A Phase II Trial of anlotinib combined chemotherapy as second-line and above therapy in HER2-negative advanced breast cancer

Ting Xu[1], Quan Gu[2], Shiyi Li[1], Lili Zhang[2*], Yuan Yuan[2*]

[1]Department of Oncology, The Affiliated Cancer Hospital of Nanjing Medical University；[2]Department of Chemotherapy, Jiangsu Cancer Hospital

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Abstract

There are currently no standard treatment and limited response to chemotherapy in the second and above line of HER2-negative advanced breast cancer.

In our retrospective study, anlotinib (a novel multi-targeted tyrosine kinase inhibitor mainly targeting angiogenesis signaling)-based treatment demonstrated effectiveness in the multi-line treatment of MBC patients who failed the standard treatment.

In this study, we assessed the efficacy and safety of anlotinib plus chemotherapy in second-line and above treatment of HER-2 negative advanced breast cancer. Meanwhile, search for biomarkers to predict the efficacy of anlotinib treatment.

Methods and Materials

In this prospective, single-arm, phase II clinical trial，we prospectively enrolled 33 patients with HER2-negative advanced breast cancer who underwent at least one-line chemotherapy or progressed within one year of receiving adjuvant therapy between August 2022 and August 2023.

All patients were treated with anlotinib in combination with chemotherapy.

96 immuno-oncology protein expression levels were measured in serum from 32 anlotinib-sensitive and insensitive patients.

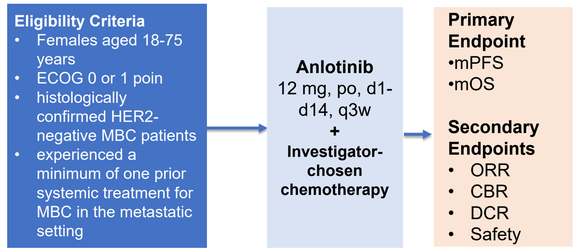


Figure 1. Study Design

Results

This study included HR+/HER2- patients (N=23) and TNBC patients (N=10). The median follow-up was 25.9 months (95% CI, 19.9-32.0) by the data cutoff date (February 2025). Median PFS (mPFS) was 8.3 (95% CI: 6.3–10.3) months, and the mOS was 22.2 (95% CI: 13.1–31.3) months . Besides, the mPFS of HR+/HER2- and TNBC was 7.4 months（95% CI, 4.5-10.2）and 10.6 months（95% CI, 7.7-13.5）respectively, and the mOS was 15.3 months（95% CI, 3.2-27.5）and 24.2 months（95% CI, 15.5-32.8）.

83.0% of HR+/HER2- patients had used cyclin-dependent kinase 4/6 inhibitors prior to anlotinib, and the mPFS was 6.8 months.

Proteomics analyses of patient serum revealed baseline differences in patients with short (non-sensitive) versus long PFS (sensitive) (P < 0.05). Compared to patients with lower levels, patients with higher expression levels of proteins, experienced shorter PFS.

Characteristics	Patients (%) (N = 33)	Characteristics	Patients (%) (N = 33)
Age, median (range), years	52(32–79)	**Dominant metastatic sites**	
ECOG PS at baseline		Bone	21(63.6)
1	33(100)	Liver	11(33.3)
Menopausal status		Lung	15(45.5)
Premenopausal	2(6.1)	Brain	5(15.2)
Postmenopausal	31(93.9)	Lymph nodes	31(93.9)
Intrinsic subtypes		**Number of metastatic sites**	
HR-positive /HER2-negative	23(69.7)	＜3	8(24.2)
Triple negative	10(30.3)	≥3	25(75.8)
Chemotherapy partner of anlotinib		**Lines of therapy of anlotinib plus Chemotherapy**	
Taxanes	11(33.3)	Median (range)	3(2–5)
Eribulin	11(33.3)	2	16(48.5)
Utidelone	6(18.2)	3	9(27.3)
Capecitabine	5(15.2)	≥4	8(24.2)

Table 1. Baseline characteristics of patients.

Results

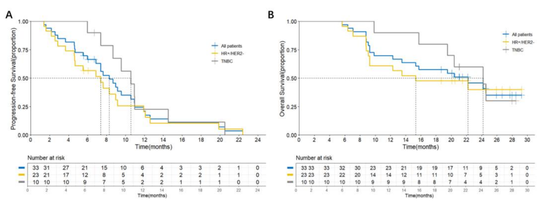


Figure 2.(A) Progression-free survival (PFS) (B) overall survival (OS)

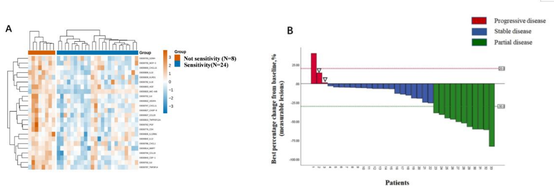


Figure 3. (A)Protein expression;(B)Waterfall plot for best percent change in target lesion from baseline

Best Response	% (n/N)
Complete response (CR)	0
Partial Response (PR)	33.3(11/33)
Stable Disease (SD)	57.6(19/33)
Progression Disease (PD)	9.1(3/33)
ORR (95%CI)	33.3(18.5-51.8)
CBR (95%CI)	60.6(42.1-77.1)
DCR (95%CI)	90.9(75.7-98.1)

Table 2. Efficacy Measures (N=33)

Results

The most frequently observed adverse events were hand-foot syndrome (100.0%), elevated triglycerides (78.8%), elevated blood sugar (63.6%), anemia (60.6%), elevated cholesterol (51.5%), hoarse voice (50.0%), epistaxis (48.5%), and leukopenia (48.5%). Dose reductions occurred in 7 (21.2%) patients due to adverse events.

Adverse events	All grades, n (%)	Grade 3/4, n (%)
Hypertriglyceridemia	27(81.8)	7(21.2)
Anemia	20(60.6)	2(6.1)
Hyperglycemia	20(60.6)	1(3.0)
Blood cholesterol increased	17(51.5)	0
Leukopenia	16(48.5)	5(15.2)
Alanine aminotransferase increased	16(48.5)	0
Neutropenia	14(42.4)	7(21.2)
Aspartate aminotransferase increased	13(39.4)	0
Epistaxis	13(39.4)	0
Hand-foot syndrome	11(33.3)	1(3.0)
Thrombocytopenia	10(30.3)	0
Gum hemorrhage	10(30.3)	0
Diarrhea	7(21.2)	0
Hypertension	7(18.2)	0
Cough	5(15.2)	0
Constipation	5(15.1)	0
Peripheral sensory neuropathy	5(15.1)	0
Blood bilirubin increased	4(12.1)	0
Fatigue	4(12.1)	0
Adverse events leading to dose reduction of anlotinib	6(18.1)	

Table 3. Adverse events(≥10%)

Conclusions

Our study suggests that anlotinib combined with chemotherapy may be an optional second-line or later strategy for patients with HER2-negative MBC. Furthermore, this study offers crucial identification of potential biomarkers for resistance to this combination therapy. However, its results need further confirmation through prospective studies with larger sample sizes.

Contact

<Yuan Yuan>
<Department of Chemotherapy, Jiangsu Cancer Hospital, Nanjing, China>
Email:yuanyuan810122@126.com
<Lili Zhang>
<Department of Chemotherapy, Jiangsu Cancer Hospital, Nanjing, China>
Email: longrenyu@sina.com

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