

## Case Report

# Response of Estrogen-Receptor-Positive Metastatic Breast Cancer to Olaparib in Late-Line Therapy

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## Keywords

Olaparib · Breast cancer · BRCA · Late line

## Abstract

Monotherapy with olaparib provides significant benefits over standard therapy in patients with a germline BRCA mutation and human epidermal growth factor receptor 2 (HER2) negative metastatic breast cancer, who had two or fewer previous chemotherapeutic regimens for metastatic disease. Olaparib was approved on July 2, 2018, in Japan for the treatment of patients with metastatic breast cancer with a BRCA mutation and HER2-negative status. Thus, the current experience with this drug is relatively limited. In this article, we report a case of luminal-type metastatic breast cancer harboring a BRCA1 mutation detected through BRACAnalysis (Myriad Genetics). Despite the late-line treatment, in this patient, olaparib was effective against metastatic breast cancer.

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## Introduction

BRCA1 and BRCA2 genes are critically involved in leading high-fidelity repair by homologous recombination (HR) [1, 2]. In tumors with HR deficiency (e.g., harboring BRCA1 and BRCA2 mutations), compensatory mechanisms for DNA damage repair are a failure. Unre-

paired DNA damage ultimately accumulates and causes cell death, a concept termed synthetic lethality [2]. Inhibition of poly(ADP-ribose) polymerase has shown marked benefits against breast cancer with HR deficiency driven by defects in BRCA1, BRCA2, or other components of this pathway [3, 4].

Among patients with human epidermal growth factor receptor 2 (HER2) negative metastatic breast cancer and a germline BRCA1 and/or BRCA2 mutation, olaparib improved progression-free survival compared with the treating physician's preferred chemotherapy regimen [5]. Subgroup analyzes showed the possibility of a clinically meaningful overall survival benefit offered by olaparib in patients who had not received previous chemotherapy for metastatic disease [6].

Following the approval of this oral poly(ADP-ribose) polymerase inhibitor on July 2, 2018, in Japan, physicians have had the opportunity to prescribe olaparib. However, experience with the use of olaparib is still relatively limited, data regarding the administration of olaparib in late-line therapy is scarce, and the number of case reports is still currently small.

### Case Report

A 53-year-old woman was diagnosed with right breast cancer (i.e., stage IIB [T2N1M0]). Immunohistochemistry performed on the primary breast cancer confirmed HER2 1+, positive estrogen receptor 30%, and positive progesterone receptor 20%. The patient was treated with neoadjuvant chemotherapy (i.e., four cycles of doxorubicin and cyclophosphamide every three weeks followed by 12 cycles of weekly paclitaxel). Subsequently, a breast-conserving surgery and axillary dissection were performed. The remnant of invasive cancer in the breast specimen was 3 mm in diameter, and there was no residual cancer in the lymph nodes. Standard radiation therapy after the breast-conserving surgery was performed, and anastrozole was administered as adjuvant endocrine therapy for five years.

At the age of 61 (postoperative year 8), locoregional recurrence was detected. This recurrence was removed through a surgical operation. Immunohistochemistry performed on the recurrence confirmed HER2 1+, positive estrogen receptor 60%, positive progesterone receptor 60%, and Ki67 70%. Subsequently, the patient received 5-FU, epirubicin, and cyclophosphamide for three months; paclitaxel for three months; letrozole for three years; fulvestrant for one month; palbociclib and fulvestrant for three months; palbociclib and letrozole for one month; and capecitabine for three months, in this order. When clinical assessment with capecitabine led to the diagnosis of disease progression, the 66-year-old patient had multiple liver metastases, multiple mediastinal lymph metastases, and pleural dissemination.

Capecitabine was administered as seventh-line therapy. BRCAAnalysis (Myriad Genetics) detected a BRCA1 mutation (1135insA); hence, olaparib was administered as eighth-line treatment. Genetic counseling revealed that the patient's father had prostate cancer, one of the BRCA-associated cancers.

Despite the late-line treatment, six months after the administration of olaparib, the size of almost all metastatic sites was markedly reduced, resulting in a partial response (Fig. 1). The levels of the tumor markers carcinoembryonic antigen and CA15–3 were gradually increased throughout 12 months prior to the administration of olaparib, reached their peak at the time of administration, and rapidly declined after the administration of olaparib (Fig. 2). A major adverse event was grade 3 anemia detected five months after treatment, and the dose of olaparib was reduced according to the severity of the anemia (Fig. 3). Other adverse events observed were grade 1 fatigue and nausea.

## Discussion

In the US, 5–10% of breast cancer cases are thought to be hereditary. Most inherited cases of breast cancer are associated with two susceptibility genes (i.e., BRCA1 and BRCA2) [7–10]. In Japan, genetic testing revealed that 17.7 and 13.3% of proband cases harbored BRCA1 and BRCA2 mutations, respectively. Additionally, the percentage of triple-negative disease among patients with BRCA1 mutations was 62.2%, whereas the percentage of the luminal type among those with BRCA2 mutations reached 82.9%. These findings suggested that breast cancer occurring in carriers of BRCA1 mutations is more likely to be triple-negative. On the other hand, 29.7% of the patients with BRCA1 mutations had luminal-type breast cancer [11]. In the present case, our patient had luminal-type breast cancer with a germline BRCA1 mutation.

The OlympiAD trial involved 302 patients with metastatic breast cancer and a BRCA mutation, who had received an anthracycline and a taxane in either an adjuvant or a metastatic setting and no more than two previous chemotherapy regimens for metastatic disease. Those randomly assigned to receive treatment with olaparib experienced improved progression-free survival relative to those who received standard therapy with the treating physician's preferred single-agent chemotherapy [5]. Our patient received an anthracycline and a taxane in the neoadjuvant setting and as front-line therapy for metastatic disease. In the US, olaparib was approved by the Food and Drug Administration for the treatment of germline BRCA-mutated breast cancer on January 12, 2018. In Japan, olaparib was approved while our patient was receiving seventh-line therapy with capecitabine. She had the chance to receive this new anticancer agent as eighth-line therapy after disease progression. Her response to olaparib was drastic, with a significant improvement observed in liver and lymph node metastases. Additionally, soon after the administration of olaparib, the levels of the tumor markers carcinoembryonic antigen and CA15–3 decreased. The present case suggests that olaparib should be considered even as late-line therapy in patients harboring a germline BRCA mutation.

In the OlympiAD study, anemia was cited as the most frequent reason for dose reduction in patients receiving olaparib; the reported frequency of anemia was 40%, and dose reduction was necessitated in 13.7% of the patients [5]. Our patient experienced anemia (up to grade 3), which was alleviated through dose reduction.

Prior to the approval of olaparib in Japan, clinicians were hesitant to suggest BRCA1/2 testing for patients with breast cancer, even in the presence of a strong family history. Clinicians would offer a standard therapy, which was often a nontargeted therapy, and recommend the screening of family members or relatives on the basis of a guideline even if the patient harbored a germline BRCA mutation. Following the approval of olaparib, clinicians can provide targeted therapy to patients with metastatic disease; thus, they are less hesitant to suggest BRCA1/2 testing. The availability of olaparib declined the threshold in handling BRCA-related breast cancer and/or ovarian cancer syndrome.

In conclusion, our patient did not have a strong family history of BRCA-associated cancer, and her breast cancer subtype was not triple-negative. However, genetic testing revealed the presence of a BRCA1 mutation. Although olaparib was used as front-line treatment in the OlympiAD study, in the present case, this agent was associated with good response even as late-line therapy.

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### Statement of Ethics

Informed consent was provided by the patient.

### Disclosure Statement

The authors have no conflicts of interest to declare.

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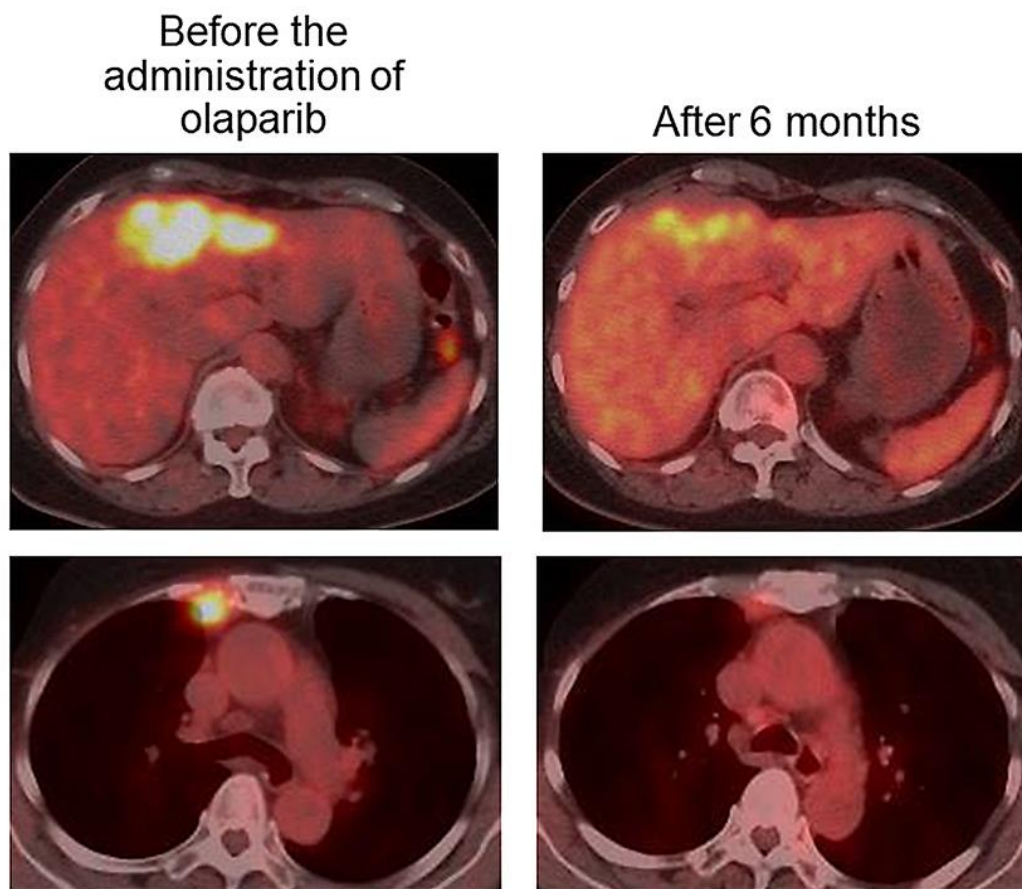
### Author Contributions

R. Matsunuma and T. Kumeda wrote the main manuscript. All authors critically reviewed the manuscript for important intellectual content.

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**Fig. 1.** PET-CT showing that the standardized uptake value in liver and mediastinal lymph metastases decreased six months after treatment with olaparib.

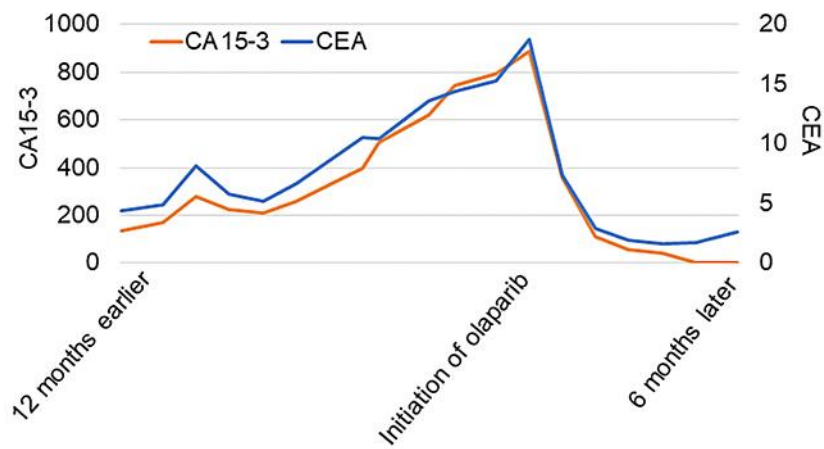


Fig. 2. Levels of CA15-3 and CEA before and after the administration of olaparib.

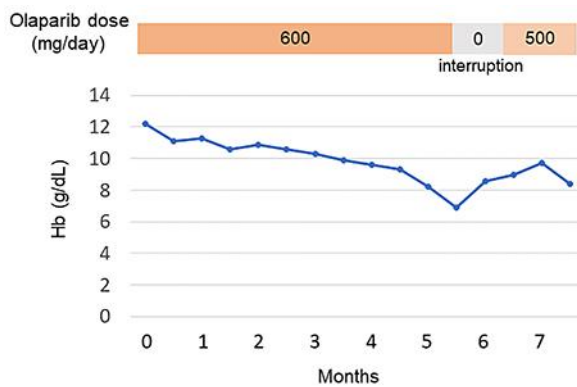


Fig. 3. Level of Hb after the administration of olaparib and olaparib dose.