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# Safety and Efficacy of Combination of Niraparib in The Treatment of Advanced Breast Cancer: A Case Report

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## 1. Abstract

BRCA is a common susceptibility gene for breast cancer, PARP inhibitors are target drugs for BRCA mutation. The most of clinical trails and case reports of PARP inhibitors are monotherapy. Rare focus on the combination of other therapies. We herein report the first case of a breast cancer patient who underwent the combination of Niraparib with chemotherapy and the combination of Niraparib with endocrine therapy and Immunotherapy in the hope of bringing new views to the clinical application of PARP inhibitors.

### 1.1. Background

Breast cancer(BRCA) mutation plays an importment role in breast cancer [1]. Mutations in breast cancer 1(BRCA1) and breast cancer 2(BRCA2) are detected in at least 5% of patients with breast cancer [2]. In carriers of BRCA1 or BRCA2 mutations, the risk of developing breast cancer by 80 years of age is as high as 70%, compared with a 10% risk for women in the general population [3]. Treatment options are limited for patients with BRCA-mutated breast cancer at present. As a target drug for BRCA mutation, poly ADP-ribose polymerase (PARP) inhibitors, which participate gene damage repair are now being investigated for the treatment of breast cancer. Some experiments indicate that the combination of PARP inhibitors with other therapies play a greater effect. However, most clinical trails just focus on PARP inhibitors its own. We herein report the first case of a breast cancer patient who underwent the combination of Niraparib with chemotherapy and the combination of Niraparib endocrine therapy and Immunotherapy in the hope of bringing new views to the clinical application of PARP inhibitors.

## 2. Case Presentation

The patient is a 50-year-old woman who was diagnosed with right breast cancer through an ultrasound-guided core needle biopsy performed on an initial mass of the right breast in October 2017. The breast cancer subtype was luminal B type and was positive for estrogen receptor(ER), progesterone receptor (PR) and nagetive for human epidermal growth factor receptor 2(HER2) and Ki-67marker index is 30% on immunohistochemistry (IHC). From November 2017 to February 2018, six cycles of TA regimen neoadjuvant chemotherapy (pirubicin 90mg d1, docetaxel 140mg d1) was administered. On March 20 2018, the modified radical mastectomy for right breast cancer was performed. Based on the postoperative pathology results ((pathology number: 2018-08284)), The breast cancer subtype was still luminal B type and was positive for ER, PR and HER2(HER2 2++, FISH-) and Ki-67marker index is 7% on IHC. The tumor cell density is 40%, compared with the CNB (2017-33546) tumor cell density before chemotherapy, which is 70%. Considering its histological grade after chemotherapy is G3. There was sentinel lymph node metastasis (1/6). She subsequently received hormone therapy with tamoxifen. In January 2020, the patient had no obvious cause of coughing. On January 23, 2019, the chest computed tomography showed nodules in both lungs. The patient didn't receive any trentment. In March 2020, systemic metastases were detected in her hilum of left lung, lymph nodes and bone. The bronchoscopy biopsy result showed metastatic breast cancer and was positive for ER, PR and nagetive for HER2(0) on

IHC. The gene detection result of the biopsy specimen showed BRCA1 was positive on July 2020. From July 2020 to November 2020, six cycles of TP regimen chemotherapy (paclitaxel 0.5g d1+ lobaplatin 20mg d2) with combination of Niraparib 200mg/day were completed. From January 2021 until now, Niraparib 200mg/day with combination of Fulvestrant 500mg/28d and Durvalumab 1000mg/month was administered as maintenance therapy. The patient has been receiving Zoledronic Acid for the treatment of bone metastasis from July 2020 so far. The whole Treatment process is showed in Figure 1.

## 3. Discussion

As a common malignant tumor among women in China, breast cancer threatens the life quality and health of women to a certain extent. The important means to reduce the mortality of breast cancer are early detection, early diagnosis and early treatment [4]. The prognosis of patients with advanced breast cancer stays poor though the mortality rate of breast cancer has a decreasing trend [5]. Breast cancer has a strong genetic background, so the detection of susceptibility gene mutations can effectively screen high-risk groups, which is convenient for early prevention and control. Research datas show that BRCA is a common susceptibility gene for breast cancer. In addition, the detection of BRCA gene has been carried out in developed countries. BRCA1 and BRCA2 genes are tumor suppressor genes that can inhibit the occurrence of malignant tumors and play an important role in the process of double-stranded gene damage and repair [6]. PARP is activated by identifying gene fragments of structural damage. In addition, it participates in base excision repair. It is an important molecule in gene damage repair and plays an important role in the process of gene damage repair and apoptosis [7]. PARP and BRCA are both the key factors affecting the pathway of gene damage repair. The BRCA1/2 mutation tumor cells cannot repair DNA double strand break through homologous recombination and will rely more on the DNA repair pathway mediated by PARP, and the level of PARP expression and the sensitivity to PARP inhibitors is Proportional [8]. Simultaneous inhibition of BRCA and PARP provide a synergistic lethal effect on tumor cells [9]. The therapeutic effect of PARP inhibitors in patients with BRCA mutation breast cancer provides hope for targeted therapy. Combination of drugs can enhance the activity of PARP inhibitors and

### 3.1. Promote the Further Study of PARP Inhibitors

The choice of treatment for patients with advanced breast cancer is of great importance. In addition, because of the lack of standard treatment after first-and second-line rescue treatment, how to help patients make correct treatment choices is a challenge for every oncologist. The characteristics of this case were obvious: symptomatic visceral metastasis, heavy tumor load, obvious clinical symptoms, positive hormone receptor (ER/PR) in primary and metastatic lesions, but progressed within 2 years after endocrine therapy. The patient visited our hospital for the first time in June 28 2020. After perfecting the relevant examination and fully evaluating the patient's condition, the treatment plan was as follows: ①TP rescue chemotherapy+Niraparib 200mg/day×6 cycle; ②Maintenance therapy: Niraparib 200mg/day+Durvalumab 1000mg/month+Fulvestrant 500mg/28d. According to the results of chest CT, the patient showed a good response to the six circle of salvage chemotherapy combined with target therapy. (Figure 2) The patient's symptoms were significantly reduced and the curative effect of six circle was evaluated as PR after the salvage chemotherapy combined with target therapy. During the maintenance therapy, the patient showed good tolerance and had no adverse reactions. The curative effect was evaluated as SD (Figure 3). According to the 2020 Chinese Version of The Expert Consensus On The Application of Platinum Drugs for Advanced Breast Cancer, platinum-containing regimens are recommended for the rescue treatment of advanced breast cancer with BRCA gene mutation [10]. A prospective phase III randomized clinical trial, BROCADE3, published in the Lancet Oncology, included patients with germline BRCA mutation and HER2-negative advanced breast cancer who had previously received ≤ 2-line cytotoxicity therapy. The study evaluated the efficacy of Veliparib in addition to carboplatin plus paclitaxel in patients with advanced breast cancer with BRCA gene mutation. The control group received carboplatin combined with paclitaxel and placebo. The median follow-up was more than 35 months. The median PFS of the test group was 14.5 months (90%CI 12.5-17.7 months) and that of the control group was 12.6 months (90%CI 10.6-14.4 months). The difference was statistically significant (HR=0.71,90%CI 0.57-0.88,P=0.0016) [11]. Experimental studies have also shown that PARP inhibitors can enhance the efficacy of radiotherapy and alkylating agents and platinum chemotherapy by inhibiting the repair of DNA damage and promoting the apoptosis of tumor cells, especially in women with hereditary BRCA mutations in ovarian and breast cancer [12]. However, there is no unified view on the efficacy of PARP inhibitors combined with platinum drugs. As a consequence, more clinical studies are needed to confirm it. Previous studies have indicated that breast cancer patients with BRCA mutations have higher histological grades, ki-67 expression and benefit less from endocrine therapy[13]. And the Oncotype-Dx recurrence risk score of BRCA mutant and ER positive patients is higher than that of non-BRCA mutant patients [14]. With the development of targeted therapy, "endocrine + targeting" has gradually become a new strategy for the treatment of advanced breast cancer. For hormone receptor positive patients with BRCA mutations, some clinical trails are undergoing to explore the strategy of PARP inhibitors combined with endocrine therapy. Two international Phase II Trials are still recruiting patients now. One in Korea(NCT03594396) is studying on the safety run-in of neoadjuvant therapy with an aromatase inhibitor in combination with Durvalumab in postmenopausal patients with hormone-receptor-positive breast cancer. Another in America(NCT04053322) is working on the efficacy of Durvalum-

ab plus Olaparib plus Fulvestrant in metastatic or locally advanced ER-positive, HER2-negative breast cancer patients. The treatment of PARP inhibitors blocked the repair of DNA damage, abnormal existence of DNA in the cytoplasm. In addition, it further activated the STING pathway, resulting in the up-regulation of immune cells and PD-L1 in tumors. Experimental studies have shown that PARP inhibitors and immunotherapy have a synergistic effect [15]. The phase I/II MEDIOLA study evaluated the efficacy of Olaparib combined with Durvalumab in patients with gBRCA1/2 mutant metastatic breast cancer. Among the 30 assessable patients, 80% reached the main end point of disease control at 12 weeks, and the ORR of Olaparib combined with Durvalumab reached 63.3% [16]. The single-arm and phase II TOPACIO study evaluated the efficacy of Niraparib combined with Pembrolizumab in the first-line treatment of mTNBC. As a result, among the patients with BRCA mutation, the ORR was 57%, the disease control rate (DCR) was 80%, and the median PFS was 8.3 months [17]. Patients may have varying degrees of adverse reactions during the treatment of PARP inhibitors, most of which are mild or moderate (grade 1-2). Hematological and gastrointestinal adverse reactions are the most common. Most of the grade 3-4 adverse reactions were hematological adverse reactions. Among the hematological adverse reactions, anemia is the most common hematological adverse reaction in the use of PARP inhibitors, with an overall incidence of 37%-50%, and 19%- 25%for grade3- 4. The incidence of thrombocytopenia was 14%-61%. The incidence of grade 3-4 thrombocytopenia was 1%-34%. The total incidence of neutropenia was 18%-30%, of which 4%-20% was grade 3-4 adverse reactions. However, hematological safety can be controlled through active dose adjustment and close hematological monitoring. In all clinical research centers related to PARP inhibitors, no patient terminated treatment due to hematological events [18-20]. Besides, in the BGB-290-102study, some patients (70.8%) received dose reduction treatment, but the dose reduction did not have a significant effect on the efficacy [21]. The patient in this case was diagnosed with mild anemia on admission. According to the study, the incidence of hematological adverse reactions decreased significantly when the dose of nilapalil was adjusted to 200mg/qd. As a consequence, the dose of Niraparib in this case was set as 200mg/ days, and there was no severe adverse reaction so far (Table 1).

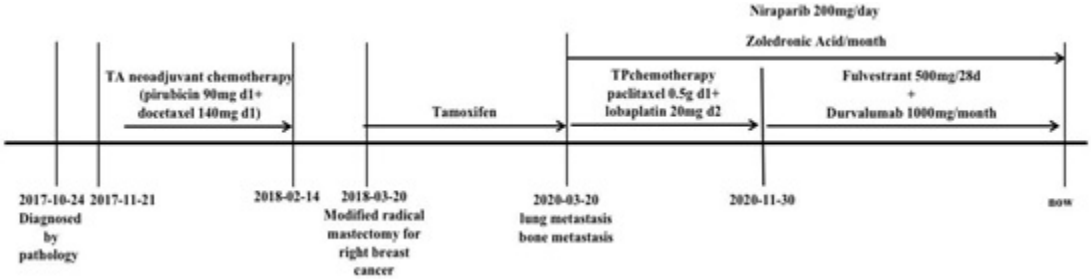


**Figure 1**. Clinical course of treatment of the case.

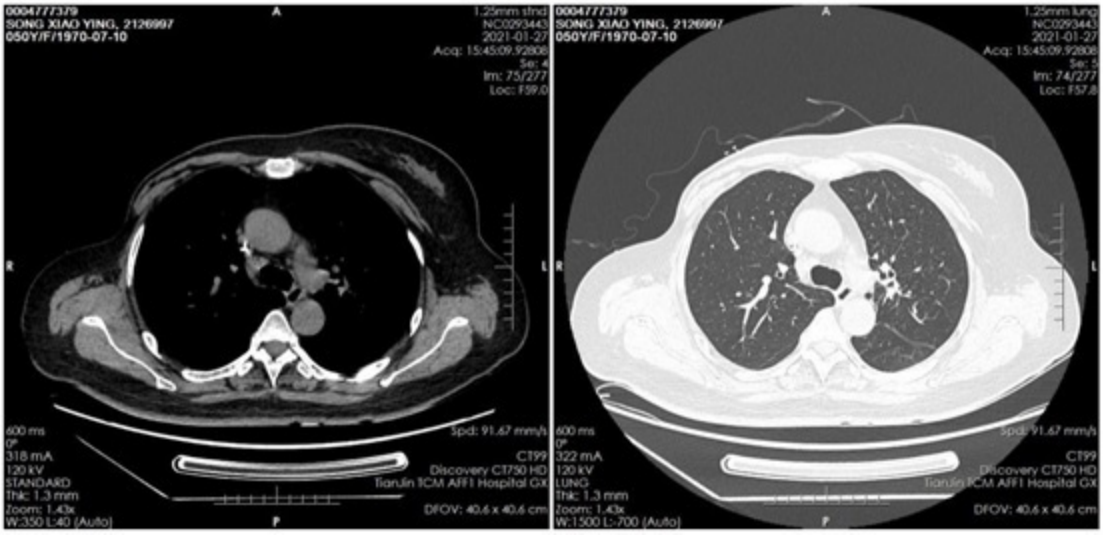


**Figure 2: A**. Chest computed tomography before six circle of salvage chemotherapy combined with target therapy (June 28, 2020), B: Chest computed tomography after six circle of salvage chemotherapy combined with target therapy (November 10, 2020).

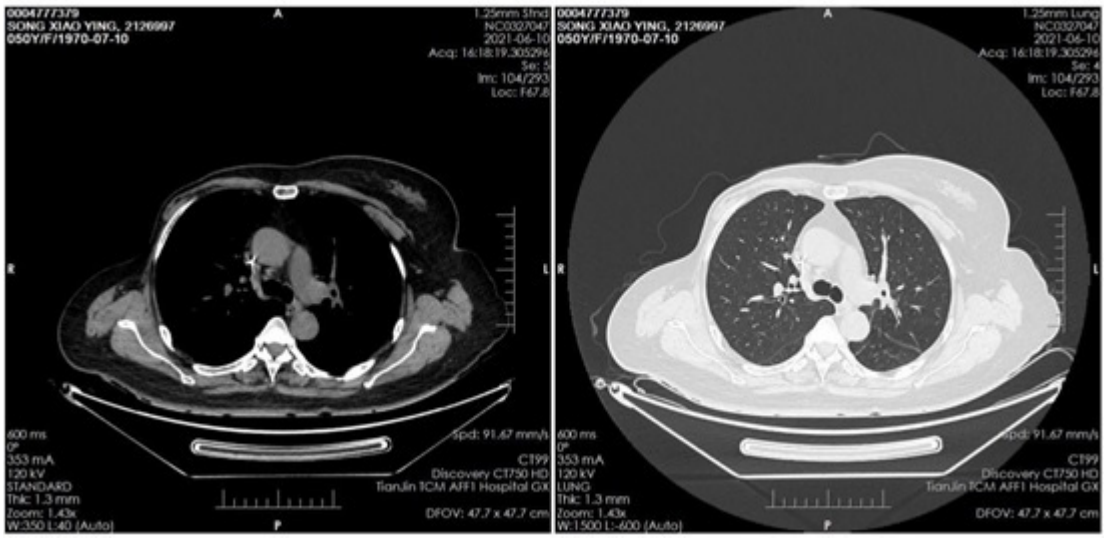


**Figure 3**: Chest computed tomography after eight circle of endocrine therapy combined with targettherapy (June 10, 2021).

**Table 1:** Change of Hematological Text.

| Date | 2020.06.29 | 2020.08.31 | 2020.10.27 | 2020.12.28 | 2021.02.20 | 2021.04.16 | 2021.06.09 |
|---|---|---|---|---|---|---|---|
| Leukocyte (3.5–9.5)$10^9$/L | 6.16 | 3.53 | 4.41 | 3.92 | 4.54 | 4.61 | 6.78 |
| Hemoglobin（115-150）g/L | 108 | 94 | 83 | 84 | 101 | 102 | 114 |
| Platelet(125–350)$10^{12}$/L | 307 | 150 | 99 | 134 | 158 | 197 | 283 |

## 4.1. Conclusion

The selection of potential combination drugs is the key to enhance the efficacy of PAPR inhibitors. the application range of PARP inhibitors will be wider, and more PARP inhibitor combination strategies will continue to emerge in the future. It is expected that this case can provide some help for application of PARP inhibitors. Moreover, it is also believed that the continuous maturity of genetic testing technology and the development of large-scale clinical trials may help to choose a reasonable combination therapy. Finally, it contributes to improve the prognosis of advanced breast cancer.

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