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Efficacy and Safety of Third-Line Apatinib plus Chemotherapy in Metastatic Triple-Negative Breast Cancer Patients: A Multicenter, Retrospective, Cohort Study

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Apatinib is a tyrosine kinase inhibitor (TKI) that targets vascular endothelial growth factor receptor 2 (VEGFR2) as an effective anti-angiogenic agent. The current study intended to explore the treatment efficacy and safety profile of third-line apatinib plus chemotherapy in metastatic triple-negative breast cancer (mTNBC) patients. This multicenter, retrospective, cohort study analyzed 97 mTNBC patients who underwent third-line apatinib plus single-agent chemotherapy (N = 45) or single-agent chemotherapy (N = 52). The objective response rate (44.4% vs. 19.2%, *P* = 0.007) and disease control rate (77.8% vs. 48.1%, *P* = 0.003) were higher in the apatinib plus chemotherapy group than in the chemotherapy group. The apatinib plus chemotherapy group had a longer median progression-free survival (PFS) [6.9 (95% confidence interval, CI: 5.2-8.6) vs. 4.3 (95%CI: 3.2-5.4) months, *P* = 0.008] and overall survival (OS) [11.6 (95% CI: 9.3-13.9) vs. 9.0 (95% CI: 7.3-10.7) months, *P* = 0.012] than the chemotherapy group. Further adjustment of multivariate Cox's regression analysis verified that apatinib plus chemotherapy (vs. chemotherapy) resulted in a longer PFS (*P* = 0.003) and OS (*P* = 0.010). There was no difference in adverse events between the two groups, except that the incidence of hypertension was higher in the apatinib plus chemotherapy group than in the chemotherapy group (*P* = 0.018); meanwhile, the grade 3-4 adverse events in the apatinib plus chemotherapy group included hypertension (13.3%), neutropenia (8.9%), nausea and vomiting (4.4%), fatigue (4.4%), leukopenia (4.4%), thrombocytopenia (2.2%), and hand-foot syndrome (2.2%). Third-line apatinib plus chemotherapy may achieve a more satisfying survival benefit and no obvious safety concerns in mTNBC patients compared with mono-chemotherapy. However, more large-scale, randomized studies are warranted for further validation.

Keywords: apatinib; chemotherapy; metastatic triple-negative breast cancer; survival profile; third-line
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Introduction

Triple-negative breast cancer (TNBC) represents a heterogeneous and aggressive branch of breast cancers that accounts for approximately 11%-20% of the total cases (Borri and Granaglia 2021; Derakhshan and Reis-Filho 2022). Typically, metastatic TNBC (mTNBC) indicates an even poorer treatment outcome (Al-Mahmood et al. 2018). The treatment of mTNBC remains challenging, and based on patients' physical status and benefit expectations, chemotherapies with single or double agents are applied (Hwang et al. 2019; Li et al. 2020). However, for those who fail to respond or relapse after first- or second-line treatment, therapeutic options are still limited (Li et al. 2020; Won and Spruck 2020). Fortunately, according to the recommendation of the Chinese Society of Clinical Oncology guidelines for breast cancer, an anti-angiogenic drug (bevacizumab) plus chemotherapy could serve as an alternative choice for third-line therapy in mTNBC patients (Schilling et al. 2019; Li et al. 2020).

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Apatinib, a tyrosine kinase inhibitor (TKI) targeting vascular endothelial growth factor receptor 2 (VEGFR2), is another anti-angiogenic drug approved in China (Scott 2018; Zhao et al. 2018). Interestingly, a few small-sample studies have shown that apatinib exhibits acceptable efficacy in mTNBC patients (Hu et al. 2014; Hu et al. 2020; Liu et al. 2021). For instance, one single-armed study reported that apatinib plus chemotherapy realizes an objective response rate (ORR) of 35.5% and a disease control rate (DCR) of 87.1% in heavily pretreated mTNBC patients (Hu et al. 2020). Additionally, it has also been shown that apatinib with or without chemotherapy realizes a median progression-free survival (PFS) of 6 months and a median overall survival (OS) of 10 months in mTNBC patients pretreated with multiline therapy (Liu et al. 2021). However, the benefit of apatinib for third-line mTNBC still needs more profound validation by a larger sample-sized study; meanwhile, the previous findings still lack a control group to validate the superiority of third-line apatinib in mTNBC patients.

Hence, the current two-center, retrospective, cohort study aimed to further compare the treatment efficacy and tolerance between third-line apatinib plus chemotherapy and mono-chemotherapy in mTNBC patients.

Methods

Patients

Between March 2019 and December 2021, ninety-seven patients with mTNBC who received apatinib plus single-agent chemotherapy (named the apatinib plus chemotherapy group) or single-agent chemotherapy (named the chemotherapy group) as third-line therapy were included in this two-center, retrospective, cohort study. The inclusion criteria were as follows: (1) pathological diagnosis of TNBC; (2) confirmed tumor metastasis by imaging or pathology; (3) disease progression after second-line standard chemotherapy; (4) Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0 or 1; (5) at least one detectable lesion via Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 criteria; and (6) aged more than 18 years. The exclusion criteria were as follows: (1) history of using anti-angiogenesis agents; (2) uncontrolled hypertension; and (3) other primary cancers. The Ethics Committee of Hubei Cancer Hospital approved the current study with approval number 2021-159-002.

Clinical data and drug administration

Clinical characteristics of patients with mTNBC were retrieved from the electronic medical record system, including demographics, medical histories, and disease characteristics. Fifty-two patients in the chemotherapy group received capecitabine or etoposide as third-line therapy until disease progression or severe toxicity. The common usage of capecitabine was 1,000 mg/m^2 twice a day on days 1-14 of a 3-week treatment cycle (Huang and Yin 2018). The common usage of etoposide (oral) was 60 mg/m^2/day on days 1-10 of a 3-week treatment cycle (Yuan et al. 2015). If intolerable toxicity occurred, etoposide was reduced to 35 mg/m^2/day.

Forty-five patients in the apatinib plus chemotherapy group received apatinib combined with capecitabine or etoposide as third-line therapy until disease progression or severe toxicity. The recommended protocol of capecitabine or etoposide was the same as administration in the chemotherapy group. The recommended usage of apatinib was 500 mg/day every day for a 3-week treatment cycle (Li et al. 2018). When intolerable toxicity occurred, the dose of apatinib could be tapered to 250 mg/day.

The main treatments for mTNBC and metastatic lesions were systemic chemotherapy or apatinib plus chemotherapy in our study. For some of the specific metastatic lesions, such as liver metastasis, local therapy such as transarterial chemoembolization was performed, but it was not the main treatment for the disease.

Efficacy and safety assessments

The disease response was evaluated every 1-2 months by computed tomography (CT) or magnetic resonance imaging (MRI). The complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), ORR, and DCR were evaluated under RECIST. Then, the best treatment response was evaluated in each patient. All patients were followed up every 2-3 months, and the last follow-up date was April 30, 2022. PFS was defined as the interval from starting treatment to disease progression or death. OS was classified as the interval from starting treatment to death. The adverse events (AEs) were recorded and graded via the National Cancer Institute Common Terminology Criteria 4.0.

Statistical analysis

The statistical analyses were processed via SPSS V 25.0 (IBM Corp., Armonk, NY, USA). The figures were drawn via GraphPad Prism V 8.10 (GraphPad Software Inc., San Diego, CA, USA). The comparisons between groups were evaluated using Student's t test, Chi-square test, Fisher's exact test, and Mann-Whitney U test. Survival analyses were carried out based on the log-rank test and Kaplan-Meier curve. After all factors were included, independent predictors of PFS or OS were evaluated via multivariate Cox proportional hazards regression using the stepforward method. A P value < 0.05 was considered significant.

Results

Study flow

A total of 138 mTNBC patients were retrospectively screened, among which 41 cases were excluded. Then, according to the chosen therapy, patients were defined as the chemotherapy group (N = 52) and apatinib plus chemotherapy group (N = 45) to receive corresponding treatments. Subsequently, demographics, disease features, and treat-

ment outcomes were collected and evaluated. More detailed information on the study flow is listed in Fig. 1.

Baseline characteristics

The mean age (± standard deviation) was 54.3 ± 7.8 and 52.7 ± 8.3 years in the chemotherapy group and the apatinib plus chemotherapy group, respectively (P = 0.338, Table 1). Regarding menopausal status, 20 (38.5%) and 32 (61.5%) patients in the chemotherapy group were premenopausal and postmenopausal, respectively; meanwhile, 22 (48.9%) and 23 (51.1%) patients in the apatinib plus chemotherapy group were premenopausal and postmenopausal, respectively (P = 0.301). Moreover, 15 (28.8%) and 37 (71.2%) patients in the chemotherapy group had ECOG PS scores of 0 and 1, respectively; meanwhile, 18 (40.0%) and 27 (60.0%) patients in the apatinib plus chemotherapy group had ECOG PS scores of 0 and 1, respectively (P = 0.248). In addition, 39 (75.0%) and 13 (25.0%) patients in the chemotherapy group received capecitabine and etoposide, respectively; meanwhile, 30 (66.7%) and 15 (33.3%) patients in the apatinib plus chemotherapy group were administered capecitabine and etoposide, respectively (P = 0.366). In addition, 41 (91.1%) patients received surgery previously in the apatinib plus chemotherapy group, while 49 (94.2%) patients received surgery previously in the chemotherapy group. More detailed information is listed in Table 1.

Clinical response

Generally, the best clinical response (P = 0.001), ORR (P = 0.007), and DCR (P = 0.003) were higher in the apatinib plus chemotherapy group than in the chemotherapy

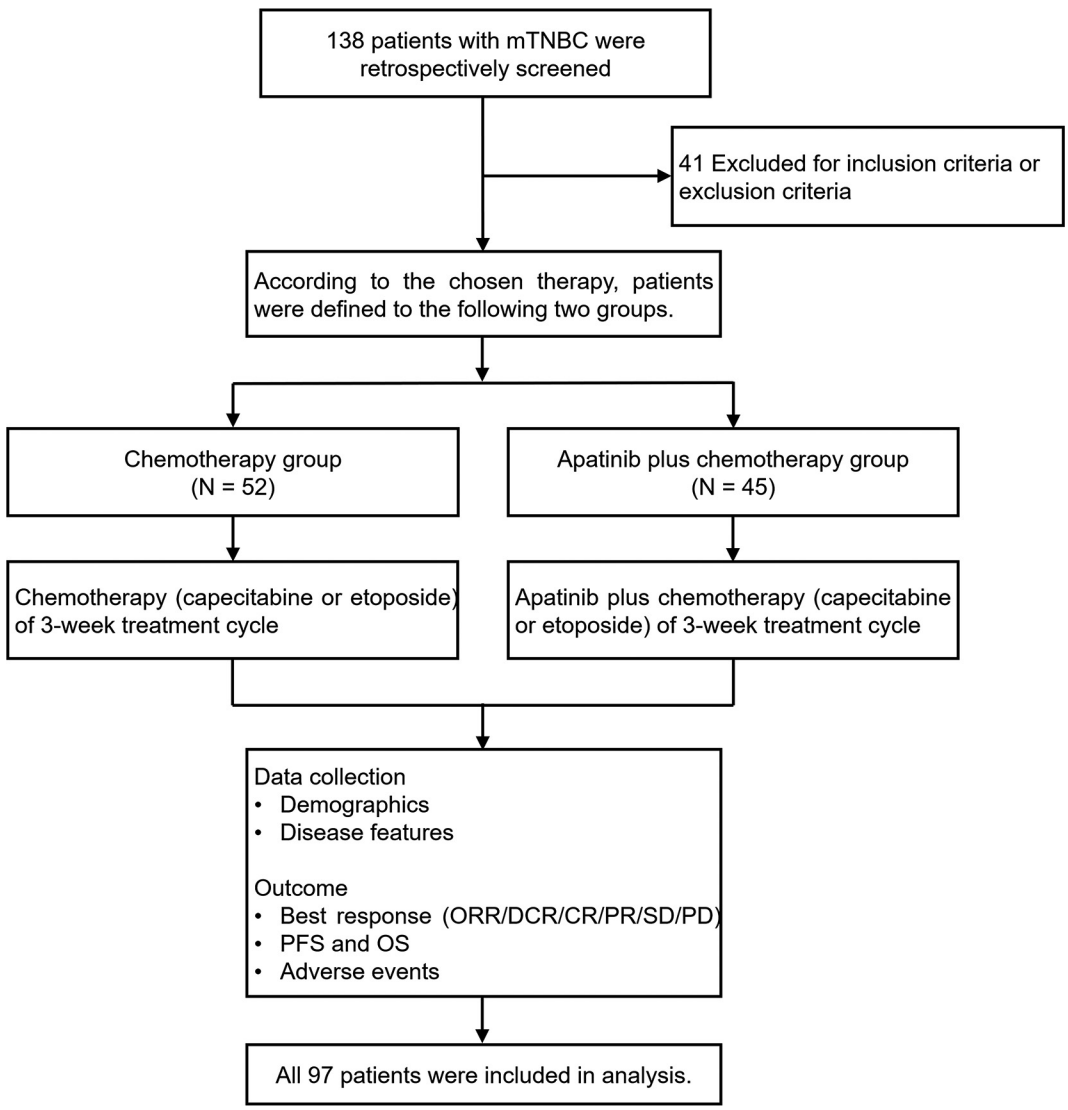

Fig. 1. Study flow of the present study.
mTNBC, metastatic triple-negative breast cancer; ORR, objective response rate; DCR, disease control rate; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; PFS, progression-free survival; OS, overall survival.

Table 1. Baseline characteristics of patients with mTNBC.

Items	Chemotherapy (N = 52)	Apatinib plus chemotherapy (N = 45)	*P* value
Age (years), mean ± SD	54.3 ± 7.8	52.7 ± 8.3	0.338
Menopausal status, n (%)			0.301
Premenopausal	20 (38.5)	22 (48.9)	
Postmenopausal	32 (61.5)	23 (51.1)	
History of surgery, n (%)			0.554
No	3 (5.8)	4 (8.9)	
Yes	49 (94.2)	41 (91.1)	
History of chemotherapy, n (%)			NR
No	0 (0.0)	0 (0.0)	
Yes	52 (100.0)	45 (100.0)	
History of radiotherapy, n (%)			0.734
No	9 (17.3)	9 (20.0)	
Yes	43 (82.7)	36 (80.0)	
ECOG PS, n (%)			0.248
0	15 (28.8)	18 (40.0)	
1	37 (71.2)	27 (60.0)	
Metastatic site, n (%)			
Lung	29 (55.8)	26 (57.8)	0.842
Liver	16 (30.8)	15 (33.3)	0.787
Bone	16 (30.8)	19 (42.2)	0.241
Lymph node	30 (57.7)	28 (62.2)	0.650
Others	19 (36.5)	17 (37.8)	0.900
Metastatic site number, n (%)			0.288
1	10 (19.2)	7 (15.5)	
2	28 (53.9)	21 (46.7)	
≥ 3	14 (26.9)	17 (37.8)	
Treatment lines, n (%)			NR
3	52 (100.0)	45 (100.0)	
Chemotherapy regimen, n (%)			0.366
Capecitabine	39 (75.0)	30 (66.7)	
Etoposide	13 (25.0)	15 (33.3)	

mTNBC, metastatic triple negative breast cancer; SD, standard deviation; NR, not reach; ECOG PS, Eastern Cooperative Oncology Group Performance Status.

group (Table 2). Detailed tumor volume changes from baseline in each patient from all analyzed subjects (Fig. 2A), in each patient from the apatinib plus chemotherapy group (Fig. 2B), and in each patient from the chemotherapy group (Fig. 2C) after therapy are presented. In addition, the CR rate, PR rate, SD rate, PD rate, ORR, and DCR in the apatinib plus chemotherapy group were 0.0%, 44.4%, 33.3%, 22.2%, 44.4%, and 77.8%, respectively. Meanwhile, the CR rate, PR rate, SD rate, PD rate, ORR, and DCR in the chemotherapy group were 0.0%, 19.2%, 28.8%, 51.9%, 19.2%, and 48.1%, respectively.

Progression and survival profile

The median PFS was 6.9 (95% confidence interval, CI: 5.2-8.6) months and 4.3 (95% CI: 3.2-5.4) months in the apatinib plus chemotherapy group and the chemotherapy group, respectively; the apatinib plus chemotherapy group had a longer PFS than the chemotherapy group (P = 0.008, Fig. 3A). The median OS was 11.6 (95% CI: 9.3-13.9) months and 9.0 (95% CI: 7.3-10.7) months in the apatinib plus chemotherapy group and the chemotherapy group, respectively; the apatinib plus chemotherapy group also had a longer OS than the chemotherapy group (P = 0.012, Fig. 3B).

Adjustment

Adjustment by multivariate Cox regression further verified that apatinib plus chemotherapy was superior to chemotherapy alone in extending PFS [hazard ratio, HR: 0.501 (95% CI: 0.319-0.789), P = 0.003, Table 3] and OS

Table 2. Clinical response between chemotherapy group and apatinib plus chemotherapy group.

Items	Chemotherapy (N = 52)	Apatinib plus chemotherapy (N = 45)	*P* value
Clinical response, n (%)			0.001
CR	0 (0.0)	0 (0.0)	
PR	10 (19.2)	20 (44.4)	
SD	15 (28.8)	15 (33.3)	
PD	27 (51.9)	10 (22.2)	
ORR, n (%)			0.007
Yes	10 (19.2)	20 (44.4)	
No	42 (80.8)	25 (55.6)	
DCR, n (%)			0.003
Yes	25 (48.1)	35 (77.8)	
No	27 (51.9)	10 (22.2)	

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

[HR: 0.509 (95% CI: 0.305-0.849), $P = 0.010$, Table 4]. In addition, it was also reported that metastatic site number ≥ 3 (vs. 1) was independently correlated with decreased PFS [HR: 2.147 (95% CI: 1.141-4.040), $P = 0.018$] and OS [HR: 3.274 (95% CI: 1.437-7.460), $P = 0.005$].

AEs

Generally, there was no difference in (hematological and non-hematological) AEs between the apatinib plus chemotherapy group and the chemotherapy group (most $P > 0.05$, Table 5), except that hypertension had a higher incidence in the apatinib plus chemotherapy group than in the chemotherapy group ($P = 0.018$). Furthermore, grade 3-4 AEs in the apatinib plus chemotherapy group mainly included hypertension (13.3%), neutropenia (8.9%), nausea and vomiting (4.4%), fatigue (4.4%), leukopenia (4.4%), thrombocytopenia (2.2%), and hand-foot syndrome (2.2%). Furthermore, grade 3-4 adverse events were not different between the apatinib plus chemotherapy group and the chemotherapy group (all $P > 0.05$). In addition, no treatment-related death occurred during the therapy in either group.

Discussion

Considering the patients' own health status and life expectancy, single-agent chemotherapy was mainly recommended for multiple-line therapy of mTNBC patients (Li et al. 2020). However, the ORR and DCR are still unfavorable (Li et al. 2018; Valerio et al. 2021). For instance, one study revealed that the ORR in mTNBC patients receiving multiple-line, single-agent chemotherapy was 23% (Valerio et al. 2021). In addition, another study illuminates that third-line, single-agent chemotherapy realizes an ORR and DCR of 13.4% and 31.8% in mTNBC patients, respectively (Li et al. 2018). In the current study, the ORR and DCR in mTNBC patients receiving third-line apatinib plus chemotherapy were 44.4% and 77.8%, respectively, which were higher than the ORR (19.2%) and DCR (48.1%) in patients receiving chemotherapy alone. These findings reveal that the combination of apatinib and chemotherapy as third-line treatment enhances the therapeutic efficiency in mTNBC patients, which provides an alternative choice for mTNBC patients who fail to respond or experience disease progression after second-line treatment. In addition, a possible explanation could be that apatinib inhibits tumor progression and promotes the anti-tumor efficacy of cytotoxic drugs in solid carcinoma; thus, apatinib may exhibit synergistic efficacy with chemotherapy in the third-line treatment of mTNBC (Feng and Qin 2018; Xu et al. 2019; Zhang et al. 2020; Chi et al. 2022).

Apart from the treatment response, preceding studies have also evaluated the progression and survival profile of mTNBC patients receiving third-line chemotherapy treatment (Li et al. 2018; Schmid et al. 2018). For instance, one study revealed that mTNBC patients receiving third-line mono-chemotherapy have a median PFS of 3.5 months (Li et al. 2018). Similarly, another study disclosed that third-line single-agent chemotherapy realizes a median PFS of 5.5 months and an OS of 17.6 months in mTNBC patients (Schmid et al. 2018). In the present study, mTNBC patients receiving third-line apatinib plus chemotherapy had a median PFS and OS of 6.9 and 11.6 months, respectively, which realized a longer PFS and OS compared with chemotherapy alone. A possible explanation for this discovery could be that apatinib plus chemotherapy could realize a better ORR and DCR than chemotherapy alone, as discussed above, which would be linked with a more satisfying survival; thus, third-line apatinib plus chemotherapy would contribute to a longer PFS and OS than chemotherapy alone in mTNBC patients.

Several previous studies have explored the safety profile in mTNBC patients receiving chemotherapy: grade 3-4 AEs mainly include neutropenia, anemia, thrombocytope-

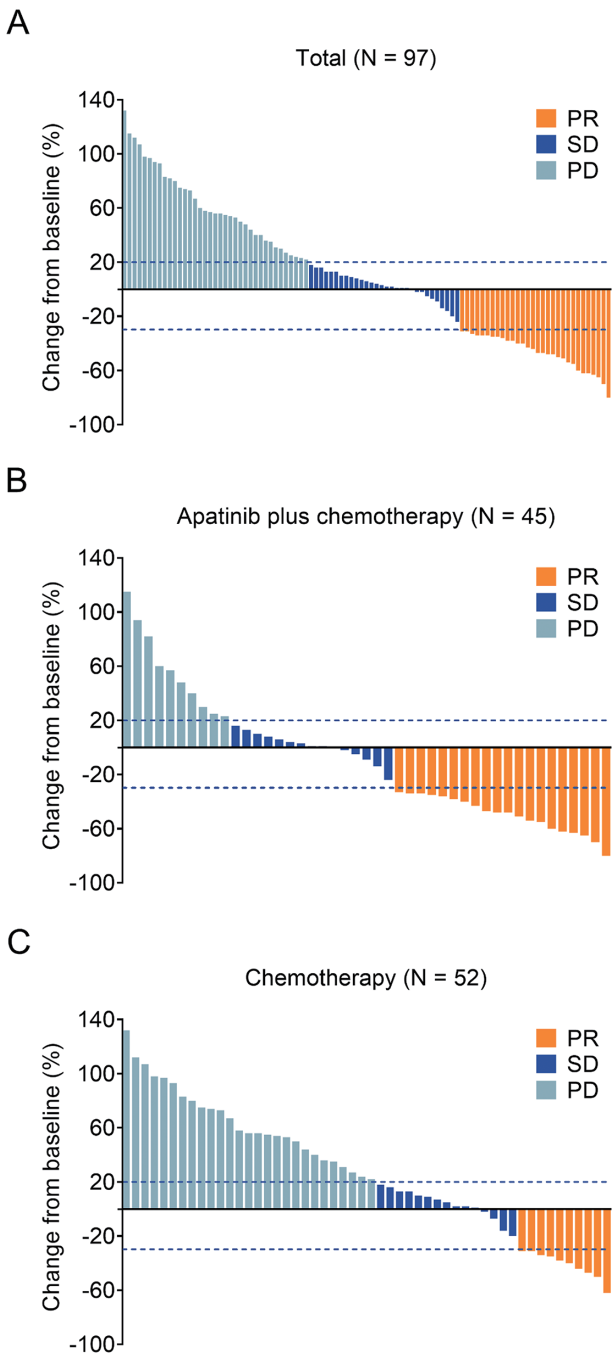

Fig. 2. Tumor volume change after treatment.
The change in tumor volume after treatment from baseline in total metastatic triple-negative breast cancer (mTNBC) patients (A), the apatinib plus chemotherapy group (B), and the chemotherapy group (C). PR, partial response; SD, stable disease; PD, progressive disease.

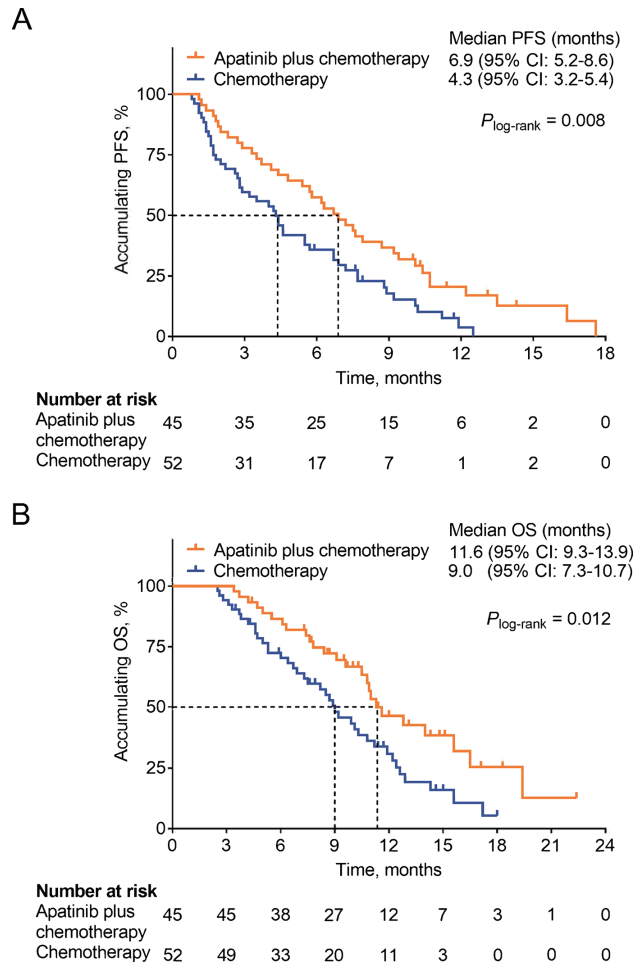

Fig. 3. Comparison of accumulating progression-free survival (PFS) and overall survival (OS).
Comparisons of accumulating PFS (A) and OS (B) of mTNBC patients between the apatinib plus chemotherapy group and the chemotherapy group.

nia, fatigue, and peripheral neuropathy (Li et al. 2018; Schmid et al. 2018; Manthri et al. 2020). In our study, there was no difference in AEs between patients receiving chemotherapy alone and patients receiving apatinib plus chemotherapy, except that the incidence of hypertension was higher in patients with third-line apatinib plus chemotherapy than in patients undergoing chemotherapy alone. The explanation was that hypertension was a common adverse reaction of apatinib due to its anti-angiogenesis effect on blood vessels; therefore, the hypertension incidence was higher in the apatinib plus chemotherapy group than in the chemotherapy group. Furthermore, grade 3-4 AEs in the apatinib plus chemotherapy group mainly included hypertension, neutropenia, nausea and vomiting, fatigue, leukopenia, thrombocytopenia, and hand-foot syndrome. In particular, the above information indicates that apatinib plus chemotherapy (versus chemotherapy alone) does not increase the safety concerns of mTNBC patients. These discoveries indicate that apatinib plus chemotherapy deserves further clinical popularization.

Some limitations still existed: (1) The sample size in the current study was relatively small; thus, the statistical power might be less strong. (2) All patients were enrolled from central China; therefore, patient selection bias should not be neglected (Enzenbach et al. 2019). (3) It was revealed that apatinib could synergize with immune checkpoint inhibitors in solid carcinomas; meanwhile, some pre-

Table 3. Factors related to progression-free survival (PFS) by multivariate Cox's proportional hazards regression analysis.

Items	*P* value	HR	95% CI	
			Lower	Upper
Treatment (Apatinib plus chemotherapy vs. Chemotherapy)	0.003	0.501	0.319	0.789
Metastatic site number				
1	Ref.			
2	0.557	1.193	0.662	2.148
≥ 3	0.018	2.147	1.141	4.040

HR, hazard ratio; CI, confidence interval.

Table 4. Factors related to overall survival (OS) by multivariate Cox's proportional hazards regression analysis.

Items	*P* value	HR	95%CI	
			Lower	Upper
Treatment (Apatinib plus chemotherapy vs. Chemotherapy)	0.01	0.509	0.305	0.849
Metastatic site number				
1	Ref.			
2	0.120	1.870	0.849	4.118
≥ 3	0.005	3.274	1.437	7.460

HR, hazard ratio; CI, confidence interval.

Table 5. Adverse events.

Items	Chemotherapy (N = 52)			Apatinib plus chemotherapy (N = 45)			*P* value[a]	*P* value[b]
	Total	Grade 1-2	Grade 3-4	Total	Grade 1-2	Grade 3-4		
Hematological								
Neutropenia, n (%)	25 (48.1)	22 (42.3)	3 (5.8)	27 (60.0)	23 (51.1)	4 (8.9)	0.240	0.701
Leukopenia, n (%)	17 (32.7)	15 (28.9)	2 (3.8)	16 (35.5)	14 (31.1)	2 (4.4)	0.767	1.000
Thrombocytopenia, n (%)	11 (21.2)	11 (21.2)	0 (0.0)	11 (24.4)	10 (22.2)	1 (2.2)	0.700	0.464
Anemia, n (%)	14 (26.9)	13 (25.0)	1 (1.9)	10 (22.2)	10 (22.2)	0 (0.0)	0.593	1.000
Non-hematological								
Hypertension, n (%)	21 (40.4)	19 (36.6)	2 (3.8)	29 (64.4)	23 (51.1)	6 (13.3)	0.018	0.139
Nausea and vomiting, n (%)	26 (50.0)	24 (46.2)	2 (3.8)	26 (57.7)	24 (53.3)	2 (4.4)	0.444	1.000
Fatigue, n (%)	30 (57.7)	29 (55.8)	1 (1.9)	24 (53.3)	22 (48.9)	2 (4.4)	0.666	0.595
Hand-foot syndrome, n (%)	24 (46.2)	24 (46.2)	0 (0.0)	22 (48.9)	21 (46.7)	1 (2.2)	0.788	0.464
Anorexia, n (%)	17 (32.7)	17 (32.7)	0 (0.0)	21 (46.7)	21 (46.7)	0 (0.0)	0.160	NR
Pruritus, n (%)	13 (25.0)	13 (25.0)	0 (0.0)	14 (31.1)	14 (31.1)	0 (0.0)	0.503	NR
Elevated transaminase, n (%)	10 (19.2)	9 (17.3)	1 (1.9)	11 (24.4)	11 (24.4)	0 (0.0)	0.534	1.000
Elevated bilirubin, n (%)	9 (17.3)	9 (17.3)	0 (0.0)	7 (15.6)	7 (15.6)	0 (0.0)	0.817	NR
Diarrhea, n (%)	6 (11.5)	6 (11.5)	0 (0.0)	7 (15.6)	7 (15.6)	0 (0.0)	0.562	NR

[a]Test for Total
[b]Test for Grade 3-4.
NR, not reach.

vious studies illustrated that third-line immune checkpoint inhibitors revealed a fine efficacy in treating mTNBC patients; thus, our forthcoming study would evaluate the efficacy and tolerance of immune checkpoint inhibitors plus apatinib in mTNBC patients (Liu et al. 2020; Wang et al. 2020). (4) The present study was a retrospective, cohort study; therefore, a randomized controlled trial might be needed to further validate the efficacy and tolerance of apatinib-based, third-line therapy in mTNBC patients.

Collectively, third-line apatinib plus chemotherapy administration may realize a more favorable treatment response, longer PFS and OS, and no increased safety con-

cerns compared with chemotherapy alone in mTNBC patients. However, more large-scale, randomized studies are warranted for further validation.

Conflict of Interest

The authors declare no conflict of interest.

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