Apatinib combined with chemotherapy in patients with previously treated advanced breast cancer: An observational study

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Abstract. Locally advanced or metastatic disease accounts for the majority of breast cancer-associated cases of mortality. Treatment options for patients with locally advanced or metastatic disease are limited. The current study aimed to explore the efficacy and safety of apatinib combined with chemotherapy in patients with previously treated advanced breast cancer in real-world clinical practice. A total of 85 patients with advanced breast cancer, who had previously been exposed to anthracyclines or taxanes, received combined treatment. Tumor response was evaluated by a computed tomography scan based on the Response Evaluation Criteria in Solid Tumors. Adverse events were graded based on the Common Terminology Criteria for Adverse Events. The Kaplan-Meier method and a log-rank test were used to analyze the univariate discrimination of progression-free survival (PFS) and overall survival (OS) by demographic data, baseline clinical information and toxicities. The combined effects of these variables were analyzed by a Cox proportional hazards regression model. At a median follow-up time of 9.7 months, 73 patients exhibited disease progression and 48 had succumbed to the disease. During the follow-up, 19 patients demonstrated a partial response (PR) and 53 patients achieved stable disease (SD), with an objective response rate of 23.2%. Additionally, 39 patients demonstrated a PR or SD for ≥24 weeks, with a clinical benefit rate of 47.6%. The median PFS was 4.4 months [95% confidence interval (CI)=2.8-6.0] and the median OS was 11.3 months (95% CI=8.9-13.8). No treatment-associated mortalities occurred. The most common adverse events of all grades included myelosuppression (49.4%), gastrointestinal reaction (45.9%) and fatigue (43.5%). Proteinuria was an independent predictive factor for PFS and OS. Apatinib combined with chemotherapy appeared to be efficacious for pretreated advanced breast cancer, with acceptable toxicity for real-world clinical practice.

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Introduction

Breast cancer is the most frequently diagnosed cancer type in females, with an estimated 1.68 million new cases worldwide in 2012 (1). Breast cancer is also the leading cause of cancer-associated cases of mortality in females, accounting for ~520,000 mortalities per year worldwide (1). In China, breast cancer ranks first among cancer types diagnosed in females, with 270,000 new cases per year (2). Despite the declining trend in the mortality rate of breast cancer, advanced breast cancer is predominantly an incurable malignancy, with an overall survival (OS) ranging from 2 to 3 years (3). The primary goals of treatment are symptomatic palliation and disease control. Treatment options for advanced breast cancer include chemotherapy, hormone therapy and human epidermal growth factor receptor 2 (HER2)-targeted therapy, however, the majority of patients eventually develop drug resistance (4). Novel therapeutic approaches for such patients are urgently required.

Angiogenesis serves an important role in tumor growth, invasion and metastasis in breast cancer (5-7). Vascular endothelial growth factor (VEGF) and VEGF receptors (VEGFRs) are key proteins regulating vascular development during angiogenesis (7). Previously, combinations of modern chemotherapeutic agents with targeted biologic agents, including anti-angiogenic agents, have led to marked improvements in the clinical efficacy of advanced breast cancer. Bevacizumab is a monoclonal antibody that binds to VEGF and inhibits the development of tumor vasculature (8). Bevacizumab has been demonstrated to significantly improve the response rate and increase progression-free survival (PFS) when combined with paclitaxel in first-line treatment of metastatic breast cancer (9). Several anti-angiogenic tyrosine kinase inhibitors (TKIs), including sorafenib (10,11) and sunitinib (12-15), have also been evaluated in the treatment of advanced breast cancer. The combination of anti-angiogenic TKIs with specific chemotherapeutic agents, particularly sorafenib combined with capecitabine, has demonstrated promising results in the treatment of advanced breast cancer (16-19). In clinical practice, treatment with anti-angiogenic agents combined with chemotherapy is recommended for patients with advanced breast cancer following failure of prior standard therapy (20).

Apatinib is an orally administered, novel, small-molecule VEGFR TKI. By selectively binding to VEGFR-2, apatinib inhibits subsequent VEGFR-2 autophosphorylation, leading to decreased VEGF-mediated endothelial cell migration, proliferation and tumor microvascular density (21). Apatinib monotherapy has demonstrated objective efficacy and acceptable toxicity for pretreated advanced breast cancer in previous phase II clinical trials (22,23). Apatinib combined with chemotherapeutic agents may provide greater clinical benefit for patients with advanced breast cancer following prior standard therapy. However, to the best of our knowledge, no study has documented the efficacy of this combined therapy in actual clinical practice. Therefore, the current study sought to evaluate the efficacy and safety of apatinib combined with chemotherapeutic agents in advanced breast cancer following multiple lines of treatment and to explore the predictive or prognostic factors associated with apatinib efficacy. To the best of our knowledge, this is the first study reporting the outcome of apatinib treatment combined with chemotherapeutic agents in advanced breast cancer.

Patients and methods

Ethics statement. The present study was approved by the National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (Beijing, China). Additionally, due to the retrospective design of the current study and patient anonymization, the review board determined that informed consent was not required. All methods were performed in accordance with relevant guidelines and regulations.

Patients. The current study retrospectively reviewed the medical data of 85 Chinese patients (83 females and 2 males) with pretreated metastatic or locally advanced breast cancer who received apatinib combined with chemotherapy at the National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College between July 2015 and May 2017. The median age of the patients included in the study was 54 years (range, 30-71 years).

Eligible patients had to: i) Be ≥18 years of age; ii) have been treated with at least one prior chemotherapeutic regimen for advanced disease; and iii) have received anthracycline- or taxane-containing neoadjuvant or adjuvant therapies. If patients had a history of other malignancies within the previous 5 years, abnormal laboratory findings or severe comorbid illness, they were not included in the current study. Patients were also excluded if they were enrolled in clinical trials that had an impact on their daily clinical practice.

Treatment. Patients received apatinib combined with plant-derived chemotherapeutic agents, including vinorelbine, etoposide and paclitaxel, or non-plant-derived chemotherapeutic agents, including gemcitabine, cyclophosphamide, capecitabine and platinum. Apatinib was administered daily with an initial dose of 450 or 500 mg depending on the patient's age and disease status and at the discretion of their physician. Adverse events (AEs) were graded according to the Common Terminology Criteria for AEs (version 4.03) (24). Treatment was discontinued in the case of disease progression, unacceptable toxicity or mortality. Computed tomography was performed at baseline and following every two cycles of combined treatment. The tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1) (25). The PFS, OS, objective response rate (ORR), clinical benefit rate (CBR) and incidence of AEs were calculated.

Data collection. Demographic and baseline clinical information of patients was described using standard descriptive and analytical methods. PFS was defined as the time from the start of combined treatment to the date of documented disease progression or mortality from any cause. OS was defined as the time from the start of combined treatment to the date of mortality from any cause or the most recent date patients were known to be alive. ORR was defined as the proportion of patients who achieved a PR or a confirmed complete response (CR). CBR was defined as the proportion of evaluable subjects with CR, PR or stable disease (SD) for ≥24 weeks (26).

Statistical analyses. All statistical analyses were completed using SPSS software (IBM Corp., Armonk, NY, USA; version 20.0). PFS and OS were estimated using the Kaplan-Meier method. In addition, the Kaplan-Meier method and log-rank test were used to analyze the univariate discrimination of PFS and OS by demographic data, baseline clinical information and toxicities. Furthermore, the combined effects of these variables on both PFS and OS were examined in multivariate analysis using Cox proportional hazards regression models. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics. A total of 85 patients with pretreated distantly metastatic or locally advanced breast cancer received

apatinib combined with chemotherapy at the National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College between July 2015 and May 2017. The baseline patient characteristics are presented in Table I. The majority of patients (68.2%) had an Eastern Cooperative Oncology Group (27) performance status of 0-1. For breast cancer molecular type, 35 patients (41.2%) were diagnosed with triple-negative breast cancer (TNBC), 42 patients (49.4%) had hormone receptor-positive breast cancer and 16 patients (18.8%) had HER2-positive breast cancer. Furthermore, 35 (41.2%) patients exhibited histological grade I-II tumors, 34 (40.0%) patients exhibited grade III tumors, while the remaining 16 patients exhibited unknown tumor grade. A total of 39 patients (45.9%) had stage I-II disease and 36 patients (42.3%) had stage III disease. Tumors >2 cm were detected in 55.3% of the patients.

All 85 patients had received at least one chemotherapeutic regimen for advanced disease. Patients with hormone receptor-positive disease had previously been administered at least one regimen of endocrine treatment. Following prior treatment, local recurrence occurred in 15 patients (17.6%). For tumor metastasis, the most common metastatic site was the lymph nodes (64 patients, 75.3%); 50 patients (58.8%) were identified to have regional lymph node metastases and 41 patients (48.2%) were identified to have distant lymph node metastases. Other metastatic sites included the lung (44.7%), bone (38.8%), liver (37.6%), chest wall (35.3%), pleura (16.5%), brain (12.9%), skin (10.6%) and muscle (4.7%). A total of 44 patients (51.8%) had more than three metastatic sites.

Additionally, all patients had previously received anthracycline- or taxane-based chemotherapy and 52.9% of patients had been treated with more than three lines of chemotherapy. Furthermore, 40 patients (47.0%) had a disease-free survival (DFS) of >24 months following initial treatment.

Efficacy outcomes. Among 85 patients, 56 (65.9%) received apatinib combined with plant-derived chemotherapy and the remaining 29 patients (34.1%) were administered apatinib combined with non-plant-derived chemotherapy (Table I). During the combined treatment, 27 patients experienced transient discontinuation or dose modification due to AEs. In addition, treatment was discontinued in 5 cases due to severe AEs, with a median treatment period of 1.2 months (range=0.5-7.0 months).

With a median follow-up of 9.7 months (range= 2.3-25.8 months), 73 of 85 patients had progressive disease (PD) and 48 mortalities occurred. As demonstrated in Fig. 1, the median PFS was 4.4 months [95% confidence interval (CI)=2.8-6.0 months] and the median OS was 11.3 months (95% CI=8.9-13.8 months). In addition, during combined treatment, 6 patients changed to apatinib monotherapy due to severe myelosuppression or gastrointestinal reaction. The patients who received apatinib combined with chemotherapy followed by apatinib maintenance treatment exhibited a median PFS of 14.7 months (range=7.3-17.3 months).

Among 85 patients, 82 were evaluable for response assessment. A total of 19 patients achieved a PR and 53 patients achieved SD, with an ORR of 23.2% at the best response. Additionally, 39 patients had a PR or SD for ≥24 weeks, demonstrating a CBR of 47.6%.

Table I. Patient characteristics at baseline.

Characteristic	n (%)
Age, years	
<55	43 (50.6)
≥55	42 (49.4)
ECOG performance status	
0-1	58 (68.2)
2	2 (2.4)
Unknown	25 (29.4)
Molecular type	
Triple-negative breast cancer	35 (41.2)
Hormone receptor-positive breast cancer	42 (49.4)
HER2-positive breast cancer	16 (18.8)
Histopathologic grade	
I-II	35 (41.2)
III	34 (40.0)
Unknown	16 (18.8)
TNM stage	
I-II	39 (45.9)
III	36 (42.3)
Unknown	10 (11.8)
Tumor size, cm	
≤2.0	27 (31.8)
>2.0	47 (55.3)
Unknown	11 (12.9)
Local recurrence	15 (17.6)
Metastatic sites	
Lymph node	64 (75.3)
Regional lymph node	50 (58.8)
Distant lymph node	41 (48.2)
Lung	38 (44.7)
Bone	33 (38.8)
Liver	32 (37.6)
Chest wall	30 (35.3)
Pleura	14 (16.5)
Brain	11 (12.9)
Skin	9 (10.6)
Muscle	4 (4.7)
Metastasis ≥3 sites	44 (51.8)
DFS duration, months	
≤24	35 (41.2)
>24	40 (47.0)
Unknown	10 (11.8)
Lines of combined treatment, lines	
≥3	40 (47.1)
>3	45 (52.9)
Chemotherapeutic agents	
Plant-derived agents	56 (65.9)
Non-plant-derived agents	29 (34.1)

ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; DFS, disease free survival.

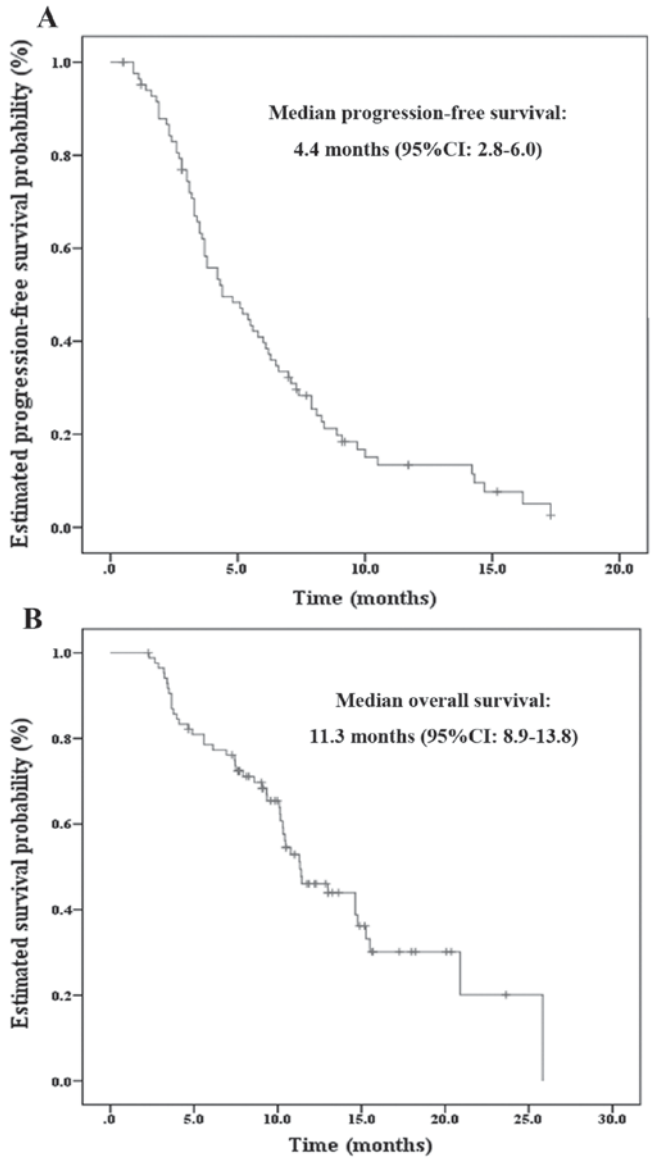

Figure 1. Kaplan-Meier curve of PFS and OS of patients with pretreated advanced breast cancer who received apatinib combined with chemotherapy. (A) Kaplan-Meier curve of PFS, which indicated a median PFS of 4.4 months (95% CI=2.8-6.0). (B) Kaplan-Meier curve of OS, which indicated a median PFS of 11.3 months (95% CI=8.9-13.8). PFS, progression-free survival; OS, overall survival; CI, confidence interval.

Although the PFS was longer for patients who achieved remission (comprising patients with CR or PR; n=19) compared with those that did not (n=63), a significant difference was not identified [7.0 months (95% CI=5.6-8.4 months) vs. 3.8 months (95% CI=2.9-4.7 months); P=0.157; Fig. 2A]. Furthermore, no significant difference was identified in OS between these patients [11.4 months (95% CI=5.8-17.0 months) vs. 11.3 months (95% CI=8.7-14.0 months); P=0.827; Fig. 2B]. The PFS and OS were also compared between patients who gained a clinical benefit (referring to patients with CR, PR or SD for ≥24 weeks; n=39) with those who did not gain a clinical benefit (n=43). A significantly longer PFS and OS were identified in patients who gained a clinical benefit compared with those that did not [PFS=8.1 months (95% CI=6.7-9.5) vs. 3.2 months (95% CI=2.8-3.6 months), P<0.001; OS=15.3 months (95% CI=14.2-16.4) vs. 10.1 months (95% CI=8.2-12.0 months), P<0.001, Fig. 2C and D].

Safety. No treatment-associated mortalities occurred. A total of 5 patients discontinued apatinib due to severe AEs, including myelosuppression (3 cases), gastrointestinal reaction (1 case) and mucositis (1 case). The top ten AEs for all grades are presented in Table II. The most common AEs for all grades included myelosuppression (49.4%), gastrointestinal reaction (45.9%), fatigue (43.5%), hypertension (37.6%), hand-foot skin reaction (25.9%), pain (20.0%) and proteinuria (16.5%). Myelosuppression (31.8%), gastrointestinal reaction (8.2%) and hypertension (8.2%) were the most common AEs for grade III or IV. Due to severe myelosuppression or gastrointestinal reaction, 6 patients changed to apatinib monotherapy as maintenance therapy. Most toxicities were limited to patients with grade I or II and were therefore tolerable and manageable.

Univariate and multivariate analysis. By univariate analysis, the difference in PFS and OS between patients with different demographic data, baseline clinical information and toxicities was first assessed using Kaplan-Meier analysis and a log-rank test. As presented in Table III, a significantly longer PFS was identified in patients who had received combined treatment with ≤3 lines of therapy (P=0.038) or who exhibited proteinuria during combined treatment (P=0.047). Furthermore, the following factors were identified to be significantly associated with OS: Lines of combined treatment, number of metastatic sites, hypertension, hand-foot skin reaction and proteinuria (P<0.05).

In addition, a multivariate model containing all these variables was established (Table IV). In multivariate analysis, the presence of proteinuria during combined treatment was associated with a significantly longer PFS [hazard ratio (HR)=0.398; 95% CI=0.173-0.915; P=0.030]. Additionally, a significantly longer OS was identified in patients with ≤3 lines of combined treatment (HR=0.419; 95% CI=0.202-0.869; P=0.019) and in patients who exhibited proteinuria during combined treatment (HR=0.160; 95% CI=0.031-0.826; P=0.029).

Case presentation. The patient management is presented in Fig. 3. A 54-year-old Chinese female patient with invasive ductal carcinoma in her left breast underwent a modified radical mastectomy in January 2011. The pathological stage of her cancer was T2N0M0. The estrogen receptor (ER) and progesterone receptor (PR) immunohistochemistry data were scored according to the Allred scoring system and staining was considered positive if the Allred score was ≥3. HER2 expression was reported as positive if >30% of tumor cells demonstrated strong (3+) membrane staining. Immunohistochemistry revealed positive staining for ER and PR but negative staining for HER2. The patient was prepared to receive anthracycline-taxane-based adjuvant chemotherapy. However, due to intolerable toxicity, adjuvant chemotherapy was discontinued following two cycles of anthracycline treatment and tamoxifen was subsequently received.

In September 2012, the patient underwent bilateral ovariectomy, followed by letrozole therapy. One month later, the patient changed to anastrozole due to intolerable toxicity during letrozole treatment.

Table II. Summary of top ten adverse events.

Adverse events	All grades (n=85) n (%)	Grade III or IV (n=37) n (%)	Grade I or II (n=78) n (%)
Myelosuppression	42 (49.4)	27 (31.8)	15 (17.6)
Gastrointestinal reaction	39 (45.9)	7 (8.2)	32 (37.6)
Fatigue	37 (43.5)	1 (1.1)	36 (42.4)
Hypertension	32 (37.6)	7 (8.2)	25 (29.4)
Hand-foot skin reaction	22 (25.9)	3 (3.5)	19 (22.4)
Pain	17 (20.0)	3 (3.5)	14 (6.5)
Proteinuria	14 (16.5)	1 (1.1)	13 (15.3)
Mucositis	13 (15.3)	3 (3.5)	10 (11.8)
Elevated transaminase	13 (15.3)	0 (0.0)	13 (15.3)
Hemorrhage	10 (11.8)	0 (0.0)	10 (11.8)

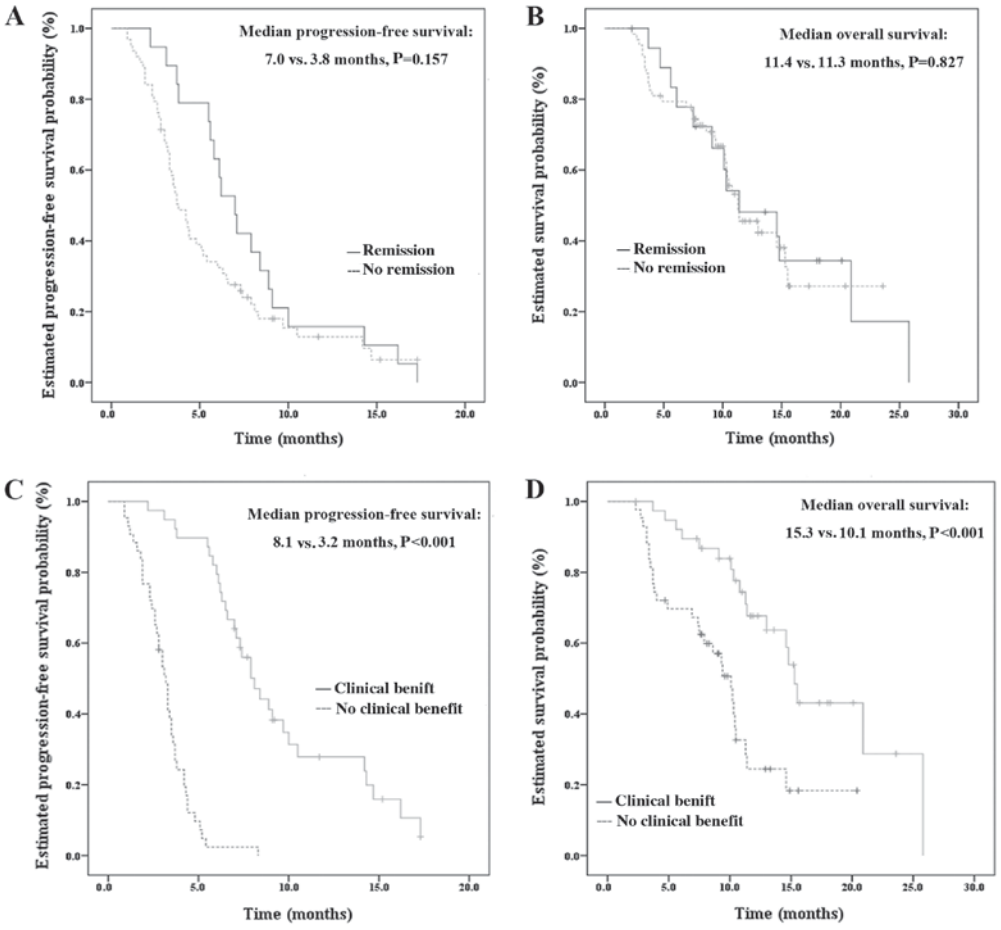

Figure 2. Kaplan-Meier curves of PFS and OS in subgroup analysis. (A) Kaplan-Meier curve of PFS comparing patients who achieved remission following apatinib combined with chemotherapy, with a median PFS of 7.0 months, and those who did not, with a median PFS of 3.8 months. No significant difference was identified between these patients (P=0.157). (B) Kaplan-Meier curve of OS comparing patients who achieved remission following apatinib combined with chemotherapy, with a median PFS of 11.4 months, and those who did not, with a median PFS of 11.3 months. No significant difference was identified between these patients (P=0.827). (C) Kaplan-Meier curve of PFS comparing patients who achieved a clinical benefit following apatinib combined with chemotherapy, with a median PFS of 8.1 months, and those who did not, with a median PFS of 3.2 months. A statistically significant difference was identified between these patients (P<0.001). (D) Kaplan-Meier curve of OS comparing patients who achieved a clinical benefit following apatinib combined with chemotherapy, with a median PFS of 15.3 months, and those who did not, with a median PFS of 10.1 months. A significant difference was identified between these patients (P<0.001). PFS, progression-free survival; OS, overall survival.

In December 2012, local recurrence was identified in the patient's left chest wall. Local resection followed by radiotherapy was performed and endocrine therapy with exemestane was administered.

Table III. Subgroup analysis to compare median PFS and OS between patients with different characteristics.

	Progression-free survival		Overall survival	
Characteristic	Median PFS, months (95% CI)	P-value	Median OS, months (95% CI)	P-value
Age, years		0.105		0.918
<55	4.2 (3.4-5.0)		14.6 (9.0-20.2)	
≥55	6.0 (4.9-7.1)		11.3 (10.1-12.5)	
Molecular type		0.961		0.458
TNBC	5.2 (3.4-7.0)		11.4 (8.0-14.8)	
Non-TNBC	4.3 (2.5-6.1)		11.3 (9.9-12.7)	
Molecular type		0.844		0.272
Hormone receptor-positive	3.7 (2.1-5.3)		11.4 (6.2-16.6)	
Hormone receptor-negative	5.2 (3.3-7.1)		11.3 (9.7-12.9)	
Molecular type		0.846		0.82
HER2-positive	5.8 (3.5-8.1)		11.3 (8.4-14.2)	
HER2-negative	4.4 (2.9-5.9)		11.4 (8.0-14.8)	
Lines of combined treatment, lines		0.038		0.036
≤3	5.8 (2.0-9.6)		14.6 (9.9-19.3)	
>3	4.2 (3.2-5.2)		10.3 (7.9-12.7)	
Histological grade		0.562		0.45
I-II	4.8 (3.3-6.3)		11.3 (9.9-12.7)	
III	4.3 (2.3-6.3)		11.4 (7.9-14.9)	
TNM stage		0.111		0.481
I-II	6.0 (4.0-8.0)		13.0 (9.7-16.3)	
III	3.8 (2.8-4.8)		10.2 (9.0-11.4)	
Tumor size, cm		0.585		0.357
≤2	4.8 (2.7-6.9)		14.6 (9.9-19.3)	
>2	4.4 (2.6-6.2)		10.5 (9.6-11.4)	
Visceral metastasis		0.53		0.955
No	3.8 (3.2-4.4)		11.4 (5.5-17.3)	
Yes	5.2 (3.7-6.7)		11.3 (8.5-14.1)	
Chest wall metastasis		0.365		0.392
No	4.8 (3.3-6.3)		11.4 (8.4-14.4)	
Yes	4.4 (2.1-6.7)		10.3 (7.8-12.8)	
Lymph node metastasis		0.207		0.766
No	5.5 (2.6-8.4)		11.3 (9.9-12.7)	
Yes	4.2 (2.8-5.6)		11.4 (7.1-15.7)	
Number of metastatic sites, n		0.407		0.02
<3	5.5 (2.5-8.5)		14.6 (10.1-19.2)	
≥3	4.3 (3.4-5.2)		10.3 (9.4-11.2)	
Hypertension		0.959		0.016
No	4.3 (2.5-6.1)		10.4 (9.2-11.6)	
Yes	5.2 (3.4-7.0)		25.8 (NE-NE)	
Hand-foot skin reaction		0.419		0.046
No	4.2 (3.4-5.0)		10.5 (9.3-14.0)	
Yes	5.5 (4.0-7.0)		NE (NE-NE)	
Proteinuria		0.047		0.001
No	4.2 (3.0-5.5)		10.5 (9.4-11.6)	
Yes	7.4 (2.5-12.4)		25.8 (NE-NE)	
Chemotherapeutic agents		0.611		0.283
Plant-derived agents	4.2 (3.1-5.3)		10.4 (9.5-11.3)	
Non-plant-derived agents	5.4 (3.3-7.5)		14.6 (10.9-18.3)	

CI, confidence interval; TNBC, triple-negative breast cancer; HER2, human epidermal growth factor receptor 2. NE, not evaluated.

Table IV. Multivariate Cox proportional hazard models predicting PFS and OS for patients receiving apatinib combined with chemotherapeutic agents.

	PFS		OS	
Variable	HR (95% CI)	P-value	HR (95% CI)	P-value
Age, years				
<55 vs. ≥55	1.498 (0.864-2.598)	0.150	0.684 (0.337-1.387)	0.292
Molecular type				
TNBC vs. non-TNBC	1.582 (0.491-5.099)	0.491	0.497 (0.090-2.753)	0.423
Hormone receptor-positive vs. negative	1.617 (0.574-4.551)	0.363	0.390 (0.086-1.769)	0.222
HER2-positive vs. negative	1.321 (0.434-4.026)	0.624	0.320 (0.069-1.495)	0.147
Lines of combined treatment, lines				
≤3 vs. >3	0.573 (0.327-1.004)	0.052	0.419 (0.202-0.869)	0.019
Histological grade				
I-II vs. III	0.985 (0.566-1.712)	0.956	0.967 (0.483-1.934)	0.924
TNM stage				
I-II vs. III	0.536 (0.283-1.015)	0.056	0.575 (0.263-1.257)	0.165
Tumor size, cm				
≤2 vs. >2	1.058 (0.588-1.903)	0.851	0.822 (0.395-1.712)	0.601
Visceral metastasis				
Yes vs. no	1.236 (0.616-2.477)	0.551	0.848 (0.342-2.101)	0.722
Chest wall metastasis				
Yes vs. no	1.848 (0.912-3.745)	0.089	2.242 (0.893-5.628)	0.086
Lymph node metastasis				
Yes vs. no	1.027 (0.487-2.164)	0.944	0.490 (0.190-1.263)	0.140
Number of metastatic sites, n				
<3 vs. ≥3	1.029 (0.556-1.902)	0.928	0.495 (0.224-1.098)	0.084
Hypertension				
Yes vs. no	1.786 (0.937-3.404)	0.078	1.122 (0.486-2.588)	0.788
Hand-foot skin reaction				
Yes vs. no	0.655 (0.333-1.289)	0.221	0.492 (0.196-1.238)	0.132
Proteinuria				
Yes vs. no	0.398 (0.173-0.915)	0.030	0.160 (0.031-0.826)	0.029
Chemotherapeutic				
Plant-derived vs. non-plant-derived agents	1.055 (0.632-1.761)	0.837	1.459 (0.754-2.823)	0.262

PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; TNBC, triple-negative breast cancer.

In September 2014, local recurrence was again identified in the patient's left chest wall. Following local resection, toremifene was administered as endocrine therapy.

In January 2015, local recurrence was identified in the patient's left chest wall for a third time and the recurrent tumor lesions enlarged gradually. Next, six cycles of docetaxel and capecitabine were administered. SD was achieved following two and four cycles of treatment but therapy failed following six cycles.

The patient decided to stop treatment with further hormone therapy due to the economic burden. Following consultation, the patient was treated with vinorelbine, cisplatin and apatinib (500 mg per day). Following two cycles, the maximum diameter of the tumor in the patient's left chest wall reduced in size from 4.5 to 3.1 cm (Fig. 4). PR was subsequently achieved according to RECIST. In January 2016, the patient developed PD and achieved a PFS of 6 months.

Discussion

To the best of our knowledge, the current study is the first to evaluate the efficacy and safety of apatinib combined with chemotherapeutic agents in patients with advanced breast cancer who were previously exposed to anthracyclines or taxanes. In the current study, the median PFS of all 85 patients was 4.4 months (95% CI=2.8-6.0 months) and the median OS

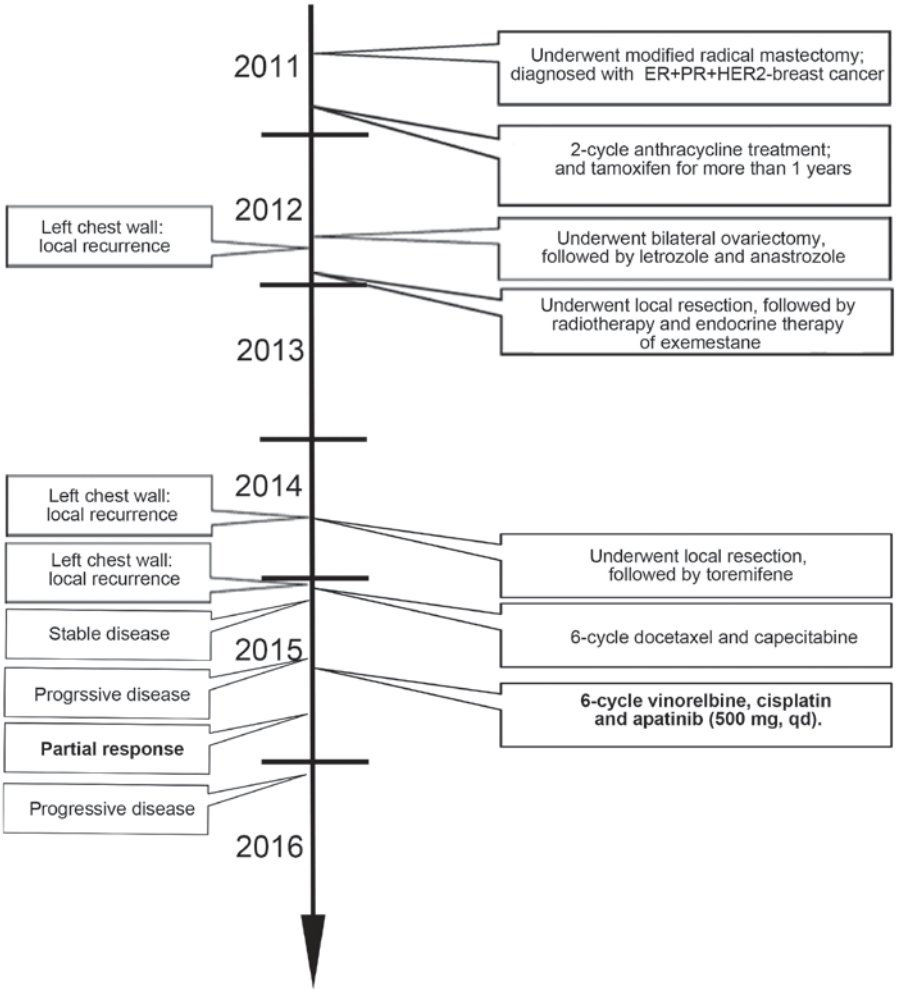

Figure 3. Patient management of a typical patient with advanced breast cancer who received apatinib (500 mg per day) combined with vinorelbine and cisplatin. This patient received heavy pretreatment and still achieved a partial response following combined treatment. The patient's progression-free survival was 6.0 months. ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; qd, every day.

was 11.3 months (95% CI=8.9-13.8 months). Among the 82 patients eligible for efficacy analysis, the ORR was 23.2% (19/82) and the CBR was 47.6% (39/82). These results indicated that apatinib combined with chemotherapy performs efficiently in the treatment of advanced breast cancer.

Previously, apatinib monotherapy has demonstrated success in treating advanced breast cancer following standard treatment. Hu *et al* (22,23) performed two prospective, multicenter, phase II trials to evaluate the efficacy and safety of apatinib as a single agent in patients with pretreated metastatic TNBC or non-TNBC. Following their results, among 56 patients with TNBC available for response evaluation, the median PFS and OS were 3.3 months (95% CI=1.7-5.0 months) and 10.6 months (95% CI=5.6-15.7 months), respectively, and the ORR and CBR were 10.7% and 25.0%, respectively (22). Among 38 patients with advanced non-TNBC who were pretreated with anthracycline, taxanes and capecitabine, apatinib monotherapy achieved a median PFS and OS of 4.0 months (95% CI=2.8-5.2 months) and 10.3 months (95% CI=9.1-11.6 months), respectively, and an ORR of 16.7% and a disease control rate (DCR) of 66.7% among 36 evaluable patients (23). In the subgroup analysis in the current study, the patients with TNBC achieved a median PFS of 5.2 months and a median OS of 11.4 months, which was longer than that of patients with TNBC reported by Hu *et al* (22). In addition, the median PFS and OS of patients with non-TNBC were 4.3 and 11.3 months, respectively, which were longer than those of patients with non-TNBC reported by Hu *et al* (23). Although these findings arise from different study populations and measurements, they are encouraging since the efficacy of combined therapy appears to be superior to apatinib monotherapy in advanced breast cancer.

During combined treatment, no treatment-associated cases of mortality occurred. Five patients (6%) discontinued apatinib due to severe AEs. Most of the AEs were manageable following symptomatic treatment, dose adjustment or dose interruption. As reported previously, myelosuppression is the most common apatinib-associated haematologic toxicity (22,23,28) and is characterized by thrombocytopenia, leukopenia, neutropenia and anemia. In the current study, 42/85 (49.4%) patients exhibited myelosuppression during combined treatment. In addition, hypertension, hand-foot skin reaction and proteinuria are the most common non-hematologic toxicities during apatinib treatment (22,23,28); this accounted for the fourth (32/85), fifth (22/85) and seventh (14/85) most common AEs of all grades in the current study. Fatigue is one of the most commonly reported AEs among patients with advanced solid tumors,

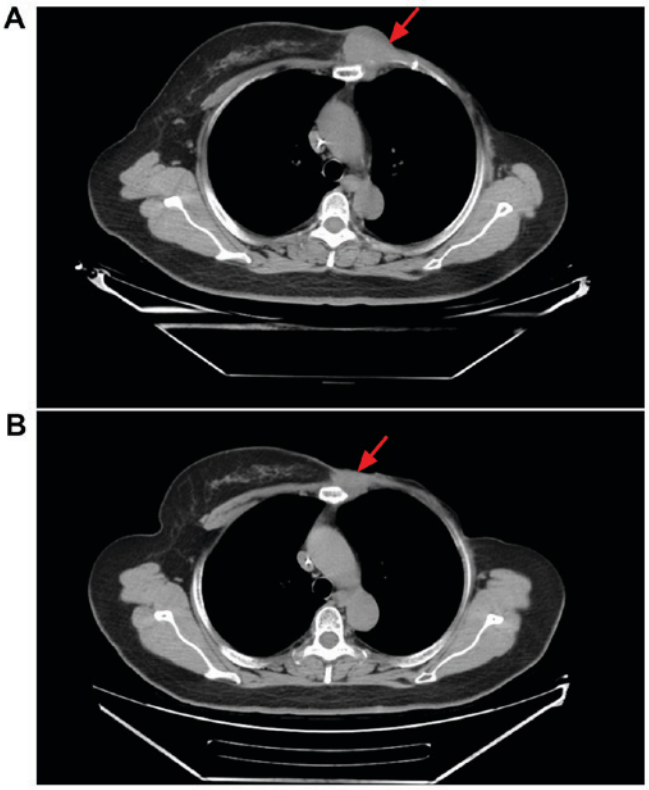

Figure 4. Computed tomography scans of the left chest wall of a 54-year-old woman with advanced breast cancer (A) before and (B) after treatment with apatinib (500 mg per day) combined with vinorelbine and cisplatin. Following two cycles of treatment, the maximum diameter of the tumor in the patient's left chest wall decreased in size from 4.5 to 3.1 cm. The patient achieved a partial response.

including lung cancer and thyroid tumors, during or following apatinib treatment (29,30). In the current study, 37/85 (43.5%) patients developed fatigue. The toxicity profile in our study was similar with that reported previously (22,23,28).

In apatinib-treated advanced gastric cancer, the PFS was previously identified to be strongly associated with OS (31). Recently, Huang *et al* (32) applied mediation analysis to apatinib phase III clinical trial data. In their study, the mediating effect of apatinib on patient OS was systematically quantified through PFS, post-progression survival and the DCR (32). Following the results, Huang *et al* demonstrated that PFS and DCR were the significant mediators of the association between apatinib treatment and OS, indicating that the tumor response to apatinib treatment may be associated with patient OS. The current study investigated the association between the response to apatinib treatment and patient survival outcome, including PFS and OS, in apatinib-treated advanced breast cancer. Based on the current results, no significant difference was identified in either PFS or OS between patients who achieved remission and those who did not. However, PFS and OS were significantly prolonged in patients who achieved a clinical benefit following apatinib treatment. These results suggested that not only the ORR but also the CBR may be used to predict patient survival outcome.

Most patients (52.9%) received apatinib combined with chemotherapy as >3 lines of therapy in the current study. For heavily pretreated advanced breast cancer (≥3 lines), the patients were difficult to treat in the majority of cases because they had received several lines of potent cytotoxic and hormonal therapies. Non-responsiveness or refractoriness to cytotoxic agents generally leads to poor efficacy of third and subsequent lines of chemotherapy, with response rates ranging between 10 and 20% (33,34). Additionally, due to the heterogeneous nature of breast cancer, patients substantially vary in symptoms, growth rate and responsiveness to therapy, and numerous patients receive several lines of chemotherapy, occasionally provided until mortality (35). In addition to anti-angiogenic activity, apatinib has been identified to reverse ATP-binding cassette sub-family B member 1 (ABCB1)- and ATP-binding cassette sub-family G member 2 (ABCG2)-mediated multidrug resistance (MDR) by directly inhibiting ABCB1 and ABCG2 transport function, resulting in an elevated intracellular concentration of the substrate chemotherapeutic drug (36,37). Therefore, apatinib has been selected for reversal of MDR in gastric cancer cells (38,39). In the current study, patients who had received at least two lines of prior therapy achieved a median PFS of 4.2 months and a median OS of 10.3 months following apatinib combined with chemotherapy treatment, durations that were longer than those in previous studies of chemotherapy alone (35). These promising results indicated that the combined therapy may be effective for heavily pretreated advanced breast cancer.

Predictive biomarkers are urgently required to identify specific patients who are more sensitive to therapies and to avoid exposure to useless toxic agents. Demographic characteristics, baseline clinical information and AEs attributed to therapies may be used as predictive biomarkers. Hypertension, proteinuria and hand-foot skin reaction are common AEs associated with angiogenesis inhibitors that target the VEGF pathway. A recent study indicated that the presence of AEs, including hypertension, proteinuria and hand-foot skin reaction, was a viable biomarker for apatinib monotherapy in treating gastric cancer (40). In addition, Fan *et al* (41) revealed that hypertension was an independent predictive factor for PFS and CBR in patients with metastatic breast cancer following apatinib monotherapy. In contrast to the results for apatinib treatment alone, only proteinuria was a predictive factor for apatinib combined with chemotherapeutic agents in prolonging PFS and OS in advanced breast cancer in the current study. Although a significant difference was identified in OS when patients were stratified based on the presence of hypertension or hand-foot skin reaction, when other variables were considered, hypertension or hand-foot skin reaction were not independent factors associated with patient OS in multivariate analysis. In addition to proteinuria, the lines of combined treatment may be used to predict patient survival outcome in the current study. Certainly, these findings should be confirmed in a further prospective clinical trial.

Furthermore, no statistically significant difference was identified in either PFS or OS between patients with different molecular types (TNBC vs. non-TNBC; HER2-positive vs. HER2-negative; and hormone receptor-positive vs. negative), indicating that apatinib combined with chemotherapy may be used for the treatment of pretreated advanced breast cancer regardless of molecular type. For patients with HER2-positive breast cancer, HER2-targeted therapy is first recommended. However, due to the heavy economic burden, a number of

patients refuse to receive HER2-targeted therapy. Based on the results in the current study, apatinib combined with chemotherapy may be considered a treatment choice for such patients who are unwilling to receive HER2-targeted therapy.

The current study is a real-world observational study. Several limitations, including using a retrospective design and being a single-center study may inevitably lead to bias. Additionally, the difference in chemotherapy regimens may increase the occurrence of AEs. However, based on the promising outcome of apatinib monotherapy in breast cancer, the results of the current study further demonstrated that apatinib combined with chemotherapeutic agents may bring clinical benefits for patients with pretreated advanced breast cancer. Furthermore, the presence of proteinuria may be a predictive factor for the efficacy of the combined treatment. Considering the manageable toxicity and lack of treatment-associated cases of mortality, this combined treatment presents a new alternative therapy for patients with pretreated advanced breast cancer.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

AZ, PY and BX participated in the conception and design of the study. All authors collected and interpreted the data. AZ, JW, YF, YL, RC, PZ, QL and FM performed the statistical analysis. AZ drafted the manuscript, and PY and BX edited it critically. All authors gave final approval of the version to be published.

Ethics approval and consent to participate

This study was approved by the National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (Beijing, China). Due to the retrospective design of the current study and patient anonymization, the review board determined that informed consent was not required.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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