Olaparib is effective for recurrent urothelial carcinoma with BRCA2 pathogenic germline mutation: first report on olaparib response in recurrent UC

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***Abstract*:** Urothelial carcinoma (UC) is a common malignancy of the lower and upper urinary tract. Recurrent UC has poor prognosis due to delayed diagnosis and a lack of clinical management guidance, especially for upper urinary tract UC. Patients with germline or somatic BRCA1/2 mutations are a special population in UC. No evidence is available so far on the effectiveness of poly ADP-ribose polymerase inhibitor (PARPi) in this population. Here, we report a 60-year-old female patient diagnosed with left ureter high-grade UC. Recurrent lesions were found 20 months after radical surgery. Computed tomography (CT) examination showed a slightly high-density soft tissue mass (3.2 × 3.1 cm) on the left posterior wall of the abdomen (waist), soft tissue mass adjacent to the left inner wall of the pelvis (3.2 × 4.2 cm), and multiple enlarged lymph nodes to the left of abdominal aorta. A next-generation sequencing (NGS)-based 605-gene panel detected a novel BRCA2 pathogenic germline mutation c.1670T>A (p.L557*), and a series of somatic insertion and deletion (INDEL) mutations of BRCA1, RB1, and JAK2, and single nucleotide variation (SNV) mutations of TP53, KMT2D, MET, ROS1, and IL7R. The above lesions were reduced significantly or disappeared (partial response, PR) after a 3-month Olaparib treatment, and the patient's general condition remained well. In conclusion, this study proved for the first time that PARPi was effective for UC treatment in patients carrying germline BRCA2 pathogenic mutations, providing new treatment options for such patients. In addition, the circulating tumor DNA (ctDNA) test can be used for drug selection and response monitoring in UC treatment.

Keywords: BRCA1, BRCA2, germline, olaparib, PARPi, ureter, urothelial carcinoma

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Introduction

Urothelial cancer (UC) is a general term for malignancies originating from urothelium of renal pelvis, calyx, ureter, and bladder. UC belongs to transitional cell carcinoma and is a type of common malignancy of the urinary system. Bladder cancer is most commonly seen in UC, while upper urinary tract UC accounts for about 5% of all UC.[1] Risk factors for upper urinary tract UC include smoking, occupational exposure, and aristolochic acids. Recent studies have found that high-grade UC is associated with cell cycle dysregulation, usually with a poor prognosis, high relapse rate, and accompanied by progression. There is a high risk of invasion and metastasis for high-grade UC, which exhibits more diverse molecular alterations than low-grade UC.[2,3] Radical nephroureterectomy is currently the standard method of treatment of upper urinary tract UC. In recent years, percutaneous endoscopic surgery has been used widely. Its advantages include high safety, less trauma, fast recovery, high overall survival rate, and fewer complications, and it is a better method for

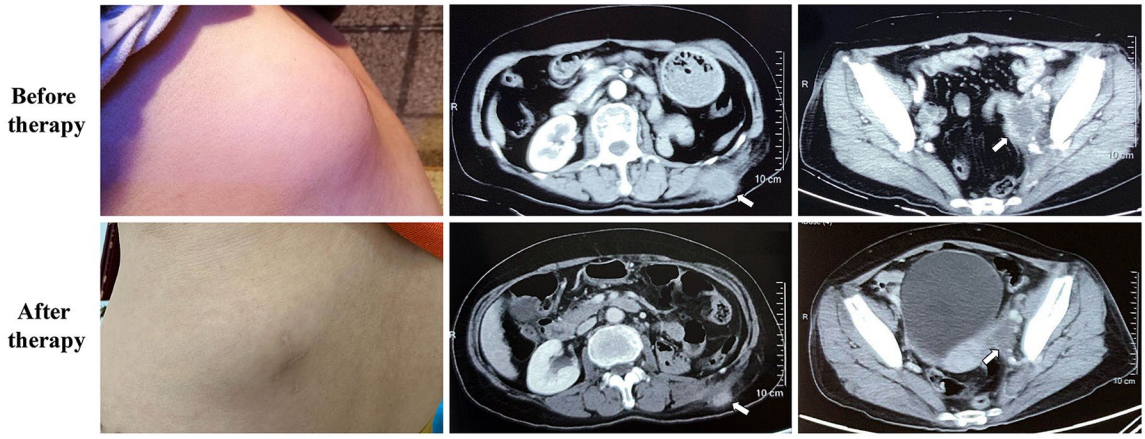

Figure 1. Images of the lesion changes reflected the therapeutic response following Olaparib therapy. The waist lesion can be observed from the body surface and reduced after therapy (left column). CT images show that the waist lesion reduced following Olaparib therapy (middle column, arrows indicate the lesion). CT images show that the pelvic lesion reduced following Olaparib therapy (right column, arrows indicate the lesion).
CT, computed tomography.

patients with normal contralateral renal function.[4,5] In addition, chemotherapy, targeted therapy, and immunotherapy are also used to treat patients with upper urinary tract UC. For example, Erdafitinib was the first approved targeted drug for patients with locally advanced or metastatic UC with FGFR2 or FGFR3 gene mutations.[6] The United States Food and Drug Administration (FDA) also approved several immune checkpoint inhibitors (ICIs) for the treatment of metastatic UC.[7]

More recently, it was found that a small fraction of patients with UC carry pathogenic (P) or likely pathogenic (LP) germline mutations. In terms of BRCA1/2 germline mutations, one recent study reported that 1.4% (8/586) of UC patients carried BRCA1 and 1.5% (9/586) of UC patients carried BRCA2 P/LP germline mutations,[8] and another study reported that 2.3% (20/867) of UC carried BRCA1 and 2.1% (18/867) of UC carried BRCA2 P/LP germline mutations.[9] Although PARPi have been used widely in the treatment of hereditary breast and ovarian cancer (HBOC) patients with germline BRCA1/2 mutations, it was unclear whether PARPi is effective for UC patients with BRCA1/2 germline mutations, as no such observation has been reported in UC. In this study, we reported for the first time the treatment of recurrent UC with Olaparib in a patient carrying a BRCA2 pathogenic germline mutation, and observed partial response to Olaparib. Our study proved for the first time the effectiveness of PARPi in the treatment of recurrent UC.

Case presentation

Here, we report a 60-year-old Chinese woman, presenting to a local hospital due to hematuria and diagnosed with left upper tract UC in March 2018. She had a left laparoscopic radical nephroureterectomy in the same month. Postoperative pathological examination confirmed invasive high-grade UC. Immunohistochemistry showed GATA-3 (+), CKH (+), CK7 (+), CK20 (–), P63 (+), CgA (–), Syn (–), CKL (weak +), β-Catenin (+), Ki-67 (+, 25%), CK18 (+), and P40 (+). She was discharged and recovered well after surgery, and had gemcitabine and cisplatin (GC) combined chemotherapy for four cycles. In November 2019, the patient came to hospital with left back and abdominal pain. Computed tomography (CT) examination showed a slightly high-density soft tissue mass shadow of 3.2×3.1 cm on the posterior wall of the left abdomen, a dense soft tissue mass shadow on the left internal iliac lymph nodes (3.2×4.2 cm, thick-walled annular enhancement in contrast-enhanced CT), and multiple enlarged lymph nodes to the left of the abdominal aorta (maximum diameter of about 1.5 cm) (Figure 1 before therapy). All masses and enlarged lymph nodes were highly suspected to be metastatic lesions. The patient's left back pain later worsened, accompanied by a loss of appetite, and a "goose egg" size mass was found at the left waist (Figure 1 before therapy). In order to identify potential targets for systematic treatment, blood samples were collected from the patient, and the germline DNA was tested with a next-generation sequencing

Table 1. Genomic alterations detected from plasma ctDNA by 605-gene panel.

Gene name	Amino acid change	Nucleotide change	AF%	
			January, 2020	April, 2020
BRCA2	L557*	c.1670T>A	germline	germline
BRCA1	Y1845Pfs*3	c.5533_5534del	13.42	0.25
TP53	N247I	c.740A>T	12.26	0.54
KMT2D	R2687*	c.8059C>T	10.21	0.21
RB1	E554Gfs*6	c.1661_1695del	2.87	
ROS1	S1891T	c.5672G>C	4.6	
JAK2	M84Vfs*6	c.250_251del	2.45	
IL7R	V400M	c.1198G>A	2.91	
MET	N1239Y	c.3715A>T	9.3	

AF, allele frequency; ctDNA, circulating tumor DNA; del, deletion.

(NGS)-based 605-gene panel and the status of 58 hereditary cancer related genes were reported (Supplemental Table S1), and the somatic circulating tumor DNA (ctDNA) was tested with the same NGS-based 605-gene panel (Supplemental Table S2). The test results suggested that the patient carried a novel germline BRCA2 nonsense mutation p.L557* (c.1670T>A), as well as somatic INDEL mutations, including BRCA1 p.Y1845Pfs*34 (c.5533_6634del), RB1 p.E554Gfs*6 (c.1661_1695del), JAK2 p.M84Vfs*6 (c.250_251.del), and somatic SNV mutations in TP53, KMT2D, MET, ROS1 and IL7R (Table 1). Among them, the germline BRCA2 c.1670T>A mutation was discovered for the first time (list of all germline mutations for this patient is provided in Table 2). Based on the above test results, the patient started taking Olaparib orally (300 mg/tablet, bid, po). At 3 months after the initiation of Olaparib therapy, CT reexamination revealed a reduction of the left lumbar mass (Figure 1 after therapy) and a reduction of the abnormal enhanced mass in the original left kidney area (Figure 1 after therapy). Multiple enlarged lymph nodes to the left of the abdominal aorta became smaller or disappeared. The overall response achieved partial response (PR). The repeated ctDNA test after 3 months of treatment showed reduction in mutation allele frequency in BRCA1 (from 13.42% to 0.25%), TP53 (from 12.26% to 0.54%), and KMT2D (from 10.21% to 0.21%). The remaining somatic mutations were not detected in the second test (Table 1). The tumor mutational burden (TMB) decreased from 6.11 Muts/Mb to 0.76 Muts/Mb. These observations suggested that Olaparib treatment successfully controlled the tumor development and reduced the tumor burden. At the time of submission of this article, the patient has been receiving Olaparib treatment for more than 4 months with continued response.

Discussion

One of the most interesting findings of this case was that the patient carried a novel BRCA2 germline mutation (c.1670T>A). This mutation led to the formation of a stop code, which stopped transcription at L557 and formed a truncated protein. Since the full length BRCA2 protein contains 3418 amino acids, truncation at L557 led to loss of large fragment of the protein, which would have a significant impact on the protein structure, function, and activity. As far as we know, c.1670T>A has never been reported in the literature and the Clinvar database, and general population data have not reported the site either. However, Clinvar records a BRCA2 mutation of the same site, i.e., c.1670T>G. This mutation also generated a stop code and was interpreted as a pathogenic mutation. Therefore, based on the ACMG principles, c.1670T>A was also interpreted as a pathogenic mutation. As described in the Introduction, the incidence of pathogenic

Table 2. Germline mutations of the patient.

Gene name	Mutation position	Base change	Amino acid change	Mutation type	Genotype	Pathogenicity
APC	rs459552	c.5465T>A	p.V1822D	Nonsynonymous	Heterozygous	Benign
ATM	rs1801516	c.5557G>A	p.D1853N	Nonsynonymous	Heterozygous	Benign
ATM	rs659243	c.5948A>G	p.N1983S	Nonsynonymous	Heterozygous	Benign
ATM	rs1799757	c.3285-10T>-	N/A	Intron	Heterozygous	Benign
ATM	rs201773026	c.125A>G	p.H42R	Nonsynonymous	Heterozygous	VUS
AXIN2	rs2240308	c.148C>T	p.P50S	Nonsynonymous	Heterozygous	Benign
BARD1	rs2229571	c.1134G>C	p.R378S	Nonsynonymous	Heterozygous	Benign
BARD1	rs2070094	c.1519G>A	p.V507M	Nonsynonymous	Heterozygous	Benign
BLM	rs3815003	c.2555+7T>C	N/A	Intron	Heterozygous	Benign
BRCA1	rs16941	c.3113A>G	p.E1038G	Nonsynonymous	Heterozygous	Benign
BRCA1	–	c.824G>A	p.G275D	Nonsynonymous	Heterozygous	VUS
BRCA1	rs16942	c.3548A>G	p.K1183R	Nonsynonymous	Heterozygous	Benign
BRCA1	rs799917	c.2612C>T	p.P871L	Nonsynonymous	Heterozygous	Benign
BRCA1	rs1799966	c.4837A>G	p.S1613G	Nonsynonymous	Heterozygous	Benign
BRCA2	–	c.1670T>A	p.L557X	Nonsense	Heterozygous	Pathogenic
BRCA2	rs169547	c.7397T>C	p.V2466A	Nonsynonymous	Homozygous	Benign
BRCA2	rs1801426	c.10234A>G	p.I3412V	Nonsynonymous	Heterozygous	Benign
BRIP1	rs4986764	c.2755T>C	p.S919P	Nonsynonymous	Homozygous	Benign
CDH1	rs3743674	c.48+6C>T	N/A	Intron	Heterozygous	Benign
EPCAM	rs150307203	c.859-6A>G	N/A	Intron	Heterozygous	Benign
EPCAM	rs1126497	c.344T>C	p.M115T	Nonsynonymous	Homozygous	Benign
FLCN	rs3744124	c.907G>A	p.G303R	Nonsynonymous	Heterozygous	Benign
FLCN	rs8065832	c.1062+6C>T	N/A	Intron	Heterozygous	Benign
MEN1	rs2959656	c.1636A>G	p.T546A	Nonsynonymous	Heterozygous	Benign
MLH3	rs175081	c.2476A>G	p.N826D	Nonsynonymous	Homozygous	Benign
MRE11A	rs535801	c.403-6G>A	N/A	Intron	Homozygous	Benign
MSH2	rs2303426	c.211+9C>G	N/A	Intron	Homozygous	Benign
MSH2	rs2303428	c.2006-6T>C	N/A	Intron	Heterozygous	Benign
MUTYH	rs3219489	c.1014G>C	p.Q338H	Nonsynonymous	Heterozygous	Benign
PMS2	rs1802683	c.2570G>C	p.G857A	Nonsynonymous	Heterozygous	Likely benign

(Continued)

Table 2. (Continued)

Gene name	Mutation position	Base change	Amino acid change	Mutation type	Genotype	Pathogenicity
PMS2	–	c.706-4->T	N/A	Intron	Heterozygous	VUS
PMS2	rs60794673	c.706-4T>-	N/A	Intron	Heterozygous	Benign
PMS2	rs1805321	c.1408C>T	p.P470S	Nonsynonymous	Heterozygous	Benign
PMS2	rs1805326	c.2007-4G>A	N/A	Intron	Heterozygous	Benign
PMS2	rs2228006	c.1621A>G	p.K541E	Nonsynonymous	Homozygous	Benign
POLD1	rs1726801	c.356G>A	p.R119H	Nonsynonymous	Heterozygous	Benign
POLD1	rs1726802	c.463+8G>T	N/A	Intron	Heterozygous	Benign
PTEN	rs12573787	c.10G>A	p.G4R	Nonsynonymous	Homozygous	Benign
PTEN	rs11202592	c.511C>G	p.L171V	Nonsynonymous	Heterozygous	Benign
PTEN	rs2943772	c.194G>C	p.C65S	Nonsynonymous	Homozygous	Benign
PTEN	rs71022512	c.154+1T>-	N/A	Splicing	Homozygous	Benign
RB1	rs3092904	c.2664-10T>A	N/A	Intron	Heterozygous	Benign
RET	rs1799939	c.2071G>A	p.G691S	Nonsynonymous	Heterozygous	Benign
STK11	rs183406870	c.921-10G>A	N/A	Intron	Heterozygous	Likely benign
TP53	rs1042522	c.215C>G	p.P72R	Nonsynonymous	Homozygous	Benign
TSC1	rs118203716	c.2626-4T>-	N/A	Intron	Heterozygous	Benign
TSC1	rs1073123	c.965T>C	p.M322T	Nonsynonymous	Heterozygous	Benign

VUS, variant of uncertain significance.

BRCA mutations in UC is low, and there has been no report of the therapeutic effect of PARPi. Therefore, our study represents the first report on PARPi response in a recurrent UC patient with a BRCA1/2 pathogenic germline mutation, and provided important evidence for future therapy.

BRCA1 and BRCA2 somatic mutations are not uncommon in high-grade upper urinary tract UC.[10] An interesting finding in this study was that the patient carried both a BRCA2 germline mutation and a BRCA1 somatic mutation, and both of them were pathogenic. Recent studies have shown similar response rates of PARPi therapy in patients with somatic or germline BRCA mutations, suggesting that patients are likely to benefit from PARPi therapy whether germline or somatic BRCA mutations are detected.[11] In this case, the identification of both germline and somatic BRCA mutations ensured the good response to PARPi. BRCA1 and BRCA2 are involved in a series of crucial biological processes, including DNA damage repair, transcription activation and suppression, cell cycle regulation, and maintenance of genome stability. Olaparib has been approved for the treatment of patients with ovarian cancer, fallopian tube cancer, primary peritoneal cancer, and pancreatic cancer carrying BRCA1 and BRCA2 pathogenic mutations. Its efficacy in other cancers is also under investigation. There are few data on PARPi efficacy in UC treatment, but there are a couple of ongoing clinical trials designed to evaluate the safety and efficacy of PARPi in UC as monotherapy or in combination with other drugs. This includes two ongoing phase II clinical trials [ClinicalTrials.gov identifiers: NCT03448718 and NCT03375307] investigating Olaparib monotherapy in UC

patients, but specific efficacy data have not been reported.[12] A comprehensive literature search identified only one reported UC patient with BRCA2 germline mutation who benefited from Olaparib treatment.[13] Somatic homozygous deletion of BRCA2 (BRCA2 loss) and BRCA2 I2672V germline mutation were detected in this report, while the pathogenicity of BRCA2 I2672V was not certain, therefore, drug efficacy in this case may be strongly related to somatic BRCA2 loss. In contrast, our study reported the first case with a confirmed BRCA2 pathogenic germline mutation, with a coexisting somatic BRCA1 mutation. Thus, our report provides strong evidence in support of the application of PRAPi in UC patients with germline and/or somatic BRCA mutations.

NGS tests are recommended for patients with locally advanced, metastatic or recurrent cancers in China, as these patients generally require systematic therapy. Ideally, both tumor tissue and blood samples are collected from these patients for comprehensive examination. The information on the available targets for potential targeted therapy or immunotherapy is important for establishing the personalized therapeutic strategies. The patient in this study experienced recurrent UC with multiple metastases; therefore, the NGS test was recommended for identifying potential drug targets. Due to the unavailability of tumor tissue samples for this patient, the 605-gene panel was used to examine the blood ctDNA (somatic alterations) and genomic DNA (germline alterations). Germline alterations are usually examined as a normal control for somatic mutational calling, which is a routine procedure for NGS testing. Therefore, both somatic and germline alterations were reported for the patient. Fortunately, a pathogenic BRCA2 germline mutation and a pathogenic somatic BRCA1 mutation were identified as actionable targets for PARPi therapy. Since recurrent metastatic cancer lesions were found with the patient after GC combined adjuvant therapy, it can be suggested that the GC regime may not control the disease well, although it is the standard therapy for recurrent or metastatic UC. PARPi could be a good option in this scenario for this patient. Although no clinical trials with PARPi in UC are available in China, this patient was willing to take an investigational therapy with strict informed consent. The prospective test in this patient rationalized the necessity of NGS for target identification, and provided strong evidence for PARPi prescription.

In addition to the BRCA1/2 gene mutations, this study also detected other driver gene mutations related to tumorigenesis and cancer development. KMT2D and TP53 were reported to be common mutations in upper urinary tract UC.[14] By comparing the mutation landscape of low-grade and high-grade UC, it was found that the mutation frequency in TP53 and related pathways in high-grade tumors was significantly higher.[15] The TP53 mutation has proved to be a factor for poor prognosis for UC.[3,16] RB1 is one of the important driving genes, with a nuclear phosphorylated protein as its expression product. In addition to inhibiting the transition of the cell cycle from the G1–S phase, it also maintains genome stability and mediates apoptosis, senescence, and differentiation. Mutations in the RB1 pathway were also common in high-grade UC, and deletion mutations of chromosome 13 were the most common cause of RB1 gene inactivation.[17] Mutations of the TP53/RB1 tumor suppressor pathway may lead to TP53 and RB1 inactivation and genome instability,[18,19] which occurred in 93% of malignancies, and were also one of the pathogenic mechanisms of high-grade upper urinary tract UC.[14]

ctDNA testing has been used widely for assisting the clinical diagnosis and treatment for non-small cell lung cancer, breast cancer, gastric cancer, and esophageal cancer.[20,21] Studies have also confirmed that ctDNA detection can be used to monitor the alterations in tumor burden and gene mutation status in UC patients.[10] In this case, ctDNA effectively monitored the alterations in mutational status following PARPi treatment, in which the abundance of all somatic mutations was greatly reduced or became undetectable. This alteration was consistent with the lesion changes observed by CT, indicating that ctDNA can reflect changes in tumor burden and response to therapy. It is worth noting that, although bTMB significantly reduced after treatment, statistical clinical evidence is still needed to correlate bTMB with the response in UC.

In conclusion, our study reported for the first time that UC patients with BRCA2 pathogenic germline mutations responded well to PARPi, indicating that Olaparib can be used in the treatment of UC patients with BRCA1/2 germline and/or somatic mutations. However, the PARPi efficacy in UC treatment still needs to be confirmed by evidence from clinical trials. In addition, this study confirmed that the NGS

panel-based ctDNA test can be used for medication guidance and response monitoring in UC treatment.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Disclosure of potential conflicts of interest

The authors claim no conflicts of interest in this study.

Ethics and patient

Written informed consent was obtained from the patient before clinical samples were collected. Consent to publication was also obtained from the patient. The patient was informed the test results.

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Supplemental material

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