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# The Clinical Response to The Combination of Anlotinib and Tislelizumab in Multi-Line Treatment of a Metastasis Triple-Negative Breast Cancer Patient: A Case Report

**Qian Y[1], Zhang L[2], Xiong W[1] and Yuan Y[2*]**

[1]Department of Oncology, The Affiliated Cancer Hospital of Nanjing Medical University, Nanjing, 210009, China

[2]Department of Chemotherapy, Jiangsu Cancer Hospital &Jiangsu Institute of Cancer Research &The Affiliated Cancer Hospital of Nanjing Medical University, Nanjing, 210009, China

**[*]Corresponding author:**

Yuan Yuan.
No. 42 Baiziting, Nanjing, Jiangsu Province, China, 210009.
E-mail: yuanyuan810122@126.com

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**Keywords:**

Breast cancer; Anlotinib; Tislelizumab; Multi-line treatment; Case report

## 1. Abstract

**1.1. Background**: We report a triple-negative breast cancer (TNBC) patient who progressed rapidly after multiple lines of conventional chemotherapy. However, this patient then responded well to the combination of anlotinib and immunotherapy.

**1.2. Case Summary**: A TNBC patient who underwent anthracycline and taxane-based and platinum-involved neoadjuvant treatment developed brain and lymph node metastases eight months after the modified radical mastectomy and the adjuvant capecitabine for eight cycles and olapali for one month. After receiving the whole-brain radiotherapy, the patient was treated with the first-line treatment of gemcitabine and carboplatin and second-line treatment of vinorelbine and oxaliplatin but still developed rapidly. However, this lady then responded well to the combination of anlotinib and tislelizumab. She achieved a partial response (PR) with a progression-free survival (PFS) of more than 13 months, followed by July 2021. This combination use was well tolerant and all the adverse reactions were under grade three, which mainly included hand-foot syndrome and myelosuppression.

**1.3. Conclusion**: The combination of anlotinib and tislelizumab is a good choice for metastasis triple-negative breast cancer (mTNBC) patients to achieve good clinical efficiency and well tolerance.

## 2. Introduction

Owing to the high relapse rates and poor overall survival, triple-negative breast cancer (TNBC) is usually considered the most fatal subtype of breast cancer [1]. For patients who have received standard neoadjuvant or adjuvant treatment with anthracyclines and taxanes and recurred within a year, there is currently no standard therapy regime. Meanwhile, how to select appropriate regimens in later lines of treatments for these patients is still an intractable challenge. At the moment, chemotherapy remains the backbone therapy in the treatment of mTNBC. Platinum-based regimens are recommended in TNBC patients with BRCA1/BRCA2 mutation because of their affecting on the homologous recombination (HR) DNA repair pathway. Studies have demonstrated that platinum can benefit germline BRCA1/2 carriers more than noncarriers in both neoadjuvant and metastatic settings [2,3]. Moreover, TNBC is more likely to benefit from immune checkpoint blockade therapy than other breast cancer subtypes because of its higher immunogenicity, higher enrichment of tumor-infiltrating lymphocytes (TIL), and higher levels of programmed cell death ligand 1 (PD-L1) expression [4]. Nevertheless, the benefits of immunotherapy on TNBC patients' prognosis are still debatable, and domestic programmed death receptor-1 (PD-1) has not been approved for clinical application yet. The role that antiangiogenic agents play in the treatment of breast cancer is still under debate. Clinical trials such as the RIBBON-1 trail documented superior PFS when patients were treated with the combination of bevacizumab and failed to reach a statistically significant increase in overall survival (OS) [5]. Tyrosine kinases targeting vascular endothelial growth factor (VEGF) may also be the potential treatment approach in

TNBC [6]. Anlotinib is a new type of small-molecule tyrosine kinase inhibitor (TKI) which mainly targets vascular endothelial growth receptors (VEGFR). Anlotinib has shown efficacy in HER-2 negative metastatic breast cancer to some extent, and its combination with immunotherapy appears to act synergistically in the treatment of other cancers [7]. Despite all of this, the US Food and Drug Administration (FDA) and the Chinese Food and Drug Administration (CFDA) have not approved these anti-vascular therapies for the treatment of breast cancer yet for the lack of sufficient evidence. In this case, we report a metastasis TNBC patient with BRCA2 mutation whose disease-free survival (DFS) was only eight months. Moreover, the following chemotherapy failed in both the first-line and second-line. Nevertheless, this patient responded well to the combination of anlotinib and tislelizumab, an anti-human PD-1 monoclonal IgG4 antibody (8).

## 3. Case Presentation

A 64-year-old Chinese female with an enlarged left breast mass was admitted to the hospital in January 2018. Her family history was negative for neoplastic diseases. Physical examination revealed a 1.0×1.5 cm2 mass in the lower inner quadrant region of her left breast. The enlarged axillary lymph nodes and supraclavicular lymph nodes on the same side were also palpable, and the diameter of the lymph nodes was 4.0 cm and 2.0 cm, respectively. Breast biopsy showed invasive ductal breast cancer with vascular invasion, and the biopsy of the left supraclavicular lymph also indicated invasive carcinoma, likely metastasized from the mammary gland. Immunohistochemical (IHC) evaluation revealed that the estrogen receptor (ER), progesterone receptors (PR), and human epidermal growth factor receptor-2 (HER2) were negative and the Ki67 index was about 30%. The molecular subtype was TNBC. Based on the combination of the patient's clinical history, physical examination, laboratory results, and radiographic data, she was diagnosed with stage ⅢC breast cancer (cT1N3M0 of TNM staging system). Additionally, BRCA2 germline mutation was detected by genetic testing. Neoadjuvant treatment was recommended to this patient according to the National Comprehensive Cancer Network Guidelines and the Chinese Society of Clinical Oncology Guidelines. After eight cycles of chemotherapy with four cycles of epirubicin at 90 mg/m2 and cyclophosphamide at 600 mg/m2 every 2 weeks followed by four cycles of nab-paclitaxel at 125 mg/m2 on days 1 and 8 and cisplatin 75 mg/m2 on days 1 and 2 every 21 days, the patient was then treated with a modified radical mastectomy on the 12th of July 2018. The histopathological examination of the postoperative specimen showed no cancer in the breast. However, 3 lymph nodes were shown to contain malignant cells. The tumor was pathologically staged as ypT0N1M0 IB. Postoperatively, the patient received radiotherapy (50 Gy) to the left hemithorax and left supraclavicular fossa and 8 cycles of capecitabine. She also took Olapali for one month but stopped the drug by herself after experiencing grade 2 thrombocytopenia. In addition, in February 2019, papillary thyroid carcinoma was diagnosed and treated with surgical excision. In March 2019, the patient felt dizzy, headache, nausea, and a decrease in her left limb muscles strength. The head CT scan uncovered a mass with peripheral edema in the right side of her frontal lobe, and the mass was considered brain metastasis. Therefore, she received the whole-brain radiotherapy 12 times to a total dose of 35 Gy and the following boost dose of 15 Gy in 5 fractions. The muscle strength of her left limb recovered after radiotherapy. Nine months later, this lady was hospitalized in our ward again with the complaints of a few swollen lymph nodes in her neck. Ultrasound-guided biopsy of the enlarged cervical lymph node was performed, and the histopathological examination showed the presence of metastasis from an infiltrating carcinoma. The molecular subtype is still TNBC, which is the same as the primary site. The patient was then treated with the first-line treatment of gemcitabine and carboplatin and the second-line treatment of vinorelbine and oxaliplatin. The progression-free survival (PFS) of both chemotherapy regimens was only three months, and the evaluation of response was progressive disease (PD) and stable disease (SD), respectively (Figure 1, Figure 2). Since the previous two consecutive lines of treatment both failed within a short period of time, and the patient chose to discontinue chemotherapy, we took anti-vascular therapy combined with immunotherapy into account. Treatment continued with anlotinib in a dose of 12 mg for 14 days and suspended for 7 days combined with tislelizumab at the dosage of 200 mg every 3 weeks from June 2020. Follow-up CT scan evidence revealed that the brain and lymph node metastatic lesions obviously shrank. The patient achieved a partial response (PR) with a PFS of more than 13 months till July 2021 (Figure 3). During the treatment, the patient developed grade 1 fatigue and hand-foot syndrome as well as grade 2 thrombocytopenia. These adverse reactions improved after symptomatic treatment. Overall, the treatment was well-tolerated.

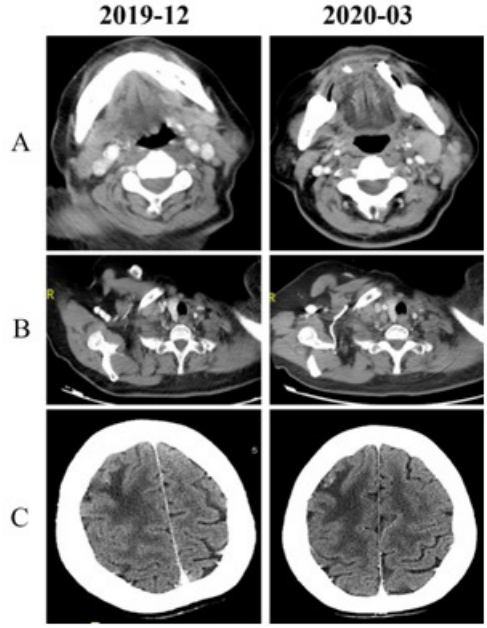


**Figure 1:** Enhanced CT scan before and after the 2 cycles of the treatment of gemcitabine and carboplatin. The left cervical lymph node (A) and the right supraclavicular lymph node (B) enlarged while the metastatic brain lesion (C) was stable. CT, computed tomography.

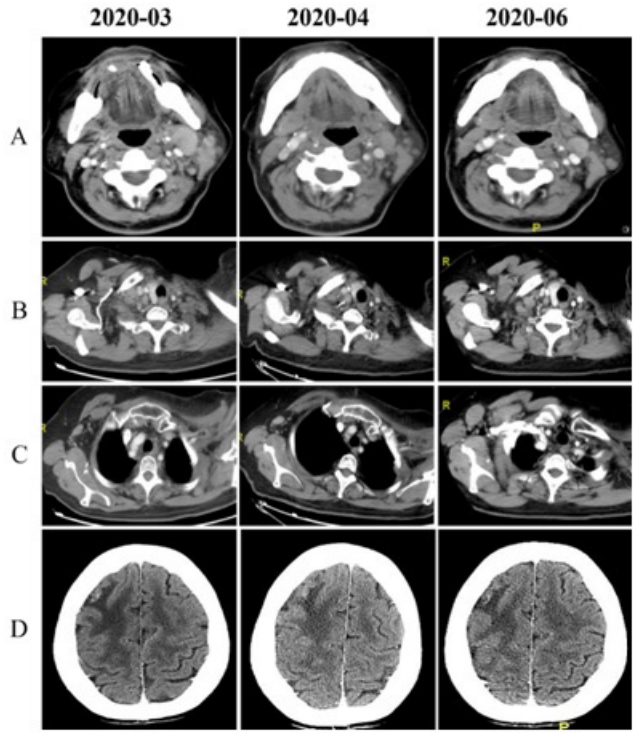


**Figure 2:** Enhanced CT scan before and after the 2 and 4 cycles of the treatment of vinorelbine and oxaliplatin. The right supraclavicular lymph node (B) and the right axillary lymph node (C) were stable after 2 cycles of treatment but significantly enlarged after another 2 cycles. The left Cervical lymph node (A) and the metastatic brain lesion (D) were stable. CT, computed tomography.

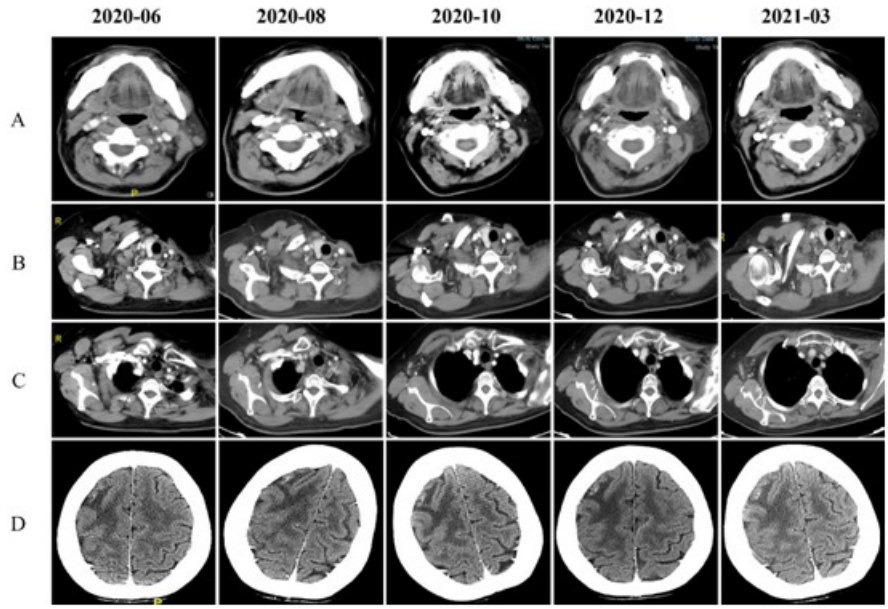


**Figure 3:** Enhanced CT scan before and after the treatment of anlotinib and tislelizumab. The left Cervical lymph node (A), the right supraclavicular lymph node (B), the right axillary lymph node (C), and the metastatic brain lesion (D) all shrunk.

## 4. Discussion

Currently, chemotherapy is still the primary treatment for TNBC, but due to the high heterogeneity of this subtype, the response to chemotherapy varies significantly among different people. In the past decade, to help guide treatment decisions, more and more studies have divided TNBC into different subtypes by analyzing the molecular characteristics of tumors. Although there have been many classifications based on different sets of criteria, the idea of hoping to use these classifications to develop more effective targeted treatments is still in an exploratory stage and has not been clinically applied. Therefore, the current treatment for triple-negative breast cancer is still based on a combination of anthracyclines and taxanes. In this case, we used four cycles of epirubicin and cyclophosphamide followed by four cycles of

nab-paclitaxel and cisplatin in the neoadjuvant chemotherapy. It is worth mentioning that whether platinum drugs should be included in neoadjuvant chemotherapy for TNBC, even for those with BRCA mutation, is still controversial. Though several studies have shown the improvement of pathological complete response (pCR), the long-term outcome is still uncertain [2,9]. Besides, the addition of platinum may also induce increased toxicity or adverse events. At present, platinum is still only recommended to patients who need better local control. Eight cycles of capecitabine were used after the adjuvant radiotherapy since this drug showed effectiveness as an adjuvant option in HER2-negative breast cancer patients with the residual invasive disease after standard neoadjuvant chemotherapy. The OlympiA trial showed that one year of adjuvant olaparib could effectively reduce recurrence and prevent progression to metastatic disease in patients with germline BRCA mutation (10). Since the patient refused to continue taking olaparib after only one month of treatment, we were unable to determine whether this PARP inhibitor played a role in this patient. When this patient recurred 8 months after the surgery, we still picked chemotherapy as our first choice. There is currently no standard chemotherapy regimen for patients who have failed the treatments with anthracyclines and taxanes. For patients with germline BRCA1/2 mutations, platinum drugs are the first choice according to existing researches [3,11]. The CBCSG 006 study demonstrated that, for mTNBC patients, cisplatin plus gemcitabine could be the preferred first-line chemotherapy strategy [12]. Since cisplatin has already been used in the neoadjuvant treatment, we chose gemcitabine and carboplatin as the replacement. After the failure of our first-line treatment, the second-line strategy of vinorelbine and oxaliplatin still did not achieve the desired effect. Considering that this patient has BRCA2 germline mutation, theoretically, platinum drugs should have a better outcome, but the result in this case was exactly the opposite. In consideration of the patient's unsatisfactory response as well as her unwillingness to chemotherapy, we changed course in the third-line therapy. The use of immunotherapy combined with antiangiogenic therapy in TNBC is not common. The use of immunotherapy on TNBC is still in its infancy with limited clinical data, and how much it could benefit TNBC patients is in conflict. The Phase III double-blind IMpassion130 trial indicated the potential value of immunotherapy as, compared with placebo, atezolizumab significantly improved median PFS of TNBC patients with positive PD-L1 protein expression when being used in combination with nab-paclitaxel as the first-line treatment [13]. Nevertheless, the following similarly designed Impassion 131 study demonstrated improvement in neither PFS nor OS when using paclitaxel as a substitute for nab-paclitaxel [14]. Pembrolizumab, a PD-1 inhibitor, also exhibited significantly longer PFS versus placebo when combined with chemotherapy among TNBC patients [15]. All these results led to the FDA approval of atezolizumab with nab-paclitaxel and pembrolizumab with chemotherapy for mTNBC patients. However, in China, PD-1 has not been approved for these patients' treatment yet. So far, results obtained from antiangiogenic treatment were not encouraging. There is a certain amount of evidence that angiogenesis plays an essential role in the occurrence, development, and metastasis of breast cancer. We expected better efficacy but results from previous clinical trials such as RIBBON-1 did not achieve the desired outcome [5]. Recent research has thrown new light on anti-vascular therapy. Increased VEGF levels can lead to immune suppression in the tumor microenvironment. The combined use of anti-vascular therapy and immunotherapy showed synergistic therapeutic effects in renal cell carcinoma and non-small cell lung cancer [16,17]. By down-regulating the expression of PD-L1 on vascular endothelial cells, anlotinib can inhibit tumor growth and this anti-tumor effect could also be enhanced with the help of immune checkpoint inhibitors [18]. The FUTURE-C-PLUS study presented at the American Society of Clinical Oncology (ASCO) Annual Meeting in 2021 evaluated the efficacy, safety of camrelizumab in combination with nab-paclitaxel and famitinib in patients with unresectable locally advanced or metastatic immunomodulatory TNBC. It showed encouraging results that the objective response rate reached 81.3%, which could be a breakthrough in the treatment of TNBC. So, taking all of that into account, we chose anlotinib and tislelizumab as our subsequent treatment, and it did help control the secondary sites in this patient for quite a long time. Another interesting thing is that, according to the results of the FUTURE-C-PLUS study, patients with BRCA1 mutations seemed to be relatively less sensitive to the regimen. However, as for our patient, the combination of immunotherapy and antiangiogenic therapy did have a good effect. It could be a contingency, or maybe some undiscovered differences exist between BRCA1 and BRCA2 (19). Another prompting question is that it seems there is some connection between VEGF signaling and platinum resistance [20]. This may have something to do with the great efficacy of anlotinib and tislelizumab on this patient. In this case, we reported a metastasis triple-negative breast cancer patient who showed an excellent response to the combination of anlotinib with tislelizumab after multiple lines of treatments. In the beginning, we made treatment plans according to guidelines and our clinical experience, but the therapeutic effects were far from satisfactory. We did not expect our later attempt turned out to be such satisfying. This suggests that for TNBC, a highly heterogeneous disease, we should not be trapped by chemotherapy when it does not work. More effective and precise classification should be made, and further exploration is needed in large clinical trials. For now, we hope that this case report will provide a new treatment option for this kind of patient. After all, this is only a case report. Since many of the speculations we have mentioned above have not been sufficiently substantiated, we cannot draw a solution that can be widely applied based on this one single case. In conclusion, the combination of anlotinib and tislelizumab could be the potential choice for multi-line treated TNBC patients to achieve good clinical efficiency and well tolerance.

## 5. Acknowledgments

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