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Comparison of apatinib and capecitabine (Xeloda) with capecitabine (Xeloda) in advanced triple-negative breast cancer as third-line therapy

A retrospective study

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Abstract

The treatment of advanced triple-negative breast cancer, which failed in first-line or second-line therapy, is a significant challenge. We conducted this retrospective study to explore the efficacy and safety of apatinib and capecitabine as the third-line treatment for advanced triple-negative breast cancer.

This retrospective study involved 44 advanced triple-negative breast cancer patients who failed in first-line or second-line therapy in Tangshan People's Hospital from January 2016 to February 2017. Twenty-two patients received apatinib and capecitabine, while 22 patients were treated with capecitabine monotherapy as third-line therapy. The progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), and adverse events were compared between 2 groups.

The apatinib and capecitabine group exhibited a higher PFS than capecitabine group ($P = .001$). Meanwhile, ORR and DCR in apatinib and capecitabine group were better than in capecitabine group ($P = .042$; .016). The 2 groups showed no significant difference in adverse events except degree I-II bleeding ($P = .021$). Both the apatinib and capecitabine and the capecitabine regimens revealed good tolerability.

The apatinib and capecitabine regimen can achieve a better efficacy and similar serious adverse events compared with capecitabine regimen as the third-line treatment for advanced triple-negative breast cancer.

Abbreviations: 5-FU = 5-fluorouracil, CR = complete response, KPS = Karnofsky performance score, PD = progressive disease, PFS = progression free survival, PR = partial response, SD = stable disease, TNBC = triple-negative breast cancer.

Keywords: advanced triple-negative breast cancer, apatinib, capecitabine, third-line therapy

1. Introduction

Breast cancer is one of the most commonly diagnosed cancers and the leading cause of cancer death among females worldwide.[1] Triple-negative breast cancer (TNBC) is a special type of breast cancer, which lacks expression of estrogen receptor (ER), progesterone receptor (PR), and *HER2* gene. TNBC accounts for 15% to 20% of newly diagnosed BC cases.[2] Because of lacking recognized therapeutic molecular biology targets, the treatment of TNBC is particularly challenging. Unfortunately, TNBC is highly proliferative and aggressiveness, rapid disease progression, high risk for recurrence, and poor prognosis.[3] Chemotherapy is the mainstay of TNBC's treatment at present,[4] and novel strategies and drugs are urgently needed.

Angiogenesis is one of the hallmarks of cancer,[5] which is vital for tumor growth, development, and metastasis. Anti-angiogenesis is an important anticancer strategy.[6] Vascular endothelial growth factor (VEGF) signaling plays an important role in angiogenesis via activation of VEGF receptor (VEGFR).[6] The VEGFR family involves 3 molecular subtypes (VEGFR-1, VEGFR-2, and VEGFR-3), which are type-II transmembrane proteins characterized by a tyrosine kinase (TK) activity.[7] Among them, VEGFR-2 is the majorly implicated in the pathological overformation of blood vessels in the context of several solid tumors.[8]

Apatinib is a novel small molecule receptor TK inhibitor selectively targeting VEGFR 2 (VEGFR-2).[9] Recently, apatinib has demonstrated its satisfying efficacy on various types of cancers such as gastric cancer,[10] breast cancer,[11] and nasopharyngeal carcinoma.[12] At the same time, it also has shown acceptable toxicities.

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Capecitabine (Xeloda) is an oral fluoropyrimidine carbamate that undergoes sequential conversion to 5-fluorouracil (5-FU).[13] The conversion to 5-FU occurs in several steps, and the final enzyme in the pathway is thymidine phosphorylase, which is located at much higher concentrations in tumor tissue than in normal tissues, the active form of the drug is mainly present at the tumor site.[14] In addition, capecitabine typically lacks cumulative toxicity with prolonged use, so is suitable for long-term administration. A number of studies have indicated that capecitabine is effective for the treatment of metastatic breast cancer as a single agent or as part of a combination regimen.[15,16] However, there is no report on the efficacy and safety of combination therapy of apatinib and capecitabine in the treatment of advanced TNBC as the third-line treatment.

In this retrospective study, we aimed to explore the efficacy and safety of apatinib and capecitabine as the third-line treatment for advanced TNBC.

2. Patients and methods

2.1. Patients

This study was a retrospective analysis, which included 44 advanced TNBC patients who failed in first-line or second-line therapy in Tangshan People's Hospital from January 2016 to February 2017. Among them, 22 patients received apatinib and capecitabine as third-line therapy, while another 22 patients treated with capecitabine monotherapy served as control. The 2 groups were matched in age, Karnofsky performance score (KPS), metastatic site, and history of chemotherapy. The inclusion criteria were as follows: age ≥18 years; definite pathological diagnosis; failure of first-line or second-line; KPS≥80; and life expectancy ≥3 months.

2.2. Drug administration

In apatinib and capecitabine group, apatinib, 500 mg, was orally administered daily on days 1 through 28 of each 4-week cycle. Capecitabine, at 12,500 mg/m^2, was orally taken twice daily for 14 days followed by a 7-day rest period until disease progression. In capecitabine group, an oral dose of capecitabine 1250 mg/m^2 was taken twice daily for 14 days followed by a 7-day rest period until disease progression.

2.3. Efficacy and safety assessments

The primary end point of our study was PFS, defined as the time from enrollment to documented tumor progression with computed tomography (CT)/magnetic resonance imaging (MRI) scan or death as a result of any cause, whichever occurred first. The secondary end points were ORR (CR +PR), DCR (CR +PR+SD), and toxicity.

Treatment efficacy was evaluated in accordance with the Response Evaluation Criteria in Solid Tumors, which were classified into complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Adverse events were assessed and graded according to the National Cancer Institute Common Toxicity Criteria version 3.0 and classified as degree 0∼ IV.

2.4. Ethical statement

The study was approved by the institutional ethics committee of Tangshan People's Hospital. All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

2.5. Statistical analysis

Pearson x^2 test or Fisher exact test was used to analyze the baseline characteristics, treatment efficacy, and adverse events. The t test was used to compare the clinical parameters between both groups. Survival analysis was done according to Kaplan–Meier method. Data were expressed as the mean ± standard deviation and $P < .05$ was considered statistically significant. The SPSS (Statistical Package for the Social Science, SPSS Inc., Chicago, IL) version 16.0 or GraphPad Prism (GraphPad Software, San Diego, CA) version 5.0 was used for all statistical analyses.

3. Results

3.1. Baseline characteristics

This retrospective cohort involved 44 advanced TNBC patients fulfilling the inclusion criteria during the period from January 2016 till February 2017. Among them, 22 patients received apatinib and capecitabine, while 22 patients received capecitabine monotherapy. The characteristics of the patients are summarized in Table 1. There was no significant difference in age, KPS, and disease characteristics between the apatinib and capecitabine group and the capecitabine group.

3.2. Treatment efficacy

Median follow-up time was 5 months (range, 2–11 months). The median PFS time of patients in apatinib and capecitabine group

Table 1

Characteristics of patients with advanced triple-negative breast cancer patients.

	Apatinib and capecitabine (n = 22)	Capecitabine (n = 22)	P
Median age, y (range)	55 (35,69)	56 (34,70)	.827
Menstrual status			.757
Premenopausal	9	8	
Postmenopausal	13	14	
Median KPS	90	90	1.000
Age at diagnosis			1.000
≤35 y	1	2	
>35 y	21	20	
Postoperative pathologic stage			.942
I–II	7	8	
III	10	9	
Unknown	5	5	
Metastatic site			
Viscera	9	10	.761
Bone	15	16	.741
Lymph node	19	17	.698
Thoracic wall	4	6	.472
Malignant serous cavity effusion	7	10	.353
Number of metastatic sites			.545
1	4	3	
2	5	7	
3	8	7	
≥4	5	5	
Treatment history			
Chemotherapy	22	22	1.000
Radiotherapy	21	19	.607
Surgery	20	21	1.000

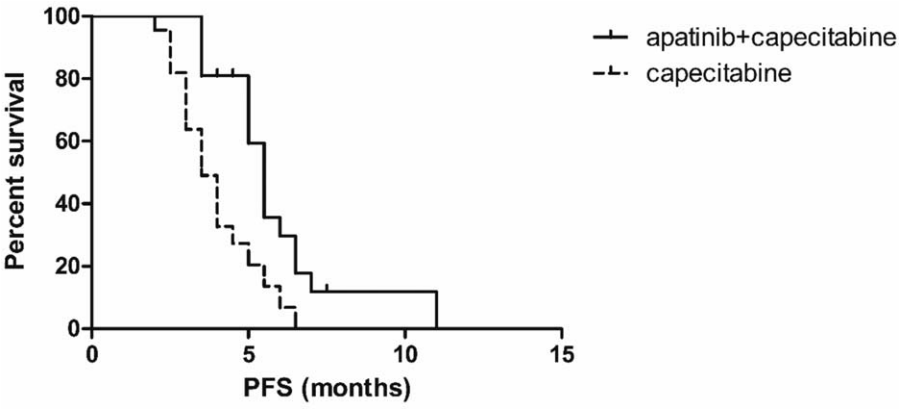

Figure 1. Kaplan–Meier curves of progression-free survival (PFS). The median PFS time of patients in apatinib and capecitabine group was 5.5 months, and for the capecitabine group was 3.5 months ($P = .001$).

was 5.5 months, and for the capecitabine group, was 3.5 months (Fig. 1). The apatinib and capecitabine group exhibited a higher PFS than capecitabine group [$P = .001$, hazard ratio (HR) = 0.2583, 95% confidence interval (95% CI) 0.1150–0.5803].

Of the total 44 patients, no patient was rated as having CR. In apatinib and capecitabine group, 9 patients (40.9%) were rated as having a PR, 6 patients (27.3%) were rated as having a SD, and 7 patients (31.8%) had a PD. ORR was 40.9%, and DCR was 68.2%. In capecitabine group, 3 patients (13.4%) were rated as having a PR, 4 patients (18.2%) were rated as having a SD, and 15 patients (68.2%) had a PD. ORR was 13.4%, and DCR was 31.8%. The ORR and DCR in apatinib and capecitabine group were better than in capecitabine group ($P = .042$; .016). There was a significant difference between the 2 groups. The apatinib and capecitabine regimen had a better efficacy than capecitabine regimen. The clinical response rates are listed in the Table 2.

3.3. Adverse events

Previous studies have reported that the main toxicities of apatinib were hypertension, proteinuria, liver dysfunction, hand–foot syndrome, thrombocytopenia, leukopenia, and neutropenia, which generally manageable.[11,17] As presented in Table 3, the most common adverse events in the patients were hypertension, neutropenia, leukopenia, fatigue, bleeding, nausea, and hand–foot syndrome. Among the 2 groups, most of adverse events were degree I-II, which were not serious. There was no significant difference in the adverse events such as hypertension, neutropenia, leukopenia, fatigue, nausea, hand–foot syndrome, or degree III-IV adverse event of bleeding between the 2 groups. Although the apatinib and capecitabine group showed higher incidence of degree I-II bleeding than the capecitabine group ($P = .021$), this degree I-II adverse event was manageable and not serious, which had no clinical significance.

Table 2

Comparison of efficacy between the apatinib and capecitabine group and the capecitabine group (n, %).

	Apatinib and capecitabine (n = 22)	Capecitabine (n = 22)	P
CR	0 (0)	0 (0)	
PR	9 (40.9%)	3 (13.4%)	.042
SD	6 (27.3%)	4 (18.2%)	.472
PD	7 (31.8%)	15 (68.2%)	.016
Objective response rate (CR+ PR)	9 (40.9%)	3 (13.4%)	.042
Disease control rate (CR + PR + SD)	15 (68.2%)	7 (31.8%)	.016

CR = complete response, PD = progression disease, PR = partial response, SD = stable disease.

4. Discussion

TNBC is a heterogeneous disease and associated with a higher risk of early relapse with visceral metastasis.[18] Because of

Table 3

Comparison of adverse events between the apatinib and capecitabine group and the capecitabine group (n, %).

	Apatinib and capecitabine (n = 22)	Capecitabine (n = 22)	P
Hypertension			
I-II	11 (50.0%)	5 (22.7%)	.060
III-IV	3 (13.6%)	1 (13.6%)	.607
Neutropenia			
I-II	12 (54.5%)	11 (50.0%)	.763
III-IV	1 (4.5%)	0 (0)	1.000
Leukopenia			
I-II	8 (36.4%)	7 (31.8%)	.750
III-IV	0 (0)	0 (0)	NA
Fatigue			
I-II	9 (40.9%)	12 (54.5%)	.365
III-IV	5 (22.7%)	1 (4.5%)	.185
Bleeding			
I-II	6 (27.3%)	0 (0)	.021
III-IV	0 (0)	0 (0)	NA
Nausea			
I-II	13 (59.1%)	16 (72.7%)	.595
III-IV	1 (4.5%)	2 (9.1%)	1.000
Hand–foot syndrome			
I-II	12 (54.5%)	14 (63.6%)	.540
III-IV	1 (4.5%)	1 (4.5%)	1.000

NA = not available.

uncommonness, aggressiveness, and impressive heterogeneity, the treatment of TNBC remains a major clinical challenge,[19] especially for the patients who failed in first-line or second-line therapy. Although a great deal of therapies have been developed to specific molecular targets, such as poly-(ADP-ribose)-polymerase inhibitors, epidermal growth factor receptor inhibitors, Src TK inhibitors, and mTOR inhibitors,[20] chemotherapy is still the mainstay of treatment.

Capecitabine has been approved for the treatment of breast cancer,[21] and it is widely used in metastatic breast cancer. It has been proved effective for the treatment of metastatic breast cancer in a number of Phase I, Phase II, and Phase III trials.[22–24] A retrospective study including 363 patients with TNBC treated with capecitabine demonstrated that capecitabine is a treatment option for patients with TNBC in advanced disease including first-line and second/third-line.[25]

Apatinib is an oral, highly potent TK inhibitor targeting VEGFR2. It Antitumor activity has been demonstrated across a broad range of malignancies, including gastric, colorectal, and breast cancer, and good tolerability in phase I study conducted in former studies.[26,27] A nonclinical trial has confirmed the encouraging efficacy and manageable safety of apatinib on pretreated metastatic breast cancer patients.[17] In a multicenter phase II study, apatinib has also been evaluated the efficacy and safety in heavily pretreated patients with metastatic TNBC.[11]

In this study, the advanced TNBC patients who failed in first-line or second-line therapy received apatinib and capecitabine or capecitabine monotherapy as the third-line treatment. The apatinib and capecitabine group exhibited a higher PFS than the capecitabine group ($P = .001$). A retrospective study with 363 TNBC patients showed that capecitabine monotherapy achieved a ORR of 21% and a DCR of 33%[25]; our study had a similar efficacy with it and the ORR in capecitabine group was 13.4%, and the DCR in capecitabine group was 31.8%. Although in apatinib and capecitabine group, it was 40.9% and 68.2%. The ORR and DCR in apatinib and capecitabine group were higher than that in the capecitabine group ($P = .042$; .016), which demonstrated that advanced TNBC patients with apatinib and capecitabine had a better efficacy than those with capecitabine monotherapy.

Between the 2 groups, the most common adverse events were nausea, hand–foot syndrome, fatigue, neutropenia, and leukopenia. We found no significant difference in the above adverse events, while the capecitabine group showed significantly lower incidence of degree I-II bleeding than the apatinib and capecitabine group ($P = .021$). However, the minor bleeding events (degree I-II) were manageable; as a result, there was no clinical significance. At the same time, no serious bleeding (degree III-IV) occurred in both groups. Overall, compared with capecitabine monotherapy, apatinib and capecitabine did not increase serious adverse events. Both the apatinib and capecitabine and the capecitabine regimens showed good tolerability.

In summary, the results of our present study, although retrospective, support that third-line treatment of advanced TNBC with the apatinib and capecitabine regimen showed better efficacy and similar serious adverse events compared with capecitabine regimen. Given the limited treatment options for advanced TNBC patients who failed in first-line or second-line therapy, apatinib and capecitabine regimen may be one of the more effective treatments. However, our study is a single-center retrospective study with a small sample size, and more prospective studies with a large sample size are needed to verify the results of our study.

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