Clinical Case Report

Durable response to olaparib combined low-dose cisplatin in advanced hepatocellular carcinoma with FANCA mutation
A case report

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Abstract

Rationale: To date, there is no actionable gene has been discovered in hepatocellular carcinoma (HCC). Tumor cells with DNA damage response and repair (DDR) gene loss-of-function mutation is sensitivity to poly-ADP-ribose polymerase (PARP) inhibitors and platinum chemotherapy in ovarian, prostate and pancreatic cancers. There is a case report demonstrated the efficacy of PARP inhibitor for *BRCA2* mutation that belongs to DDR gene in HCC, which suggested the potential role of PARP inhibitor for HCC with DDR gene mutation.

Patient concerns: We reported a 44-year-old woman with non-viral HCC who was refractory to multiple treatment including target therapy, immunotherapy, and chemotherapy. The tumor tissue was submitted to next-generation sequencing using the commercially available ACTOnco®+ (ACT Genomics, Taiwan) assay that interrogates 440 and 31 cancer-related genes and fusion genes, respectively.

Diagnosis: A truncating mutation *FANCA* p.Q1307fs was also observed. The tumor was microsatellite stable and had low tumor mutational burden of 4.5 muts/Mb.

Interventions and outcomes: Given FANCA belongs to DDR genes, the inactivation evoked the idea of using PARP inhibitor and cisplatin. Therefore, the patient started to use olaparib combined with low-dose cisplatin (30 mg/m^2, every 4 weeks) therapy in December 2019. Significant reduction in the tumor marker level in 1 month (PIVKA-II from 17,395 to 411 ng/dL) and follow-up CT scan showed stable disease. Her tumor did not progress until December 2020 with a progression-free survival of 12 months.

Lessons: We report the first case of *FANCA*-mutated HCC that responded well to olaparib and low-dose cisplatin. This addressed the potential therapeutic role of DDR gene mutation in HCC and the possible synergistic effect of PARP inhibitor and cisplatin. These findings highlight areas where further investigation and effort are needed.

Abbreviations: DDR = DNA damage response and repair, FA = Fanconi anemia, GIS = Genomic instability score, HCC = hepatocellular carcinoma, NGS = next-generation sequencing, PARP = poly-ADP-ribose polymerase, SNVs = single nucleotide variants, TMB = tumor mutational burden.

Keywords: case report, *FANCA*, hepatocellular carcinoma, homologous recombinational repair, olaparib, PARP inhibitor

1. Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide. The standard treatment includes multiple-kinase inhibitors and anti-PD-1/PD-L1. Recently, atezolizumab combined bevacizumab have been firstly recommended in advanced HCC due to the better efficacy than sorafenib. However, there is no actionable driven gene has been discovered in HCC. DNA damage response and repair (DDR) is responsible for homologous recombination repair), which is an important process when DNA double-strand breaks. Alterations of DDR genes lead to homologous recombination deficiency, genomic instability, and higher tumor mutational burden (TMB) in cancers.

Common DDR genes include *BRCA1/2, PALB2, CDK12, RAD51, CHEK2, ATM*, and *FANCA*. Among these, BRCA1/2 are well-known to increase the cancer risk.[1] The Fanconi anemia (FA) pathway, also called the FA-BRCA pathway, is an essential DNA repair pathway that recognized DNA damage and orchestrated DNA damage responses. The FA core complex that encoded by *FANCA* and *FANCG* interacts with other DNA-repair proteins to perform homologous recombination.[2] On the contrary, the mutation of *FANCA* disrupts FA-BRCA repair pathway leads to the increase of sensitivity to DNA damaging agents.

In HCC, the incidence of DDR genes mutation is up to 20.9% and *BAP1, CHEK2* are the most common. Regarding to *FANCA* mutations, the incidence is only 2% of HCC patients.[3] Poly-ADP-ribose polymerase (PARP) is a crucial protein in the DNA single-strand break repair pathway but also plays a role in double-strand break repair pathway. The inhibition of PARP leads to accumulation of unpaired single-strand break, which are converted to double-strand break. Thus, in the presence of DDR genes mutation, the use of PAPR inhibitor results in synthetic lethality in breast, ovarian, and prostate cancers.[4–8] However, the efficacy of PARP inhibitor for DDR genes mutation in HCC is unknown. In this article, we present a patient of HCC with *FANCA* mutation who achieved durable response to the combination of olaparib and low-dose cisplatin.

2. Case presentation

In October 2017, a 44-year-old female was admitted to the Veteran General Hospital with right upper quadrant abdominal fullness. A tumor sized 15 cm with diaphragm invasion was found, without portal vein thrombosis. Patient was diagnosed with HCC, pT3aN0Mx, stage IIIA, and BCLC stage B. She underwent segmentectomy but 2 months later at least 4 tumors recurred. Thus, she underwent repeated trans-arterial chemoembolization but recurrence persisted. Due to trans-arterial chemoembolization refractory, she received systemic therapy subsequently, including lenvatinib, nivolumab, gemcitabine plus cisplatin and bevacizumab, doxorubicin, dacarbazine, FOLFOX (fluorouracil, oxaliplatin), and sorafenib. Her tumor did not respond to any of the above treatment and the tumor persisted to progress. Multiple bone metastasis and left humeral pathologic fracture developed in 2019 and thus she received open reduction internal fixation and palliative radiotherapy. Systemic treatment was changed to regorafenib, and pembrolizumab. However, her tumor still progressed.

The soft tissue from left humeral metastasis was subjected to next-generation sequencing (NGS) using the commercially available ACTOnco®⁺ (ACT Genomics, Taiwan) assay that interrogates 440 and 31 cancer-related genes and fusion genes, respectively (Tables 1 and 2). A total of 24 single nucleotide variants and small insertions and deletions were identified. Neither copy number amplification nor homozygous deletion was identified. The tumor was microsatellite stable and had low tumor mutational burden of 4.5 muts/Mb. Among these alterations, the *CTNNB1* p.K335I gain-of-function mutation was considered oncogenic but not actionable. A truncating mutation *FANCA* p.Q1307fs was also observed (Fig. 1).

Given *FANCA* belongs to DDR genes, the inactivation evoked the idea of using PARP inhibitor and cisplatin.

Table 1

Gene contents of ACTOnco®⁺ assay. ACTOnco®⁺ assay identifies genetic alternations (single nucleotide variants, small insertions and deletions, and copy number variations) of 440 cancer-related genes, tumor mutational burden (TMB) and microsatellite instability (MSI) status from DNA.

ABCB1*	AURKB	CBL	CDKN2B	E2F3	FAT1	GRIN2A	JAK2	MED12	NOTCH4	PMS1	RAD51D	SLCO1B3*	TNFRSF14
ABCC2*	AXIN1	CCNA1	CDKN2C	EGFR	FBXW7	GSK3B	JAK3	MEF2B	NPM1	PMS2	RAD52	SMAD2	TNFSF11
ABCG2*	AXIN2	CCNA2	CEBPA*	EP300	FCGR2B	GSTP1*	JUN	MEN1	NQO1*	POLB	RAD54L	SMAD3	TOP1
ABL1	AXL	CCNB1	CHEK1	EPCAM	FGF1*	GSTT1	KAT6A	MET	NRAS	POLD1	RAF1	SMAD4	TP53
ABL2	B2M	CCNB2	CHEK2	EPHA2	FGF10	HGF	KDM5A	MITF	NSD1	POLE	RARA	SMARCA4	TPMT
ADAMTS1	BAP1	CCNB3	CIC	EPHA3	FGF14	HIF1A	KDM5C	MLH1	NTRK1	PPARG	RB1	SMARCB1	TSC1
ADAMTS13	BARD1	CCND1	CREBBP	EPHA5	FGF19	HIST1H1C*	KDM6A	MPL	NTRK2	PPP2R1A	RBM10	SMO	TSC2
ADAMTS15	BCL10	CCND2	CRKL	EPHA7	FGF23	HIST1H1E*	KDR	MRE11	NTRK3	PRDM1	RECQL4	SOCS1*	TSHR
ADAMTS16	BCL2	CCND3	CRLF2	EPHB1	FGF3	HNF1A	KEAP1	MSH2	PAK3	PRKAR1A	REL	SOX2	TYMS
ADAMTS18	BCL2L1	CCNE1	CSF1R	ERBB2	FGF4*	HR	KIT	MSH6	PALB2	PRKCA	RET	SOX9	U2AF1
ADAMTS6	BCL2L2	CCNE2	CTCF	ERBB3	FGF6	HRAS	KMT2A	MTHFR*	PARP1	PRKCB	RHOA	SPEN	UBE2A
ADAMTS9	BCL6	CCNH	CTLA4	ERBB4	FGFR1	HSP90AA1	KMT2C	MTOR	PAX5	PRKCG	RICTOR	SPOP	UBE2K
ADAMTSL1	BCL9	CD19	CTNNA1	ERCC1	FGFR2	HSP90AB1	KMT2D	MUC16	PAX8	PRKCI	RNF43	SRC	UBR5
ADGRA2	BCOR	CD274	CTNNB1	ERCC2	FGFR3	HSPA4	KRAS	MUC4	PBRM1	PRKCQ	ROS1	STAG2	UGT1A1*
ADH1C*	BIRC2	CD58	CUL3	ERCC3	FGFR4	HSPA5	LCK	MUC6	PDCD1	PRKDC	RPPH1	STAT3	USH2A
AKT1	BIRC3	CD70	CYLD	ERCC4	FH	IDH1	LIG1	MUTYH	PDCD1LG2	PRKN	RPTOR	STK11	VDR*
AKT2	BLM	CD79A	CYP1A1*	ERCC5	FLCN	IDH2	LIG3	MYC	PDGFRA	PSMB8	RUNX1	SUFU	VEGFA
AKT3	BMPR1A	CD79B	CYP2B6*	ERG	FLT1	IFNL3*	LMO1	MYCL	PDGFRB	PSMB9	RUNX1T1	SYK	VEGFB
ALDH1A1*	BRAF	CDC73	CYP2C19*	ESR1	FLT3	IGF1	LRP1B	MYCN	PDIA3	PSME1	RXRA	SYNE1	VHL
ALK	BRCA1	CDH1	CYP2C8*	ESR2	FLT4	IGF1R	LYN	MYD88	PGF	PSME2	SDHA	TAF1	WT1
AMER1	BRCA2	CDK1	CYP2D6	ETV1	FOXL2	IGF2	MALT1	NAT2*	PHOX2B	PSME3	SDHB	TAP1	XIAP
APC	BRD4	CDK12	CYP2E1*	ETV4	FOXP1	IKBKB	MAP2K1	NBN	PIK3C2B	PTCH1	SDHC	TAP2	XPO1
AR	BRIP1	CDK2	CYP3A4*	EZH2	FRG1	IKBKE	MAP2K2	NEFH	PIK3C2G	PTEN	SDHD	TAPBP	XRCC2
ARAF	BTG1	CDK4	CYP3A5*	FAM46C	FUBP1	IKZF1	MAP2K4	NF1	PIK3C3	PTGS2	SERPINB3	TBX3	ZNF217
ARID1A	BTG2*	CDK5	DAXX	FANCA	GATA1	IL6	MAP3K1	NF2	PIK3CA	PTPN11	SERPINB4	TEK	
ARID1B	BTK	CDK6	DCUN1D1	FANCC	GATA2	IL7R	MAP3K7	NFE2L2	PIK3CB	PTPRD	SETD2	TERT	
ARID2	BUB1B	CDK7	DDR2	FANCD2	GATA3	INPP4B	MAPK1	NFKB1	PIK3CD	PTPRT	SF3B1	TET1	
ASXL1	CALR	CDK8	DICER1	FANCE	GNA11	INSR	MAPK3	NFKBIA	PIK3CG	RAC1	SGK1	TET2	
ATM	CANX	CDK9	DNMT3A	FANCF	GNA13	IRF4	MAX	NKX2-1	PIK3R1	RAD50	SH2D1A	TGFBR2	
ATR	CARD11	CDKN1A	DOT1L	FANCG	GNAQ	IRS1	MCL1	NOTCH1	PIK3R2	RAD51	SLC19A1*	TMSB4X*	
ATRX	CASP8	CDKN1B	DPYD	FANCL	GNAS	IRS2	MDM2	NOTCH2	PIK3R3	RAD51B	SLC22A2	TNF	
AURKA	CBFB	CDKN2A	DTX1	FAS	GREM1	JAK1	MDM4	NOTCH3	PIM1	RAD51C	SLCO1B1	TNFAIP3	

*Analysis of copy number alteration not available.

Table 2

Fusion genes of ACTOnco®+ assay. ACTOnco®+ assay identifies 31 fusion genes from RNA.

ABL1	ALK	BCR	BRAF	CD74	ERG	ESR1	ETV1	ETV4	ETV5
ETV6	EZR	FGFR1	FGFR2	FGFR3	KMT2A (MLL)	MET	NRG1	NTRK1	NTRK2
NTRK3	NUTM1	PDGFRA	PDGFRB	RARA	RET	ROS1	RSPO2	SDC4	SLC34A2
TMPRSS2									

Figure 1. The next generation sequencing (NGS) results of the left humeral metastasis tumor biopsy. The NGS results showed the *FANCA* Q1307fs (c.3918dupT) that caused truncated loss-of-function *FANCA* protein.

Therefore, the patient started to use olaparib combined with low-dose cisplatin (30 mg/m², every 4 weeks) therapy in December 2019. Significant reduction in the tumor marker level in 1 month (PIVKA-II from 17,395 to 411 ng/dL) and follow-up CT scan showed stable disease (Figures 2 and 3). The patient experienced grade 1 nausea without other severe adverse events during the cancer treatment. Her tumor did not progress until December 2020 with a progression-free survival of 12 months.

3. Discussion

The case with heavily treated, metastatic, *FANCA*-mutated HCC, had stable disease to the 12-month combination treatment of olaparib and low-dose cisplatin. Our experience with this case suggested that PARP inhibitor may be a potential therapeutic option for *FANCA* mutation; PARP inhibitor combined with cisplatin may lead to synergistic efficacy with tolerable toxicity; and DDR gene mutation may respond to PARP inhibitor in HCC.
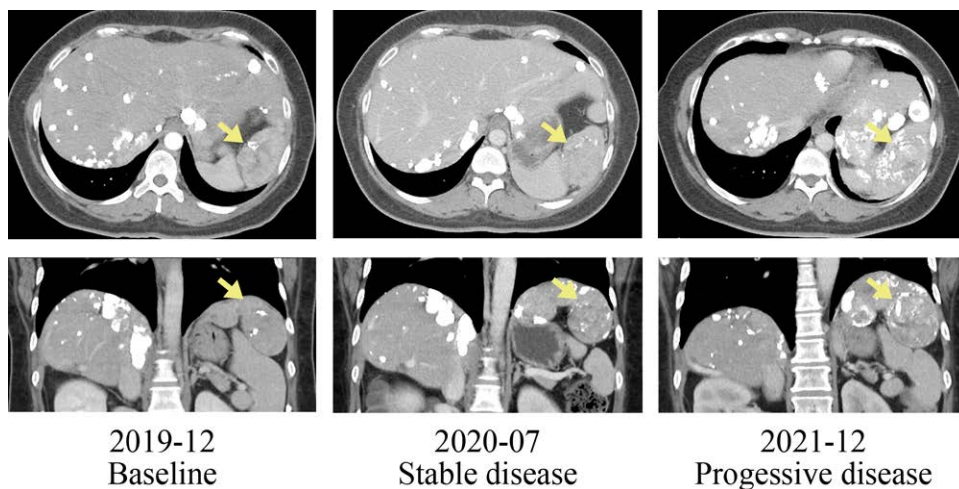

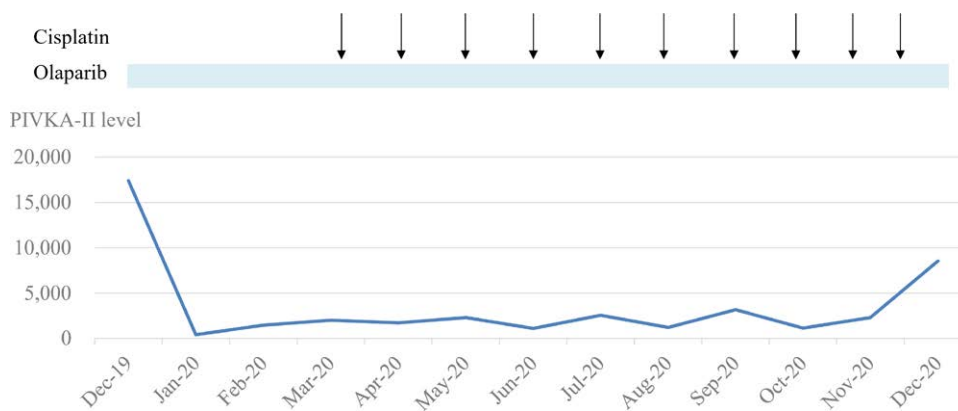**Figure 2.** Computerized tomography scan before and after treatment.

Figure 3. The dynamic change of tumor marker level (PIVKA-II).

The response for *FANCA* mutation to PARP inhibitor is not clear because of limited data. In a phase 2 clinical trial (TRITON2), 2 cases of metastatic castration-resistant prostate cancer patients with *FANCA* homozygous deletion responded to rucaparib (1 partial response and 1 stable disease).[9] Another phase 2 study of olaparib for patients with metastatic castration-resistant prostate cancer, revealed 3 patients with homozygous deletion of *FANCA*, 1 of which had partial response.[10] In yet another phase 2 study (TBCRC 048), metastatic breast cancer demonstrated 1 case of somatic *FANCA* mutation achieved stable disease with olaparib treatment.[11] A study enrolling high-grade serous ovarian cancer harboring DDR gene mutation, with the exception of BRCA, showed better response to PARP inhibitors compared with those harboring wild-type DDR gene. *FANCA* mutation is presented in 1 patient of the DDR mutation group.[12] Based on our literature review, *FANCA* mutation is rare among cancers. Although several reports showed the *FANCA* mutation is sensitive to the treatment of PRAP inhibitor, the role of PARP inhibitor in *FANCA* mutation is still controversial so far.

Genomic instability score (GIS) is calculated based on the results of homologous recombination repair mutation to predict the efficacy of PAPR inhibitor. In a phase 3 PAOLA-1/ENGOT-ov25 (NCT02477644) trial, GIS ≥ 42 was found to predict better PARP inhibitor efficacy. However, the mutation in *FANCA* gene present with a median GIS score of <42. This may explain the variable response of *FANCA* mutation to PARP inhibitor.[13]

Homologous recombination deficiency was known to render high response to the platinum agent that cross-link DNA strands leading to cell apoptosis. In addition, PARP inhibitor is being actively investigated with promising results in platinum-sensitive recurrent ovarian cancer. These provided a rationale to combine platinum agent with PARP inhibitor for the treatment of cancers with loss-of-function mutations in DDR genes. In fact, this combination has been found to improve progression-free survival in ovarian and breast cancers as opposed to those receiving chemotherapy alone.[14] Therefore, a phase 2 clinical trial to explore efficacy and safety of olaparib in combination with carboplatin and paclitaxel in ovarian cancer is ongoing [NCT01081951]. In this case, olaparib combined with a relative low dose of cisplatin showed durable response, presumably a favorable synergistic effect.

This report has several limitations. First, NGS data was obtained from tumor tissue. Therefore, whether the mutation is somatic or germline is unknown. Second, ACTOnco®+ was used for the NGS testing that provided a panel of 440 oncogenes, making the genes outside the panel and the score of genomic instability unavailable.

4. Conclusion

In conclusion, we report the first case of *FANCA*-mutated HCC that responded well to olaparib and low-dose cisplatin. This addressed the potential therapeutic role of DDR gene mutation in HCC and the possible synergistic effect of PARP inhibitor and cisplatin. These findings highlight areas where further investigation and effort are needed.

Author contributions

Conceived and designed the experiments: Y-HL, S-CC.
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Analyzed the data: K-CT, S-CC.
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Supervision: San-Chi Chen.
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