Metastatic breast cancer with double heterozygosity for the *BRCA1* and *BRCA2* genes responding to olaparib: A case report

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Abstract. Olaparib was the first poly ADP-ribose polymerase inhibitor approved for patients with cancer with mutations in either *BRCA1* or *BRCA2* in China. To the best of our knowledge, however, no study has described the efficacy of olaparib for patients with breast cancer with double mutations in *BRCA1* and *BRCA2*. The present case report describes a patient with breast cancer with deleterious germline mutations in both *BRCA1* and *BRCA2*. The 56-year-old patient with multiple metastatic breast cancer underwent breast cancer resection with 12 years interval between removal of the left and right breast. Germline mutations in both *BRCA1* (S405X) and *BRCA2* (W2990X) were identified by NGS. She received two cycles of chemotherapy with a combination of albumin-bound paclitaxel and capecitabine; the response was progressive disease. Subsequently, the patient was treated with a gradual dosage of decreasing olaparib (600 to 300 mg BID) for 6 months until grade 3 anemia could not be alleviated by giving erythropoietin and iron, and CT imaging showed a partial response (35% reduction). The patient then switched to exemestane therapy due to the continuous grade 3 anemia. In conclusion, the present study reported a female patient with double heterozygosity of BRCA1 and BRCA2 who benefited from olaparib monotherapy. Thus, olaparib may be a suitable treatment for such patients.

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Abbreviations: ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; PARP, poly ADP-ribose polymerase; PFS, progression-free survival

Key words: familial breast cancer, *BRCA* gene, next-generation sequencing, olaparib

Introduction

Breast cancer is the most common type of cancer in women; one in 9-12 women will develop breast cancer in their lifetime in developed countries. Up to 10% of all breast cancer cases are inherited, and *BRCA1* and *BRCA2* gene mutations account for the majority of families with inherited breast cancer (1).

Individuals with a mutation in either *BRCA1* or *BRCA2* genes have a significantly increased lifetime risk of breast and ovarian cancer (2-4). Olaparib, a poly ADP-ribose polymerase (PARP) inhibitor, was approved by the US Food and Drug Administration in 2014 for the treatment of *BRCA*-positive advanced ovarian cancer and by the National Medical Products Administration in 2018. There are few reports of germline mutations in both *BRCA1* and *BRCA2* (5-8). Carriers with inherited deleterious mutations in both *BRCA1* and *BRCA2* only account for 0.3% of all female *BRCA1/2* mutation carriers (5) and for 2.2% of breast cancer BRCA1/2 mutation carriers (6). Previous case reports have described such breast cancer patients but there is a lack of reports on the efficacy of olaparib on them (7,8). Similarly, clinical trials of olaparib have recruited such patients with cancer but lacked specific description of efficacy (9,10). A previous study reported that a patient with *BRCA1* and *BRCA2* double-germline mutant gastric cancer was resistant to olaparib treatment (11). To the best of our knowledge, however, there are no reports on the efficacy of olaparib in Chinese patients with breast cancer with mutations in both *BRCA1* and *BRCA2*.

Case report

The proband, a 56-year-old woman, underwent a modified radical mastectomy for left breast cancer in May 2004. The pathological diagnosis was medullary carcinoma, pT2N0M0, stage IIA, estrogen receptor $(ER)^-$, progesterone receptor $(PR)^-$ and human epidermal growth factor receptor $(HER2)1^+$. The patient received four cycles of adriamycin/cyclophosphamide (dose unknown) regimen. Right breast cancer was diagnosed during the routine follow-up examination and a modified radical mastectomy was performed in May 2016. The pathological diagnosis was invasive ductal carcinoma, pT1N2M0, stage IIIA, ER^{+++}, PR^-, $HER2^{1+}$ and Ki-67 (30%). Germline or somatic mutations were not identified at this time. Based on clinical pathology, chemotherapy with epirubicin

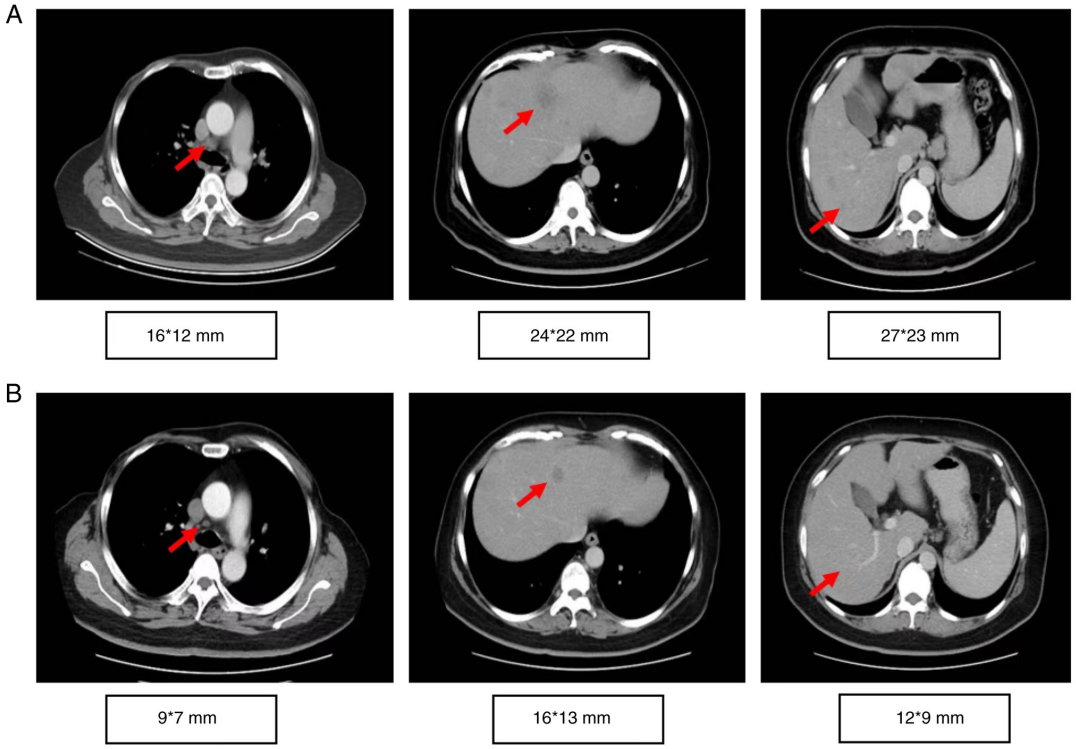

Figure 1. Computed tomography scan results before and after treatment. Computed tomography scan of the chest and abdomen (A) before initiation (December 2018) and (B) after 6 six months of olaparib therapy (June 2019). Arrows state metastatic lesions.

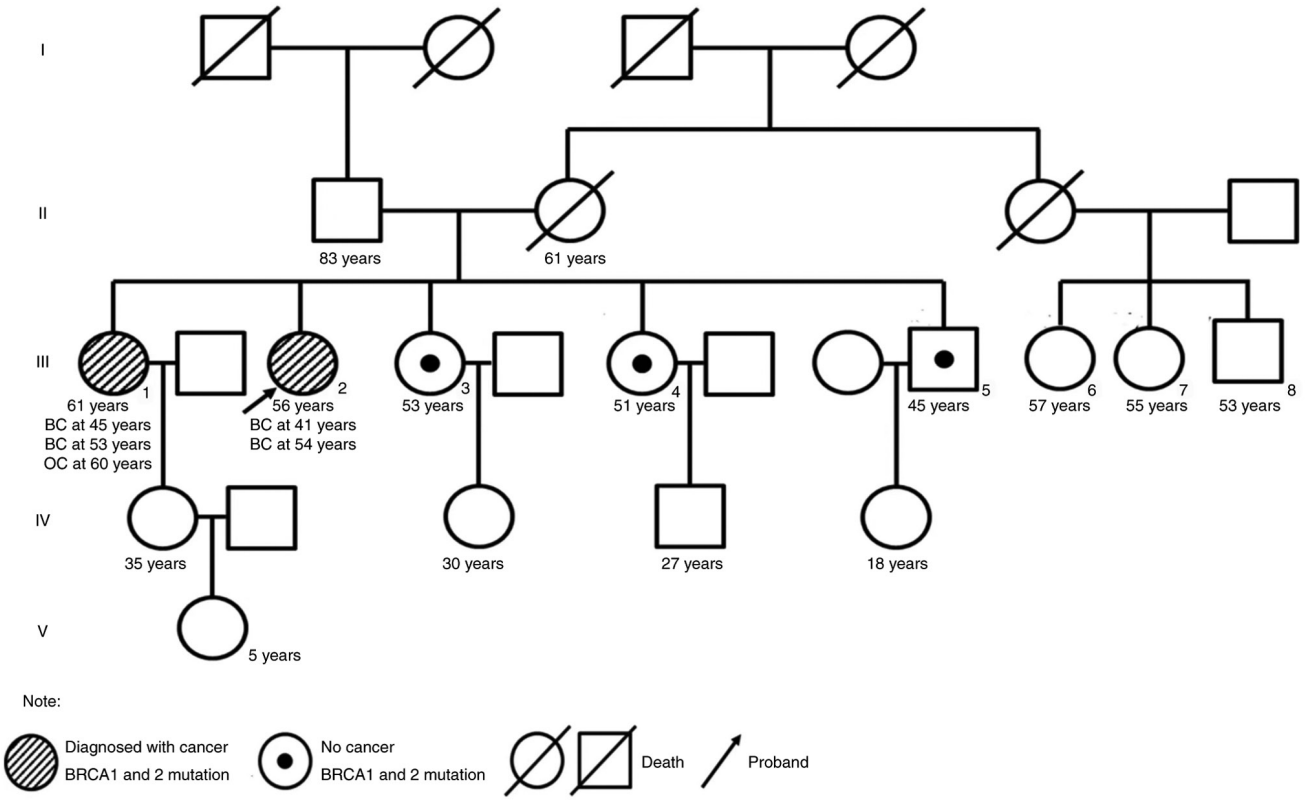

Figure 2. Pedigree of the patient's family. BC, breast cancer; OC, ovarian cancer.

(90 mg/m^2)/cyclophosphamide (600 mg/m^2) for four cycles with weekly paclitaxel (80 mg/m^2) for 12 weeks was performed from August 2016 to July 2017, followed by 5,000 cGy/25f radiotherapy targeting the chest wall and supraclavicular region. Letrozole (2.5 mg QD) was administered until multiple tumor metastases were detected in bone, liver and lymph

Table I. Timeline of the patient's medical history.

Date	Therapy	Regimen	Response
May 2004	Modified radical mastectomy for left breast cancer		
June-September 2004	Adjuvant chemotherapy	Adriamycin 60 mg/m^2, cyclophosphamide 750 mg/m^2)	NA
May 2016	Modified radical mastectomy of the right breast cancer		
August 2016-July 2017	Adjuvant chemotherapy	Epirubicin (90 mg/m^2)/cyclophosphamide (600 mg/m^2) 4 cycles followed by weekly paclitaxel (80 mg/m^2) for 12 weeks	
July-August 2017	Adjuvant radiotherapy of the chest wall and supraclavicular region	5,000 cGy/25 fractions	
August 2017-October 2018	Adjuvant endocrine therapy	Letrozole	
October-December 2018	First-line chemotherapy	Albumin-bound paclitaxel + capecitabine	Progressive disease
January-June 2019	Second-line therapy	Olaparib	Partial response

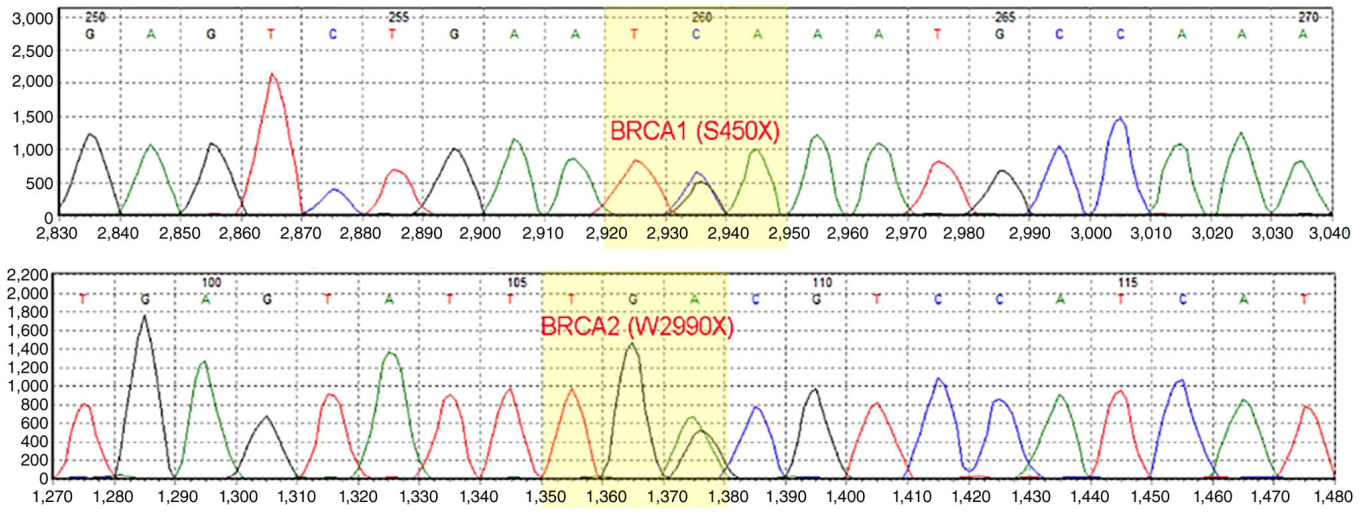

Figure 3. BRCA gene analysis demonstrated deleterious mutations in both BRCA1 and BRCA2 genes.

nodes (left cervical lymph nodes, clavicular area and internal mammary, right hilar lymph nodes and mediastinal, lung and liver hilar and retroperitoneal lymph nodes) by PET/CT in October 2018. The proband refused biopsy of the metastatic sites. The proband had multiple liver metastases with a maximum metastatic focus 3.1x2.6 cm. The tumor burden was high with multiple liver, lymph node and bone metastases. Due to primary adjuvant endocrine resistance and palbociclib, the only available CDK4/6 inhibitor in China at that time (October 2018), was not affordable for the patient, the patient received combination chemotherapy. Chemotherapy with abraxane (125 mg/m^2 d1,d8 q21d) combined with capecitabine (1 g/m^2 d1-14 q21d) was initiated but the disease continued to progress in the liver after two cycles (Fig. 1). The timeline of her past medical history is outlined in Table I. The patient had a family history of breast and ovarian cancer (Fig. 2). Targeted next-generation sequencing testing with a panel of 18 cancer genetic susceptibility genes was performed. Genomic DNA (gDNA) was extracted from paraffin-embedded section of the primary tumor with AllPrep DNA/RNA mini Kit (Qiagen 80204). The libraries of gDNA were constructed with a KAPA Hyper Prep kit (Kapa Biosystems, USA) according to the operation manual. gDNA libraries were enriched through a panel of 18 cancer genetic susceptibility genes with its custom-designed capture probes were manufactured by Agilent, USA. P5/P7 primers were adopted to amplify the enriched gDNA libraries. The amplified libraries were qualified by the 2200 Bioanalyzer (Agilent Technologies, Palo Alto, Calif) and quantified by the qBittorrent (version 3). Paired-end sequencing with reads length of 250 bp on the Hiseq X Ten platform (Illumina,

San Diego, CA) using MiSeq Reagent Kit v3 (MS-102-3001, Illumina, USA) and the loading concentration was 4 pM. The NGS raw data was initially analyzed with trimmomatic-0.36. Reads were then aligned against human reference genome (version GRCh37/hg19) with bwa (version 0.7.10). Candidate somatic mutations were determined using Samtools (version 1.3.1) and pindel (version 0.2.5b8). Finally, filter alignment and sequencing artifacts were conducted using IGV (Integrative Genomics Viewer). Double deleterious germline mutations in both *BRCA1* (S405X) and *BRCA2* (W2990X) were identified (Fig. 3). On the basis of these mutations, the proband started olaparib treatment (600 mg BID) in January 2019. The most severe adverse event was anemia (grade 3), which occurred 4 months after the start of the treatment. Other side effects, including leukopenia, thrombocytopenia, loss of appetite and nausea were mild and well tolerated. To alleviate symptoms of anemia, olaparib treatment was suspended and the proband received erythropoietin (10,000 IU 3 times/week) and ferrous succinate tablets (0.1 g 3 times/day). Olaparib treatment was resumed at a decreased dosage (450 mg/day) when anemia was reduced to grade 2 after 1 week of the treatment. Grade 3 anemia reoccurred after 2 weeks of decreased dosage olaparib, thus olaparib was suspended, and erythropoietin and ferrous succinate tablets at the aforementioned dosage were administered to relieve the anemia. Subsequently, olaparib treatment was resumed with further decreased dosage (300 mg/day). Grade 3 anemia reoccurred and olaparib treatment was terminated in July 2019. The olaparib treatment intermittently lasted for a total of 6 months and CT imaging showed a partial response (35% reduction; Fig. 1A and B). The proband did not receive chemotherapy or palbociclib because of persistent grade 3 anemia and the prohibitive cost of palbociclib. The proband received oral exemestane (25 mg qd). The patient continued treatment elsewhere and did not disclose her condition during a follow-up telephone conversation 3 months later.

The family members of the proband received genetic counseling and underwent NGS of *BRCA* genes. The same germline mutations in both *BRCA1* and *BRCA2* were identified in the proband's elder sister who was diagnosed with bilateral breast cancer at the age of 43 in 2005. Clinical information was not available. The proband's two younger sisters were carriers of the same *BRCA1* mutation and her younger brother was a carrier of the same *BRCA2* mutation. The offspring of the proband and their siblings declined genetic testing. To the best of our knowledge, no other family member has reported cancer symptoms to date.

Discussion

Hereditary breast/ovarian cancer syndrome, accounting for ~10% of breast and 15% of ovarian cancer cases, is often associated with germline mutations in *BRCA1* or *BRCA2* (3,12), which are present in 0.1-2.17% of the population worldwide (13-18). Due to the high risk of developing breast (up to 87%) and/or ovarian cancer (up to 63%), identification of carriers and surveillance is key to successful clinical management (19).

The frequency of double germline mutations in both *BRCA1* and *BRCA2* is only 0.3% in female *BRCA1/2* mutation carriers (5), which accounts for 0.64-1.80% of *BRCA1* (20) and 0.53-0.87% of *BRCA2* deleterious mutations (6,21-26). Palmirotta *et al* (27) summarized worldwide literature on double mutations in *BRCA1* and *BRCA2* from 1998 to 2017, in which Jewish Ashkenazi patients were deliberately excluded due to high mutation frequency of BRCA1 and BRCA2. Only 34 families with 56 subjects (34 probands and 22 relatives) carrying double mutations of *BRCA1* and *BRCA2* in 20 articles were reported (27). It is unclear whether double mutations increase cancer risk. In the present study, two individuals (the proband and their elder sister) with the double mutations exhibited cancer symptoms while the single mutation carriers remained healthy, indicating a potential higher risk of cancer in double mutation carriers.

The characteristics of individuals with clinically significant double heterozygosity for *BRCA1* and *BRCA2* are poorly understood (28). Bilateral breast cancer, a characteristic of familial breast cancer, was present in both the proband and their elder sister in the present case report. Furthermore, previous studies have suggested that patients with both *BRCA1* and *BRCA2* are more susceptible to gastric cancer, pancreatic cancer, uterine cancer and prostate cancer in addition to breast cancer and ovarian cancer (29,30). Palmirotta *et al* (27) reported that the phenotype of 56 cases with double heterozygosity varied from unilateral breast cancer at age 26 to asymptomatic at age 72. A total of 42 cases (75%) had a primary tumor, including 35 patients with breast, two each with ovarian and prostate, and one each with cervix, caecum and stomach cancer; 14 of these cases suffered secondary neoplasia (27).

Notably, two pathologically different breast tumors occurred in the present proband (left triple negative medullary carcinoma, and right invasive ductal breast cancer with ER^{+++}, PR^{-} and $HER2^{1+}$). More extensive sequencing on tumor somatic genetic alterations may reveal differences in tumorigenesis as well as additional potential therapeutic targets.

Treatment of *BRCA*-mutated metastatic breast cancer with olaparib is recommended by the Chinese Society of Clinical Oncology (CSCO) Breast Cancer Guidelines (31) based on the clinical data showing slower spread of hereditary breast cancer with olaparib treatment (32). To the best of our knowledge, however, the response of metastatic breast cancer with double heterozygous *BRCA1* and *BRCA2* mutations to olaparib has not been described previously. To the best of our knowledge, the present study is the first report demonstrating a partial response to olaparib in such patients. Platinum is also an effective treatment for metastatic breast cancer with *BRCA* mutations (33). There are also other potential options for patients with hormone receptor-positive, HER2 negative breast cancer including *CDK4/6* inhibitors and immunotherapy (34).

Since *BRCA1* and *BRCA2* genes are located on 13q and 17q respectively, each gene has the same probability (50%) of transmitting to the next generation (35). Genetic counseling is necessary in the medical care of familial breast cancer.

Family history and genetic counseling are key for the clinical management of patients with germline BRCA1/2 mutations (36). With the rapid development of treatment options, genetic screening for both germline and somatic mutations of BRCA is key for making clinical decisions, including type of surgery, the consideration of radiotherapy, and the value of systemic therapy in neoadjuvant and advanced settings (including response to platinum-based

chemotherapy and PARP inhibitors) (37,38). The phase III trial OlympiAD has shown that compared with standard therapy, median progression-free survival (PFS) is 2.8 months longer and risk of disease progression or death is 42% lower with olaparib monotherapy in *BRCA*-mutated metastatic breast cancer (32). Thus, olaparib is a treatment option for metastatic breast cancer with germline mutations of *BRCA1* and/or *BRCA2* (38).

The present case described a 56-year-old female patient with rare BRCA1 and BRCA2 double germline-mutant metastatic breast cancer. The patient had a family history of breast and ovarian cancer. The patient exhibited primary resistance to both letrozole and albumin-bound paclitaxel combined with capecitabine. NGS showed germline mutations of both *BRCA1* and *BRCA2*, and the patient received olaparib monotherapy. The patient achieved a partial response and PFS was 6 months, although they discontinued olaparib treatment due to continuous grade 3 anemia. Genetic testing is key to determine optimal treatment for breast cancer. In conclusion, olaparib exhibited therapeutic potential for a patient with BRCA1 and BRCA2 double germline-mutant metastatic breast cancer.

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Availability of data and materials

The datasets generated and/or analyzed during the current study are available in the GSA-human repository, https://ngdc.cncb.ac.cn/gsa-human/s/30mKWWj6.

Authors' contributions

BS and LD confirm the authenticity of all the raw data. BS and LD conceived and designed the study. BS collected cases, analyzed data analysis. BS wrote the manuscript. BS and LD revised the content. LD was responsible for treating the patient. Both authors have read and approved the final manuscript.

Ethics approval and consent to participate

The patient and her relatives took part in the program 'Genetic test of solid tumor, circulating tumor DNA and genetic diseases', which was approved by the ethics committee of Beijing Cancer Hospital (Beijing, China; approval no. 2016XJS01-ZY01). All participants provided written informed consent to participate.

Patient consent for publication

Written informed consent was obtained from the patient and her family members for publication of this case report and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

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