38.8%) received apatinib combined with taxanes, 14 (28.5%) received apatinib combined with capecitabine, 5 (10.2%) received apatinib combined with vinorelbine, 5 (10.2%) received apatinib combined with gemcitabine, 2 (4.1%) received apatinib combined with pemetrexed, 2 (4.1%) received apatinib combined with gimeracil and oteracil potassium capsules, and 2 (4.1%) received apatinib combined with irinotecan. Log-rank analysis showed no difference in PFS (P=0.392) or OS (P=0.412) between patients treated with apatinib alone and those treated with apatinib in combination with chemotherapy.

Clinical efficacies against brain metastases

Sixteen patients had brain metastases (*Table 3*). Of these patients, the ORR was 8/16 (50%) and the DCR was 13/16 (81.2%). Eleven of these patients had more than three intracranial metastases. Six patients received apatinib therapy combined with radiotherapy with an interval between radiotherapy and medication shorter than 3 months; this was described as the apatinib combined radiotherapy group. Six patients received radiotherapy and apatinib at least half a year apart and four did not receive radiotherapy; this was described as the apatinib group. The intracranial ORR and DCR of the apatinib group were 50% (5/10) and 80% (8/10), respectively, and the intracranial ORR and DCR of the apatinib combined radiotherapy group were 50% (3/6) and 83.3% (5/6), respectively (*Table 3*).

Clinical efficacy and expression of P53

Specimens from 11 of 61 patients were subjected to next-generation sequencing (NGS). The *TP53* gene of five patients was found to be wild type before and after treatment. Three of these five patients achieved SD and two achieved PR. The *TP53* gene of patient no. 11 was mutated before treatment and wild type after treatment; this patient achieved PR and reached pathologic remission. The *TP53* gene of five patients were mutated both before and after treatment. Four of these five patients achieved PD and one achieved SD. The ORR and DCR of the mutant P53 group were 0% and 20%, respectively, and the prognosis of these patients was worse than that of the wild-type P53 group (ORR 50% and DCR 100%) (*Tables 4,5*).

Single-factor and multifactor analysis

The results of Single-factor analyses of DCR showed a clear correlation between hypertension and clinical benefit (P=0.008). Age, menopausal status, histology classification, molecular typing, metastatic site, visceral metastasis, chemotherapy line, hand-foot-skin reaction (HFSR), asthenia, oral mucositis, bleeding, decreased appetite and nausea, and adverse reactions were unrelated to clinical benefit (P>0.05) (*Table 6*).

The results of multivariate regression analysis were shown in *Table 7*. Hypertension (P=0.044, HR 0.206, 95% CI: 0.044–0.960) had a strong correlation with better DCR. Age, menopausal status, metastatic site, visceral metastasis,

Table 4 TP53 mutation and clinical response to apatinib therapy

No.	TP53 mutation	End
1	Wild type	PR
10	Wild type	PR
11	Mutation: wild type	PR
14	Wild type	SD
12	Wild type	SD
2	Wild type	SD
20	Mutation	SD
5	Mutation	PD
29	Mutation	PD
37	Mutation	PD
55	Mutation	PD

PR, partial response; SD, stable disease; PD, progressive disease.

Table 5 The ORR and DCR for MBC patients with P53 mutation to apatinib therapy

P53 mutation	Number	ORR, %	DCR, %
P53 (+)	5	0.0	20.0
P53 (–)	6	50.0	100.0

ORR, objective response rate; DCR, disease control rate.

Table 6 Single factor analysis of disease control rate

Factors	χ^2	P value
Hypertension	7.023	0.008
HFSR	0.627	0.429
Fatigue	1.843	0.127
Mucositis	0.295	0.587
Bleeding	0.195	0.659
Anorexia	0.122	0.727
Nausea	0.081	0.776
Age	2.016	0.156
Menopausal state	0.973	0.265
Histology classification	0.627	0.429
Molecular typing	0.189	0.664
Metastatic sites	0.776	0.297
Visceral metastasis	0.889	0.276
Lines of chemotherapy	0.276	0.600

HFSR, hand-foot-skin reaction.

and fatigue were not independent prognostic indicators of disease control.

Discussion

As an antiangiogenic small molecule TKI, apatinib has been used to treat a variety of malignant tumors, including gastric cancer (17), esophageal cancer (18), non-small cell lung cancer (19), and breast cancer. A phase II clinical trial of apatinib monotherapy in patients with triple-negative and non-triple-negative metastatic breast tumors has been carried out (14,15). Zhu *et al.* (20) reported that the combination of apatinib and chemotherapeutic agents may be beneficial in patients with advanced pretreated breast cancer. However, research into the combination of apatinib with chemotherapy or endocrine therapy for MBC treatment remains limited. Apatinib has been reported in preclinical studies to reverse ABCB1/MDR1- and ABCG2 (BCRP/MXR/ABCP)-mediated multidrug tolerance in breast cancer cells. Apatinib blocks the transport functions of these proteins, and this reversal effect is particularly evident after treatment with anthracycline and taxane drugs. Apatinib has also been used with target therapy for cancer stem-like cells and ABCB1-overexpressing leukemia cells to increase the efficacy of chemotherapeutic drugs (21).

In the present study, one patient who had been taking bevacizumab before the administration of apatinib experienced disease progression during treatment. After the patient switched to apatinib combined with albumin paclitaxel, the breast mass rapidly reduced in size. Although the regimen was discontinued due to epistaxis, the tumor reduction allowed the patient to undergo radical mastectomy, after which pathologic remission was achieved. This patient has now completed postoperative radiotherapy that resulted in good local disease control. Although we cannot guarantee this patient will obtain any survival benefit from this treatment, her current quality of life has improved. For example, she has experienced no rupturing of breast masses, which is important in a 36-year-old woman. The functional mechanisms of the antiangiogenic drugs apatinib and bevacizumab are slightly different, and additional studies are needed to more profoundly understand these differences.

All the HER-2+ patients in the present study received trastuzumab therapy, and some received lapatinib and TDM1 therapy. These patients did not receive additional anti-HER-2 therapy for financial reasons. Apatinib was also effective in HER-2+ patients that did not respond to

Table 7 Multi factor analysis on the influence of disease control rate

Factors	HR	95% CI	P value
Age (>50 *vs.* ≤50 years old)	3.176	0.353–28.684	0.303
Menopausal state (post-menopause *vs.* pre-menopause)	0.810	0.083–7.867	0.856
Metastatic sites (>3 *vs.* ≤3)	2.414	0.532–10.943	0.253
Visceral metastasis (yes *vs.* no)	0.266	0.022–3.226	0.298
Hypertension (yes *vs.* no)	0.206	0.044–0.960	0.044
Fatigue (yes *vs.* no)	0.323	0.051–0.875	0.208

HR, hazard ratio; CI, confidence interval.

multifaceted therapies; however, determining the optimal time to begin treatment and the manner in which maximum efficacy can be achieved, still requires further exploration.

Of the 16 patients with brain metastases, 6 received apatinib therapy combined with radiotherapy with an interval between radiotherapy and medication of fewer than 3 months; these patients were the apatinib combined radiotherapy group. The single apatinib group comprised 4 patients that had never received radiotherapy and 6 patients that had received radiotherapy and apatinib at least half a year apart. Advanced breast cancer is complex; some patients develop intracranial metastasis quickly and require whole brain radiotherapy. Apatinib is used in patients after multifaceted therapy, so very few patients receive apatinib combined with whole brain radiotherapy. We believe that if the interval between radiotherapy and drug therapy is half a year or longer almost no interaction occurs between these therapies. The intracranial ORR and DCR of the apatinib group were similar to the ORR and DCR of the apatinib combined radiotherapy group. Small molecule TKIs can theoretically cross the blood-brain barrier to treat brain metastases (22,23). However, treatment with small molecule TKIs has not achieved satisfactory clinical efficacy in patients with breast cancer and brain metastases. The use of apatinib for brain metastases has not been frequently reported, and further research is required to further understand its role and clarify its mechanism.

In the present study, 11 of 61 (18%) patients underwent hematologic NGS testing before and after treatment. We found that the *TP53* gene of patient no. 11 was mutated before treatment and wild type after treatment. This patient achieved PR and reached pathologic remission. Five patients had a mutated *TP53* gene, and four of these five patients achieved PD and one achieved SD. Due to the limited number of patients tested, we could reach no definite conclusions, but the relationship between *TP53* gene mutations and breast cancer has long been a concern. In fact, *TP53* genes are the most likely gene to be mutated across tumors, yet there is no approved therapy that targets it. A study by Schwaederle *et al.* showed that there is a clinical correlation between *TP53* mutations and better PFS after receiving bevacizumab therapy (24). These results demonstrate that *TP53* mutations are independent predictors of the high expression of VEGF-A. Although most studies suggest that *TP53* mutations are correlated with the prognosis of various subtypes of breast cancer (25-27), this gene cannot be used as a predictor of therapy sensitivity in breast cancer patients. Sensitivity to apatinib treatment has been shown to be associated with the expression of ABCB1, ABCG2, and VEGFR in tumor tissue, but no presence of predictors in peripheral blood of apatinib sensitive patients has been reported. Based on these 11 patients' results, we may further study the correlation between *TP53* mutations and the efficacy of apatinib to explore whether the change from mutant to wild-type TP53 is a sign of treatment efficacy.

The most common AEs associated with apatinib treatment in our study were hypertension and hand-foot syndrome; approximately half of our patients experienced hypertension. However, our study was based on 61 patients, which is a small number. Therefore, our observations can only serve as a reference for the clinical application of apatinib and as a basis for future studies. In relation to clinical prognosis, adverse reactions during anti-angiogenesis therapy are closely associated with clinical benefit. In a study of apatinib in advanced MBC therapy, patients with hypertension and HFSR all had better PFS, CBR, and OS than those without hypertension ($P<0.05$) (28). Clinical data from the E2100 study showed that patients with levels 3 and 4 hypertension

after bevacizumab treatment had a significant benefit in OS compared to those without hypertension (38.7 *vs.* 25.3 months, P=0.02) (29). Hypertension of level 2 or greater has been found to be an independent prognostic factor of metastatic gastric cancer (P=0.009) (30). In our study, a Chi-square test was conducted on AEs revealing that hypertension had a significant association with better DCR (P=0.008) during the treatment process, but there was little association between fatigue, oral mucositis bleeding, anorexia, or nausea and DCR. Single-factor and multifactor analyses of DCR showed that hypertension was an independent prognostic factor of DCR (HR 0.206, P=0.044). Therefore, the presence of hypertension after treatment with apatinib is expected to be a marker of better disease control.

Conclusions

Apatinib showed good efficacy and manageable toxicity in patients with MBC who were unresponsive to multifaceted therapy.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/tcr-19-2588

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This research was conducted in line with the Declaration of Helsinki (as revised in 2013) and was ratified by the Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology (IORG No: IORG0003571, No. 2020-S103). All patients provided written informed consent.

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