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Case Report
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Dramatic Response to Platinum-Based Chemotherapy in a Germline PALB2 Variant Breast Cancer: A Case Report

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Abstract

Introduction: The Partner and Localizer of *BRCA2* (PALB2) is a DNA repair and tumor suppressor protein that acts by stabilizing *BRCA2*, thereby mediating DNA repair and suppressing gene instability. Mono-allelic germline mutations of *PALB2* have been reported as risk factors for breast cancer; however, their therapeutic significance is not well-known.

Case Report: We report a dramatic response to carboplatin/gemcitabine in the ninth treatment round of a patient with hormone receptor-positive advanced breast cancer with a germline *PALB2* variant. A 43-year-old woman had recurrent hormone receptor-positive metastatic breast cancer that had progressed despite hormonal therapy and chemotherapy and was hard to remove in the hospital due to the presence of liver metastasis, ascites, and lower-limb edema. Genetic analyses *via* next-generation sequencing and polymerase chain reaction identified a germline sequence variant in *PALB2* (c.1451delT, (p.Leu485fs1)). Carboplatin/gemcitabine was selected as the ninth treatment regimen, which significantly improved her symptoms and she left the hospital and began driving to the hospital by herself thereafter.

Conclusion: Our case suggests the clinical significance of germline *PALB2* variants in breast cancer as biomarkers of sensitivity to platinum-based chemotherapy.

Keywords: Advanced breast cancer, FoundationOne, *PALB2*, carboplatin

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Introduction

Gene instability is often used in drug discovery for cancer treatment. In breast cancer, a defect in Homologous Recombination (HR) caused by germline *BRCA1* and *BRCA2* (*gBRCA1/2*) variants is used in this context. Poly ADP-Ribose Polymerase (PARP) repairs DNA Single-Stranded Breaks (SSBs) by binding to DNA at the sites of SSBs and recruiting repair machinery [1]. Once PARP is inhibited, SSBs are repaired *via* HR by BRCA, and other mechanisms have been identified in breast cancer [2-5]. PARP inhibition in patients with *gBRCA1/2* variants creates DNA Double-Stranded Breaks (DSBs), and a PARP inhibitor (Olaparib) yielded a significantly better prognosis for Human Epidermal Growth Factor Receptor 2 (HER2)- negative breast cancer in germline *gBRCA1/2* variant carriers in randomized phase 3 trials [6,7].

The Partner and Localizer of BRCA2 (PALB2), which was identified as a BRCA2-interacting partner, has emerged as a tumor suppressor protein that modulates BRCA1/2 in DNA repair [8]. In patients with breast cancer, the *PALB2* predicted promoter region was mostly hypermethylated among those with hereditary breast cancer [9], and germline pathogenic variants were detected in 0.4% (28/7051) of Japanese patients [10]. However, the clinical significance of PALB2 in breast cancer treatment remains unknown.

Platinum-based chemotherapy has been approved for treating Advanced Breast Cancer (ABC). Although carboplatin and cisplatin are major therapeutic agents in breast cancer, strong clinical evidence of their benefits compared with anthracycline or taxane does not exist. Recently, platinum-based chemotherapy has been suggested to offer responsiveness to treatment in patients with triple-

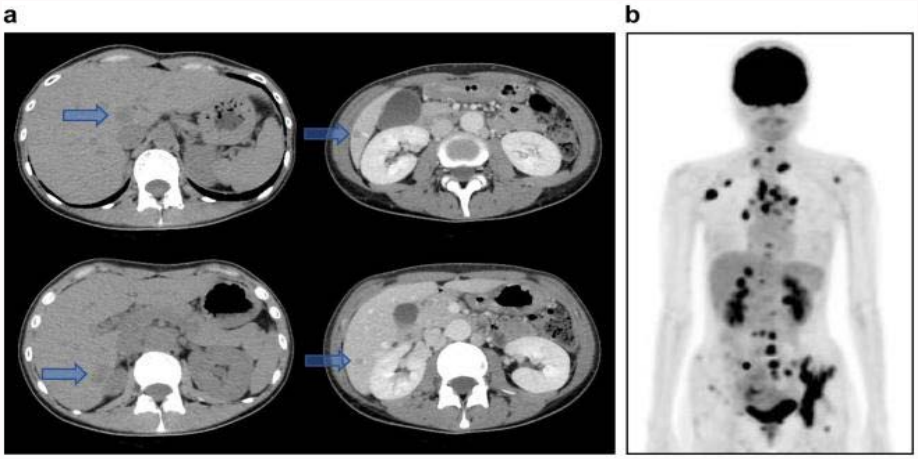

Figure 1: Computed tomography (CT) image showing multiple liver metastases (arrow, a); Fluoro-D-Glucose Positron Emission Tomography (FDG-PET)/CT showing multiple lymph nodes and bone metastasis (b).

negative breast cancer with the *BRCA1/2* mutation [11]. Therefore, platinum is preferred for managing triple-negative breast cancer with the *BRCA1/2* mutation in the National Comprehensive Cancer Network® guidelines.

Generally, the response rate after the fourth treatment is ≤ 20%; thus, some physicians recommend palliative care in these cases. We present the case of a patient with hormone receptor-positive ABC without the *BRCA1/2* variant but with a germline variant in *PALB2* who exhibited a dramatic response to carboplatin/gemcitabine after the ninth treatment.

Case Presentation

In March 2014, a 34-year-old woman was diagnosed with invasive cancer of the right breast. She underwent a lumpectomy and axillary lymph node dissection. Pathological findings were an invasive tumor with a size of 1.6 cm (pT1c), a positive Node (pN1a), Estrogen Receptor (ER)-positive status (Allred score, 8), Progesterone Receptor (PgR)-positive status (Allred score, 6), Human Epidermal Growth Factor Receptor 2 (HER2) -negative status (IHC 0), Fluorescence *in situ* Hybridization (FISH) of 2.05, Ki-67 index of 20%, and surgical margin-positive findings (DCIS). Adjuvant tamoxifen and an LH-RH agonist were administered and radiation therapy (whole breast with a boost to the tumor bed) was performed. In September 2017, distant liver, bone, and lymph node metastases were detected *via* Computed Tomography (CT) and Fluoro-D-Glucose Positron Emission Computed Tomography (FDG-PET)/CT (Figure 1); therefore, treatment for the ABC was initiated. Tamoxifen was changed to fulvestrant, and the patient responded to this treatment for nine months. Subsequently, letrozole/palbociclib for four months, high-dose toremifene for one month, and S-1 for six months were used until disease progression. A repeat biopsy was performed on an iliac bone with metastases to assess drug sensitivity, and the results were ER-positive, PgR-negative, HER2 1+, and FISH 2.3. According to these results, anti-HER2 therapy was expected to provide a response. Capecitabine/lapatinib for four months, docetaxel for six months, trastuzumab emtansine for two months, everolimus/exemestane for four months, and trastuzumab deruxtecan for four months were used. After eight therapies, the tumor occupied more than 50% of the liver and ascites increased, and the patient was hospitalized because of deterioration of her physical state (with lower-limb edema). A cfDNA-based comprehensive genomic profiling assay, FoundationOne® Liquid (Foundation Medicine, Inc, USA), was performed, and carboplatin (area under the curve of 2 on days 1 and 8) and gemcitabine (1000 mg/m^2 on days 1 and 8) were administered at a dose of 80%. The CEA and CA15-3 tumor marker levels decreased from 282 ng/ml to 108 mg/ml and from 810 U/ml to 278 U/ml, respectively, after four cycles, and abdominal bloating and lower-limb edema reduced dramatically. Surprisingly, the CT scan revealed that the liver tumor shrank to approximately 20% of its size observed before carboplatin and gemcitabine treatment, and ascites decreased (Figure 2). The genomic profiling assay revealed 11 genomic variants with a valiant allele frequency of 0.19% to 78.4% (Table 1). A high frequency of *PALB2* suggested the germline variant, and we confirmed heterozygous c.1452delT (p.Leu484fs6) as a likely pathogenic variant using mutation-specific sequencing VistaSeq℠ (LabCorp, Inc, USA). The patient's lower-limb edema completely disappeared, and she recovered enough to drive to the hospital by herself. The patient responded to gemcitabine/carboplatin for a total of eight cycles (6 months) until the liver metastases were observed to progress on CT scans. Subsequently, we expected a response to

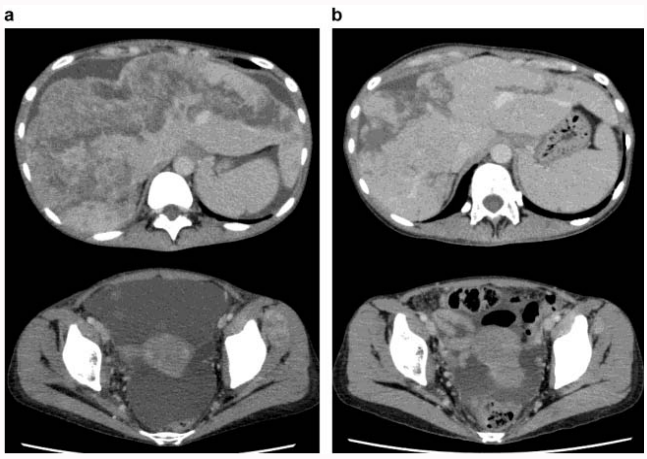

Figure 2: (a) Computed Tomography (CT) before carboplatin/gemcitabine treatment. Approximately 60% of the liver was occupied by cancer, and ascites appeared around the liver and pelvis. (b) CT after four cycles of carboplatin/gemcitabine. The tumor had shrunk and ascites had significantly decreased.

Table 1: Detected variants on FoundationOne Liquid CDx.

Gene	Variant	VAF (%)
ESR1	L536R	0.38
	V422del	0.66
	L536H	0.19
	L536P	0.75
	D538G	35.2
	Y537S	0.44
PALB2	L484fs*1	78.4
FGFR2	HTRA1-FGFR2 noncanonical fusion	0.15
PTEN	Q110*	34.2
SMAD4	T192fs*15	3.4
TP53	R280T	0.67

FoundationOne Liquid CDx revealed 11 variants and VAF in six genes. Six variants were found in *ESR1*, and a high frequency of VAF was found in *PALB2*. VAF: Variant Allele Frequency

Olaparib, a PARP inhibitor; however, it did not show the effect after three months of use. Epirubicin/cyclophosphamide was administered for two months; however, unfortunately, the patient died at our hospital.

Discussion

The PALB2 protein is encoded by the *PALB2* gene located on chromosome 16p12.2 [12]. *PALB2*, which binds to BRCA2, is involved in the repair of DSBs *via* HR [13-16]. Mono-allelic germline variants of *BRCA2* and *PALB2* predispose their carriers to breast cancer, and *PALB2* germline variants increase the breast cancer risk by a factor of 9.47 [17]. Momozawa et al. reported that *PALB2* germline pathogenic variants were detected in 0.4% (28/7051) of breast cancer patients [10]. The gene instability associated with *BRCA* pathogenic variants has been used for ABC treatment. The PARP inhibitor, Olaparib, was designed to exploit synthetic lethality. PARP binds to damaged DNA at SSBs and repairs the DNA [18,19]. Once the DNA repair of SSBs is inhibited by the PARP inhibitor, tumor cells convert to HR. However, BRCA pathogenic variant cells are deficient in the function of HR; therefore, cell death is induced by synthetic lethality [20]. As stated above, *BRCA* and *PALB* are close in the mechanism of cell stability; thus, they were expected to be targets in cancer treatment. The randomized phase III OlympiAD trial has confirmed that Olaparib significantly prolongs Progression-Free Survival (PFS) by approximately three months in patients with breast cancer carrying germline pathogenic *BRCA* variants [21]. Tung et al. reported Olaparib sensitivity in patients with germline *PLB2*-variant ABC (ORR: 82%; median PFS: 13.3 months) in a phase II study [22]. These studies suggest that germline *BRCA* and *PLB2* variants contribute to similar mechanisms of sensitivity to breast cancer treatment. In patients with ovarian cancer, the randomized phase III SOLO1 trial has shown clinical benefits regarding PFS in those with germline pathogenic variants. Interestingly, the patient who exhibited a response after platinum-based chemotherapy responded to Olaparib. This trial suggested that platinum sensitivity is related to sensitivity to Olaparib. Poggio et al. reported that platinum-based neoadjuvant chemotherapy significantly increased the pCR rate in patients with triple-negative breast cancer [23]. However, a subgroup analysis of patients carrying *BRCA* variants did not show a significant difference. The significance of germline variants in breast cancer has been revealed gradually; e.g., relationships such as "*BRCA* and *PALB2*" and "Olaparib and platinum-based chemotherapy." However, the role of *PALB2* pathogenic variants as biomarkers of breast cancer is not fully understood. Recently, comprehensive genomic profiling assaying has become widely used in clinical settings. However, most genomic variants identified in that assay do not impact sensitivity to approved drugs or have evidence for breast cancer treatment. The *PALB2* c.1451delT variant has been identified as a likely pathogenic variant according to the ClinVar database (https://www.ncbi.nlm.nih.gov/clinvar/); however, there is no evidence of an increased drug response among its carriers.

Generally, it is known that drug sensitivity drops to less than 20% after resistance to three kinds of chemotherapy. In addition, platinum-based chemotherapy does not have significant evidence *via* some clinical studies; so, the NCCN guideline is preferred only for triple-negative (hormone receptor-negative and HER2-negative) and germline *BRCA1/2* mutation breast cancer. In this case, to get a significant response though hormone receptor-positive and 9th regimen was very rare case and it might suggest new findings of germline *PALB2* variant as a biomarker of platinum-based chemotherapy sensitivity and adds new significance regarding the performance of genomic profiling assays in ABC.

In addition, we anticipated a response to Olaparib because a phase II study suggested a response in a patient with ABC who had the *PALB2* variant; however, our patient was unable to obtain any clinical benefit [22]. Most patients in the phase II study were administered one regimen of Olaparib after chemotherapy. Therefore, we assumed that it might have used Olaparib a little too late. This case also suggests that a gene profiling assay and Olaparib therapy need to be performed early enough when the tumor cells are not yet multidrug-resistant and the tumor is smaller.

Conclusion

The therapeutic significance of genomic variants in cancer cells has been revealed gradually. In breast cancer, germline BRCA pathogenic variants alone can affect clinical outcomes. However, genomic profiling assaying has been used widely in many types of cancers, several of which do not have sufficient evidence for selecting drugs. In conclusion, a dramatic response to the ninth treatment course, as in the present case, is rare; therefore, the germline *PALB2* variant may be a sensitive biomarker of platinum-based chemotherapy in breast cancer. To establish the hypothesis, the accumulation of genomic data *via* genomic profiling assays and real-world data in response to platinum-based chemotherapy are needed.

Author Contributions

Ishida treated the patient in the reported case and wrote this manuscript. Komatsu, Amano, Kiyokawa, Usami, and Ohnuki treated the reported case in different phases during the breast cancer treatment. Iwaya explained the FoundationOne Liquid assay to the patient and obtained her informed consent. Obata provided counseling for hereditary breast-ovarian cancer. Fukushima explained the mutation-specific sequencing assay to the patient and obtained her informed consent. Iwaya and Fukushima assessed the results of gene assays with the cancer genomic board.

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