CANCER DIAGNOSIS & PROGNOSIS
3: 387-391 (2023) doi: 10.21873/cdp.10229

Successful Retreatment of Metastatic Triple-negative Breast Cancer With Immune Checkpoint Inhibitors and Chemotherapy

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Abstract. *Background/Aim: The efficacy of retreatment with immune checkpoint inhibitors (ICIs) in programmed death-ligand 1 (PD-L1) positive metastatic or recurrent triple-negative breast cancer (mTNBC) remains unknown. We report a case of a patient with recurrent triple-negative breast cancer who was successfully treated with two different ICIs in combination with chemotherapy. Case Report: A 60-year-old female patient was treated with neoadjuvant chemotherapy consisting of epirubicin + cyclophosphamide (EC) followed by docetaxel (DTX). The tumor shrank with EC, but progressed with DTX. One year after the surgery, the patient presented with multiple lung metastases. The patient received combination therapy with atezolizumab and nab-paclitaxel and achieved a partial response (PR). However, the disease progressed after 6 months. She received eribulin as second-line chemotherapy for 4.5 months, and her treatment was changed to pembrolizumab, carboplatin, and gemcitabine as third-line chemotherapy. The tumor immediately reduced and disappeared after three cycles of this treatment and achieved PR. Conclusion: This case illustrated that retreatment with ICIs was effective.*

Of the breast cancer subtypes, triple-negative breast cancer (TNBC) constitutes approximately 15-20% of all breast cancers and is associated with poor prognosis and earlier recurrence (1, 2). For these patients, chemotherapy is the only available treatment option, and there is an unmet medical need for more effective treatments. Recently, immune checkpoint inhibitors (ICIs) have changed treatment paradigms for several solid tumors (3), and become the standard of care. This has changed the outcome of programmed death-ligand 1 (PD-L1) positive metastatic triple-negative breast cancer (mTNBC).

Currently, for PD-L1-positive mTNBC atezolizumab and pembrolizumab have been approved in Japan. Atezolizumab, an anti-PD-L1 agent, was the first ICI to be combined with nab-paclitaxel (nab-PTX) for PD-L1-positive mTNBC. Pembrolizumab, an anti-PD-1 agent, was the second ICI to be combined with chemotherapy [nab-PTX, paclitaxel, or gemcitabine (GEM)/carbopratin (CBDCA)]. These therapies were evaluated in the first-line setting (4, 5).

Herein, we report a case of recurrent and metastatic TNBC in which the efficacy of two different ICIs in combination with chemotherapy was observed.

Case Report

In March 2019, a 60-year-old female patient underwent follow-up computed tomography (CT) after treatment for ovarian cancer, and a 16 mm diameter mass was noted in her left breast (Figure 1A). Axillary lymphadenopathy was not observed. Laboratory data revealed that carcinoma antigen 15-3 (CA15-3) and carcinoembryonic antigen (CEA) levels were both within normal limits. She underwent a needle biopsy of the breast mass and was diagnosed with invasive ductal carcinoma of nuclear grade 3, estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative (0 score) by immunohistochemistry (IHC) with more than 90% of cells positive for the Ki-67 index. CT did not reveal any distant metastasis. She was diagnosed with triple- negative breast cancer, and the clinical stage was T1cN0M0 Stage I, according to the Union for International

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Key Words: Triple-negative breast cancer, immune checkpoint inhibitor, retreatment.

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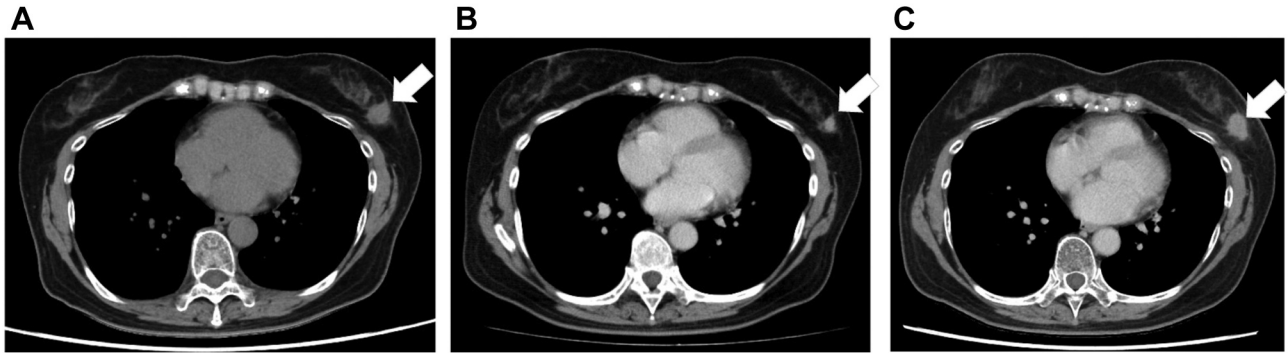

Figure 1. *Computed tomography imaging during neoadjuvant chemotherapy (NAC). A) Before treatment with NAC, a 16 mm mass in the left breast (white arrows) was identified. B) After treatment with epirubicin and cyclophosphamide, the tumor shrank (white arrows). C) After treatment with docetaxel, regrowth of tumor was observed (white arrows).*

Cancer Control (UICC) TNM Classification of Malignant Tumors (8th edition).

She was initially treated with neoadjuvant chemotherapy (NAC) of EC (epirubicin 90 mg/m^2 + cyclophosphamide 600 mg/m^2 every 3 weeks for 4 cycles), followed by docetaxel (DTX 75 mg/m^2 every 3 weeks for 4 cycles). The tumor reduced in size with EC therapy (Figure 1B) but progressed after DTX therapy (Figure 1C). She underwent a left mastectomy and sentinel node biopsy. Histology showed that the disease was pT2 (2.7 cm) and pN0. IHC demonstrated that the hormone receptor status was negative, HER2 was not over-expressed, and the Ki-67 index was 90%.

In November 2020, one year after surgery, she showed a recurrence of the tumor with multiple lung metastases, with the largest lesion measuring 45×38 mm (Figure 2A). Blood tests did not reveal elevated tumor marker levels. She also had a history of ovarian cancer, but BRCA1/2 gene mutation testing was negative. Because the PD-L1/SP142 assay was positive (immune cell expression >1%), she was treated with atezolizumab (840 mg/body every 2 weeks) + nab-PTX (100 mg/m^2 on days 1, 8, and 15 of 4 weeks) chemotherapy as a first-line treatment for mTNBC. The best response was a partial response (PR) (Figure 2B), and the disease progressed after 6 months (Figure 2C). During this treatment, she developed a grade 2 immune-related skin rash, which improved with internal and topical anti-allergic medications.

In June 2021, her treatment was changed to eribulin (1.4 mg/m^2 on days 1 and 8 of 3 weeks). The best response to eribulin was stable disease (SD). After 4.5 months, the indication for pembrolizumab was expanded to PD-L1 positive TNBC in Japan. She was confirmed to have a PD-L1/22C3 CPS ≥10%. In October 2021, her treatment was changed to pembrolizumab (200 mg/body every 3 weeks) + CBDCA (AUC 2 on days 1 and 8 of 3 weeks) + GEM (1,000 mg/m^2 on days 1 and 8 of 3 weeks) (Figure 3A). After three cycles of the treatment, CT scan revealed that the treatment efficacy was PR (Figure 3B). Immune-related adverse events were grade 2 skin rashes, similar to those caused by atezolizumab therapy, and tolerated well with the same supportive therapy as before. Because of grade 3 and 4 leucopenia and neutropenia, she received only day 1 treatment from 2 cycles of this treatment. At 11 cycles of this therapy, she developed a grade 2 allergic reaction to carboplatin, and carboplatin administration was discontinued. In November 2022, the tumors continued to reduce, and she was still undergoing combination immunotherapy (Figure 3C).

Discussion

In this case report, a female patient presented with triple-negative breast cancer and was treated with perioperative chemotherapy, but was resistant to docetaxel and relapsed relatively early. Fortunately, two types of ICI treatments in combination with chemotherapy were effective, with partial response and very few side effects.

Atezolizumab was the first ICI accepted as therapy for PD-L1 positive TNBC. The IMpassion 130 study was a randomized, double-blind, phase III trial of first-line atezolizumab in combination with nab-paclitaxel in patients with unresectable, locally advanced, or metastatic TNBC. The median progression-free survival (PFS) was 7.2 months with atezolizumab plus nab-paclitaxel arm *versus* 5.5 months with placebo plus nab-paclitaxel [hazard ratio (HR)=0.80; 95% confidence interval (CI)=0.69-0.92; p=0.002]. Among patients with PD-L1-positive tumors, the median PFS was 7.5 months *versus* 5.0 months (HR=0.62; 95%CI=0.49-0.78; p<0.001). The study met the PFS endpoint in the intent-to-treat and PD-L1-positive groups (4). The Ventana PD-L1 SP142 assay on tumor-infiltrating immune cells as a percentage of tumor area for IMpassion 130 was the companion diagnostic assay for atezolizumab.

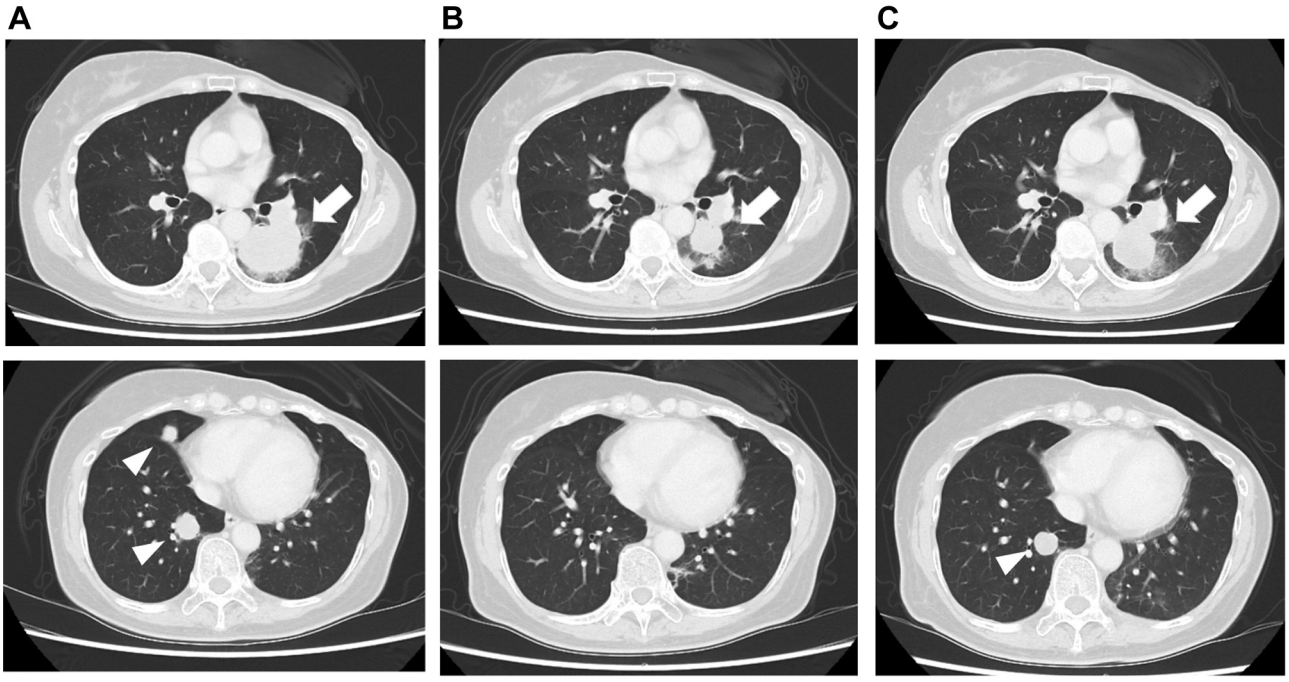

Figure 2. *Computed tomography imaging during treatment with atezolizumab and nab-paclitaxel. A) Before treatment, the presence of multiple lung metastases (white arrowheads) was observed and the largest lesion measured 45×38 mm in the left lung (white arrows). B) After 3 months of treatment, the tumor shrank (white arrows). C) After 6 months of treatment, tumor regrowth was observed (white arrows and arrowheads).*

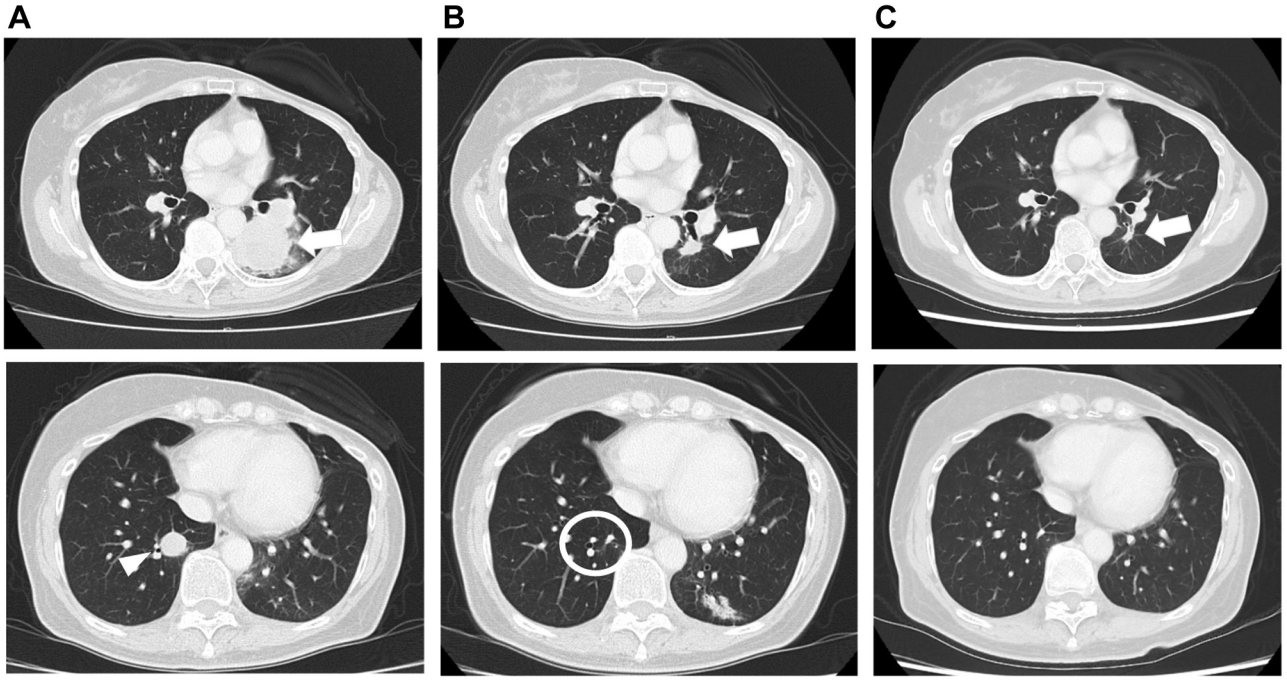

Figure 3. *Computed tomography imaging during treatment with pembrolizumab, carboplatin, and gemcitabine. A) Before treatment, multiple lung metastases were observed (white arrow and arrowhead). B) After 3 months of treatment, the tumor shrank (white arrow) and disappeared (white circle). C) After 12 months of treatment, the tumor continued to reduce (white arrows).*

Pembrolizumab was the second ICI accepted as a therapy for PD-L1 positive TNBC. A randomized, placebo-controlled, double-blind, phase III trial evaluated pembrolizumab in combination with chemotherapy (nab-paclitaxel, paclitaxel, or gemcitabine/carboplatin) for untreated locally recurrent inoperable or metastatic TNBC(KEYNOTE-335). The median PFS was 9.7 months in the pembrolizumab-chemotherapy group *versus* 5.6 months in the placebo-chemotherapy group (HR=0.65; 95%CI=0.49-0.86; p=0.0012) as first-line treatment of metastatic TNBC with a PD-L1 CPS of 10 or more (5). The median overall survival was 23.0 months in the pembrolizumab-chemotherapy group *versus* 16.1 months in the placebo-chemotherapy group (HR=0.73; 95%CI=0.55-0.95; p=0.0185) in the CPS-10 subgroup (6). The CPS via the Dako PD-L1 22C3 assay was the companion assay for pembrolizumab.

Over the last decade, ICIs have dramatically changed the systemic treatment of metastatic and recurrent solid tumors (3). The efficacy and safety of rechallenge treatment with ICI are still not well known. Several studies have already reported their efficacy for advanced melanoma (7-9), and some retrospective studies have reported the rechallenge efficacy for advanced non-small cell lung cancer (10, 11). However, predictors of efficacy in cases that respond to retreatment are not well understood. In breast cancer, only a few case reports have been published (12, 13).

In our case, both the PD-L1/SP142 and PD-L1/22C3 assays were positive for the companion diagnosis. Rugo et al. reported that these assays were not analytically equivalent at the assessed cutoffs (14); therefore both assays should be performed. In breast cancer, ICIs are not as effective as single agents (15, 16) and their therapeutic effects are enhanced when combined with anticancer agents. Therefore, combination of ICIs with a different anticancer drug has a greater therapeutic effect.

Eribulin mesylate (eribulin) is an analog of halichondrin B that inhibits microtubule extension (17). In a pooled analysis from the EMBRACE and Study 301 phase III trials, eribulin improved the median overall survival *versus* capecitabine or treatment of physician's choice (HR=0.74; p=0.006) in several patient subgroups with metastatic breast cancer (18). In preclinical studies, eribulin reversed epithelial-to-mesenchymal transition and promoted vascular remodeling in tumors (17, 19, 20). In addition, eribulin also affected the tumor microenvironment and expression of immune-related biomarkers in breast cancer (21). In the phase 1b ENHANCE-1 study, the combination of eribulin with the immune checkpoint inhibitor, pembrolizumab, was evaluated for safety and efficacy in patients with mTNBC. The activity was most enhanced in patients with PD-L1 positive TNBC (22). In our case, eribulin was administered before the second immune checkpoint inhibitor, which may have enhanced the therapeutic effect of ICI treatment in combination with chemotherapy.

Conclusion

TNBC has a poor prognosis and is expected to benefit from treatment with ICIs. However, other than PD-L1 positivity, factors that predict efficacy have not been identified. The accumulation of cases may help to predict the effect of ICIs in combination with chemotherapy.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

Authors' Contributions

All Authors (1) made substantial contributions to the study concept or the data analysis or interpretation; (2) drafted the manuscript or revised it critically for important intellectual content; (3) approved the final version of the manuscript to be published; and (4) agreed to be accountable for all aspects of the work.

Acknowledgements

The Authors would like to thank Editage (www.editage.com) for English language editing.

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Received February 23, 2023
Revised March 6, 2023
Accepted March 7, 2023