Case Reports in Oncology

Case Rep Oncol 2024;17:773–778
DOI: 10.1159/000540257
Received: March 26, 2024
Accepted: July 1, 2024
Published online: July 19, 2024

Case Report

Case Report of Complete Response to Olaparib in a Patient with Breast Cancer Brain Metastases

Kazuki Asazuma[a] Akihiko Shimomura[a, b] Yukino Kawamura[a, b]
Tomoko Taniyama[a] Chikako Shimizu[a]

[a]Department of Breast and Medical Oncology, National Center for Global Health and Medicine, Tokyo, Japan; [b]Course of Advanced and Specialized Medicine, Juntendo University Graduate School of Medicine, Tokyo, Japan

Keywords
Breast cancer · Brain metastases · Germline *BRCA1/2* mutation · Olaparib · Complete response

Abstract
Introduction: Breast cancer is the second most common cause of central nervous system (CNS) metastases. It has been shown that the median time from breast cancer diagnosis to CNS metastasis is 30.9 months and that the overall median survival after metastasis is extremely poor at 6.8 months. Although treatment options for ErbB2 Receptor Tyrosine Kinase 2 (ERBB2)-positive breast cancer brain metastasis (BCBM) have been reported, effective treatment options for ERBB2-negative BCBM, which has one of the worst prognoses, are limited. Olaparib is one of the standard treatments for germline *BRCA1/2* mutated (g*BRCA1/2*mt), ERBB2-negative, metastatic, or recurrent breast cancer. However, there is minimal existing evidence to evaluate the efficacy of olaparib in BCBM. ***Case Presentation:*** In our report, we assessed the case of a Japanese woman in her early 30s, ERBB2-negative, gBRAC2mt-positive BCBM, who achieved a complete response and prolonged progression-free survival of 9 months after the initiation of treatment with olaparib. ***Conclusions:*** Thus, our case report demonstrated the significant efficacy of olaparib in BCBM treatment. Furthermore, we highlighted the need for more studies to investigate the efficacy of olaparib and explore the efficacy of poly ADP ribose polymerase inhibitors in BCBM.

Correspondence to:
Akihiko Shimomura, akshimomura@hosp.ncgm.go.jp

Case Rep Oncol 2024;17:773–778
DOI: 10.1159/000540257

Introduction

Breast cancer is the second leading cause of central nervous system (CNS) metastases. Altundag et al. [1] reported that the median time from breast cancer diagnosis to CNS metastasis is 30.9 months, and the median survival time after metastasis is extremely low at 6.8 months. For ErbB2 Receptor Tyrosine Kinase 2 (ERBB2)-positive breast cancer brain metastases (BCBM), the efficacy of tucatinib in combination with trastuzumab and capecitabine [2], as well as lapatinib combined with capecitabine [3], has been reported; however, effective treatment options for ERBB2-negative BCBM are limited. Olaparib is one of the standard treatments in germline *BRCA1/2* mutated (g*BRCA1/2*mt), ERBB2-negative, metastatic, or recurrent breast cancer; however, there is minimal existing evidence evaluating the efficacy of olaparib in BCBM [4]. Our report examined the case of olaparib-treated BCBM with complete response (CR) and prolonged progression-free survival (PFS) of 9 months.

Case Report

We evaluated the case of a Japanese premenopausal woman in her early 30s, diagnosed with stage IV breast cancer (cT4bN3M1) in December 2018. The tumor was estrogen receptor-positive, progesterone receptor-positive, and ERBB2-negative, with a Ki-67 index of 42.9%. Computed tomography (CT) revealed multiple lymph nodes (left axillary and parasternal lymph nodes), liver, and bone metastases (Th7 vertebrae, Th11 vertebral arch, and sacrum).

As the first-line chemotherapy, the patient received nine courses of treatment with FEC every 3 weeks, which included 5-fluorouracil (5-FU; 500 mg/m^2), epirubicin (100 mg/m^2), and cyclophosphamide (500 mg/m^2), taking into consideration the equivalence of the cardiotoxic limit of epirubicin at 900 mg/m^2. The best response from FEC was the partial response. As the second-line therapy, paclitaxel (80 mg/m^2) was administered cyclically on a weekly basis for three consecutive weeks with 1 week off. However, the patient discontinued the 14th course due to chemotherapy-induced peripheral neuropathy. The best response from paclitaxel was the stable disease.

After the first-line hormonal therapy was administered for 13 months, which included tamoxifen (20 mg) every morning and leuprorelin (11.25 mg) every 12 weeks, liver metastases progressed. Subsequently, treatment was changed to a regimen of fulvestrant (500 mg) every 4 weeks, abemaciclib (150 mg) twice a day, and leuprorelin (11.25 mg) every 12 weeks as the second-line therapy.

In December 2022, after 14 months of treatment with fulvestrant, abemaciclib, and leuprorelin, the patient was brought to the emergency department with impaired consciousness. The patient was diagnosed with BCBM after a head CT scan and subsequent magnetic resonance imaging (MRI) scan of the whole brain, which revealed a contrast effect along the cerebral sulcus in combination with the clinical symptoms. After whole-brain irradiation (30 Gy/10 fraction) for BCBM, capecitabine (825 mg/m^2), which was administered twice daily for three consecutive weeks with 1 week off, was introduced cyclically as a systemic treatment.

The patient developed disseminated herpes zoster 3 months after the introduction of capecitabine, and treatment was interrupted. One month after the interruption, the patient had an absence seizure and a whole-brain MRI was performed. The scans were indicative of BM exacerbation (Fig. 1a) and the progression of liver metastases (Fig. 1b). However, no recurrence of the primary lesion was observed (Fig. 1c).

Case Rep Oncol 2024;17:773–778
DOI: 10.1159/000540257

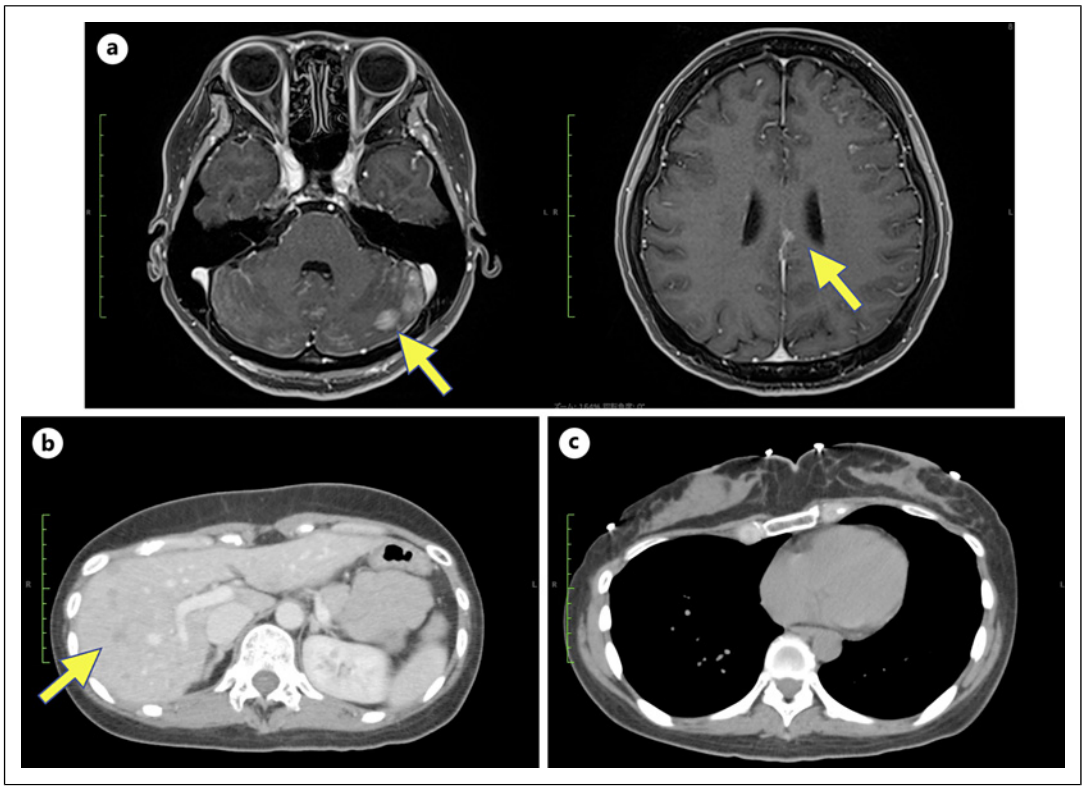

Fig. 1. a Multiple small and large enhancing lesions along the sulci and surfaces of the cerebellar hemispheres are observed. In addition, enhancing nodules in the cerebral sickle cells are noted. **b** Multiple progressively increasing and enlarging metastases in both lobes of the liver are observed. **c** No contrast nodules and no recurrence within the left breast are observed.

To determine whether there was an indication for olaparib, *BRCA* genetic testing was performed. As a result of the positive *gBRAC2mt* (c.9117G>A), treatment with olaparib (300 mg) twice daily was initiated in May 2021. A whole-brain MRI conducted 3 months after the initiation of olaparib revealed a reduction in BM, and 5 months after the initiation of olaparib, a whole-brain MRI revealed a CR of BM to olaparib. However, 9 months after the initiation of treatment with olaparib, liver metastases progressed, and olaparib was replaced by eribulin, although a whole-brain MRI still revealed a CR of BM to olaparib (Fig. 2). The patient died 15 months after the initiation of olaparib.

Discussion

This report analyzed the case of a premenopausal female patient in her early 30s, diagnosed with a g*BRCA2*mt and ERBB2-negative BCBM, treated with olaparib, and achieved a CR. Although the BCBM remained as a CR, the PFS was prolonged by only 9 months due to the progression of liver metastases. Prior to olaparib, the patient received a regimen that included antimetabolites, topoisomerase inhibitors, alkylating agents, microtubule inhibitors, hormonal agents, and a CDK4/6 inhibitor. Additionally, the patient underwent whole-brain irradiation. Gliosis/radiation necrosis was considered in the differential diagnosis; however, the patient not only exhibited changes in brain lesions but also showed progression of liver metastases. Given the response to systemic olaparib treatment, we clinically diagnosed the changes in the brain lesions as exacerbation of brain BM.

Case Rep Oncol 2024;17:773–778
DOI: 10.1159/000540257

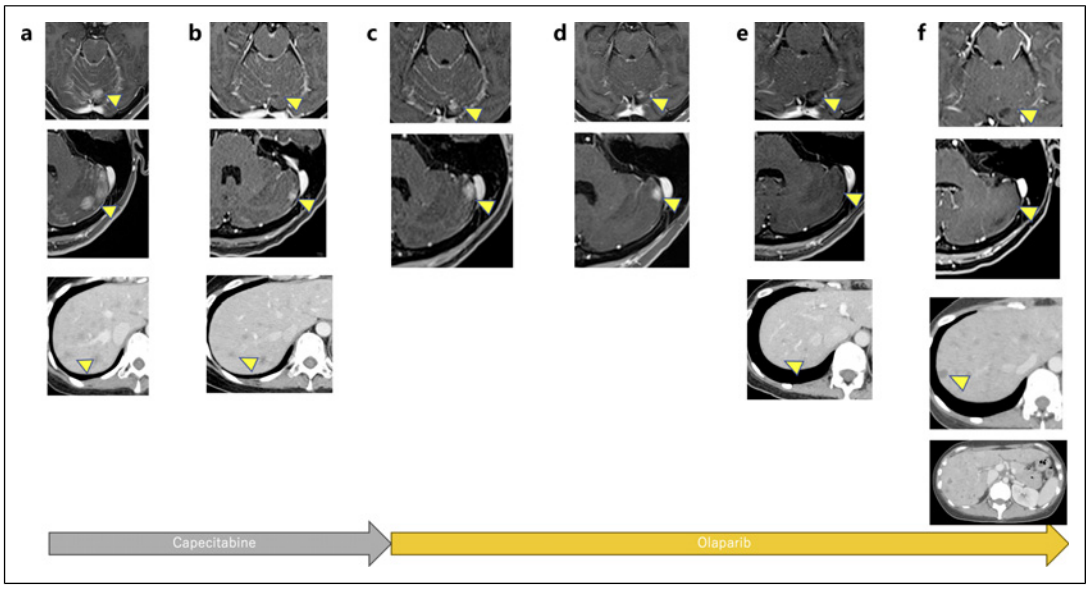

Fig. 2. Course of treatment. **a** Emergency visit for impaired consciousness and received WBRT. **b** BCBM and liver metastases achieved PR with capecitabine treatment. **c** Emergency visit for absence seizures and olaparib initiated. **d** BCBM achieved PR, (**e**) BCBM achieved CR and liver metastases achieved PR. **f** BCBM achieved CR and liver metastases progressed. WBRT, whole-brain radiotherapy; BCBM, breast cancer brain metastasis; PR, partial response; SD, stable disease; CR, complete response.

Treatment of BCBM has proven to be difficult because the blood-brain barrier (BBB), a selective barrier between the CNS and systemic circulation, inhibits drug entry [5]. However, it has recently been established that the blood tumor barrier, created by CNS tumors, is more permeable than the BBB and allows for drug entry into the CNS [6]. To the best of our knowledge, currently, only four case reports (not including this case report) have evaluated the efficacy of olaparib in BCBM. The details of the four case reports and the current case report are presented in Table 1.

Among these previous case reports, only one case reported CR [7], whereas other reports revealed progesterone receptor or SD [8–10]. In addition, one case did not have a *BRCA* mutation [8], two cases did not undergo radiotherapy previously [7, 8], and all four cases did not show any re-aggravation in the observation period. In our case, brain metastasis achieved CR and kept CR after the progression of liver metastasis. The response of brain metastasis and other metastasis to olaparib was different from previous reports. Further investigations are needed to reveal the mechanism of response to brain metastasis.

Mehta et al. [11] revealed that one of the poly ADP ribose polymerase (PARP) inhibitors, veliparib, in combination with whole-brain radiotherapy, could prolong the overall survival of BCBM. Litton et al. [12] showed that another PARP inhibitor, talazoparib, improved PFS than chemotherapy in patients with advanced breast cancer who had *BRCA* mutations. The trial included patients with a history of CNS metastases. In addition, yet another PARP inhibitor, pamiparib, has been shown to have strong penetration of the BBB in mice, and the combination of pamiparib and the chemotherapeutic agent temozolomide, has been investigated for its efficacy in BM [13]. Thus, in addition to olaparib, the efficacy of PARP inhibitors in BCBM has been suggested. This suggestion is based on the theory that BCBM may be homologous recombination deficient and more sensitive to PARP inhibitor treatment [14]. In the present case, olaparib may have penetrated the BBB, resulting in an antitumor effect.

Table 1. Reports of the olaparib administered for BCBM

Author	Age, years	g*BRCA1/2*mt	Response of BCBM to olaparib	Radiotherapy for BCBM	PFS (in months)
Exman et al. [7], 2019	48	*BRCA2*	CR	–	19
Pascual et al. [8], 2019	46	–	PR	–	4
Sakamoto et al. [9], 2019	58	*BRCA1*	PR	WBRT	22
Yamaguchi et al. [10], 2020	50	*BRCA2*	SD	SRT	14
The present case, 2023	37	*BRCA2*	CR	WBRT	9

BCBM, breast cancer brain metastasis; SRT, stereotactic radiotherapy; WBRT, whole-brain radiotherapy; PR, partial response; SD, stable disease; CR, complete response.

Our case report demonstrated the significant efficacy of olaparib in the treatment of BCBM. Furthermore, we highlighted the need for more studies to investigate the efficacy of olaparib and explore the efficacy of PARP inhibitors in BCBM.

Acknowledgments

The authors acknowledge Ms. Masayo Kawamura for her kind assistance with administrative support. Editorial support, in the form of medical writing, assembling tables, creating high-resolution images based on authors' detailed directions, collating author comments, copyediting, fact-checking, and referencing, was provided by Editage, Cactus Communications. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary File (for all online suppl. material, see https://doi.org/10.1159/000540257).

Statement of Ethics

Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images. Ethical approval is not required for this study in accordance with local or national guidelines.

Conflict of Interest Statement

Akihiko Shimomura received grants from AstraZeneca, Daiichi-Sankyo, Gilead Sciences, and Eisai, outside the submitted work; Chikako Shimizu received grants from Eli Lilly, outside the submitted work; other authors have no conflict of interest.

Funding Sources

No funding was obtained from the private or public sector for this study.

Author Contributions

Kazuki Asazuma and Akihiko Shimomura drafted the manuscript. Akihiko Shimomura revised the manuscript. Kazuki Asazuma, Akihiko Shimoura, Yukino Kawamura, Tomoko Taniyama, and Chikako Shimizu were involved in the treatment of the patient and have approved the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

References

1 Altundag K, Bondy ML, Mirza NQ, Kau SW, Broglio K, Hortobagyi GN, et al. Clinicopathologic characteristics and prognostic factors in 420 metastatic breast cancer patients with central nervous system metastasis. Cancer. 2007;110(12):2640–7. https://doi.org/10.1002/cncr.23088
2 Murthy RK, Loi S, Okines A, Paplomata E, Hamilton E, Hurvitz SA, et al. Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. N Engl J Med. 2020;382(7):597–609. https://doi.org/10.1056/NEJMoa1914609
3 Bachelot T, Romieu G, Campone M, Diéras V, Cropet C, Dalenc F, et al. Lapatinib plus capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer (LANDSCAPE): a single-group phase 2 study. Lancet Oncol. 2013;14(1):64–71. https://doi.org/10.1016/S1470-2045(12)70432-1
4 Robson M, Im SA, Senkus E, Xu B, Domchek SM, Masuda N, et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. N Engl J Med. 2017;377(6):523–33. https://doi.org/10.1056/NEJMoa1706450
5 Abbott NJ. Blood-brain barrier structure and function and the challenges for CNS drug delivery. J Inherit Metab Dis. 2013;36(3):437–49. https://doi.org/10.1007/s10545-013-9608-0
6 Lockman PR, Mittapalli RK, Taskar KS, Rudraraju V, Gril B, Bohn KA, et al. Heterogeneous blood-tumor barrier permeability determines drug efficacy in experimental brain metastases of breast cancer. Clin Cancer Res. 2010;16(23):5664–78. https://doi.org/10.1158/1078-0432.CCR-10-1564
7 Exman P, Mallery RM, Lin NU, Parsons HA. Response to olaparib in a patient with germline BRCA2 mutation and breast cancer leptomeningeal carcinomatosis. NPJ Breast Cancer. 2019;5:46. https://doi.org/10.1038/s41523-019-0139-1
8 Pascual T, Gonzalez-Farre B, Teixidó C, Oleaga L, Oses G, Ganau S, et al. Significant clinical activity of olaparib in a somatic BRCA1-mutated triple-negative breast cancer with brain metastasis. JCO Precis Oncol. 2019;3(3):1–6. https://doi.org/10.1200/PO.19.00012
9 Sakamoto I, Hirotsu Y, Nakagomi H, Ikegami A, Teramoto K, Omata M. Durable response by olaparib for a Japanese patient with primary peritoneal cancer with multiple brain metastases: a case report. J Obstet Gynaecol Res. 2019;45(3):743–7. https://doi.org/10.1111/jog.13851
10 Yamaguchi A, Taji T, Suwa H. A case of hormone receptor-positive recurrent breast cancer in which stable disease condition was achieved by olaparib. Nihon Rinsho Geka Gakkai Zasshi. 2021;82(6):1084–8. https://doi.org/10.3919/jjsa.82.1084
11 Mehta MP, Wang D, Wang F, Kleinberg L, Brade A, Robins HI, et al. Veliparib in combination with whole brain radiation therapy in patients with brain metastases: results of a phase 1 study. J Neuro Oncol. 2015;122(2):409–17. https://doi.org/10.1007/s11060-015-1733-1
12 Litton JK, Rugo HS, Ettl J, Hurvitz SA, Gonçalves A, Lee KH, et al. Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. N Engl J Med. 2018;379(8):753–63. https://doi.org/10.1056/NEJMoa1802905
13 Xiong Y, Guo Y, Liu Y, Wang H, Gong W, Liu Y, et al. Pamiparib is a potent and selective PARP inhibitor with unique potential for the treatment of brain tumor. Neoplasia. 2020;22(9):431–40. https://doi.org/10.1016/j.neo.2020.06.009
14 Diossy M, Reiniger L, Sztupinszki Z, Krzystanek M, Timms KM, Neff C, et al. Breast cancer brain metastases show increased levels of genomic aberration-based homologous recombination deficiency scores relative to their corresponding primary tumors. Ann Oncol. 2018;29(9):1948–54. https://doi.org/10.1093/annonc/mdy216