Case Report

Durable response to first-line PARP inhibition in *BRCA*-mutated metastatic cholangiocarcinoma: case report

Jarrod T. Smith[1]^, Shashank Sama[2], Vaia Florou[2], Christopher Nevala-Plagemann[2], Ignacio Garrido-Laguna[2]

[1]Department of Internal Medicine, University of Utah School of Medicine, Salt Lake City, UT, USA; [2]Department of Internal Medicine, Division of Oncology, Huntsman Cancer Institute, University of Utah School of Medicine, Salt Lake City, UT, USA

Contributions: (I) Conception and design: JT Smith, C Nevala-Plagemann, I Garrido-Laguna; (II) Administrative support: C Nevala-Plagemann, I Garrido-Laguna; (III) Provision of study materials or patients: I Garrido-Laguna; (IV) Collection and assembly of data: JT Smith, S Sama, I Garrido-Laguna; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Christopher Nevala-Plagemann, MD. Department of Internal Medicine, Division of Oncology, Huntsman Cancer Institute, University of Utah School of Medicine, Salt Lake City, UT, USA; Huntsman Cancer Institute, 2000 Circle of Hope, Room 2143, Salt Lake City, UT 84112, USA. Email: chris.nevala-plagemann@hci.utah.edu.

Background: Cholangiocarcinoma (CCA) is an increasingly prevalent malignancy worldwide, with poor outcomes even when diagnosed at an early stage. While recent trials have shown benefit from the addition of immunotherapy to standard-of-care chemotherapy, the improvement in overall survival is modest. Multiple novel therapies for advanced CCA targeting actionable genetic alterations have been approved in recent years; *BRCA1/2* mutations are identified in up to 5% of CCA patients and may be an additional target for novel treatment approaches. While *BRCA* mutations have been shown in clinical trials to predict response to poly(ADP-ribose) polymerase (PARP) inhibitors in several solid tumors including breast, ovarian, prostate, and pancreas, no similar large-scale trials have been published in CCA to date. We report here a durable response to PARP inhibitor monotherapy in *BRCA*-mutated extrahepatic CCA; to our knowledge, this is the second report of first-line PARP inhibitor monotherapy and the first reported use of the second-generation PARP inhibitor talazoparib in this setting.

Case Description: We report the case of a 79-year-old man with metastatic extrahepatic CCA harboring a somatic *BRCA1* mutation who declined chemotherapy and was instead treated in the first-line metastatic setting with the PARP inhibitor talazoparib; he experienced a complete radiographic response six months into treatment and has remained on talazoparib for over three years without evidence of disease recurrence.

Conclusions: This case adds to a growing list of retrospective studies supporting the clinical activity of PARP inhibitors in *BRCA*-mutated extrahepatic CCA. However, prospective data are clearly needed prior to adoption of this strategy in clinical practice. Fortunately, multiple trials investigating novel combination therapies utilizing PARP inhibitors in CCA are underway.

Keywords: Cholangiocarcinoma (CCA); *BRCA*; poly(ADP-ribose) polymerase inhibitor (PARP inhibitor); talazoparib; case report

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^ ORCID: 0000-0002-8455-331X.

Introduction

Background

Cholangiocarcinoma (CCA) is an increasingly prevalent malignancy worldwide (1). Outcomes in CCA remain poor even when diagnosed at an early stage, with five-year overall survival (OS) rates following surgery less than 20% (2). For patients with advanced or metastatic disease, treatment with combined gemcitabine and cisplatin has been the standard of care for over a decade (3). Recent trials comparing doublet *vs.* triplet chemotherapy regimens have failed to show a survival benefit with triplet therapy, suggesting the potential utility of cytotoxic agents may be maximized (4,5). The TOPAZ-1 trial recently showed benefit from the addition of the programmed-death ligand 1 inhibitor durvalumab to gemcitabine/cisplatin; however, the resulting improvement has been modest with a two-year OS rate of only 25% (6). Similar results with addition of pembrolizumab to gemcitabine/cisplatin were seen in the newly published phase 3 KEYNOTE-966 trial (7). Nonetheless, novel treatment options are needed to further improve outcomes in this disease.

In recent years, an expanded understanding of CCA pathobiology has revealed numerous actionable genomic alterations, leading to the approval of multiple targeted therapies for advanced CCA (8). For example, *FGFR2* fusions, which drive tumorigenesis in 10–20% of cases, can now be targeted in the second-line setting with one of three currently approved FGFR inhibitors (9). These agents include pemigatinib, which demonstrated an overall response rate (ORR) of 36% [95% computed tomography (CI): 27–45%] (10); and futibatinib, an irreversible FGFR2 inhibitor active against acquired resistance mutations, which showed an ORR of 42% (95% CI: 32–52%) (11). Another example is ivosidenib, an oral IDH1 inhibitor approved for CCA patients harboring *IDH1* mutations based on the ClarIDHy trial which showed a median OS of 10.3 months with ivosidenib compared to 7.5 months with placebo (HR 0.79; 95% CI: 0.56–1.12) (12). Additionally, several drugs with histology-agnostic approvals are being leveraged in CCA treatment. These include dabrafenib/trametinib for tumors with *BRAF* V600E mutations based on the phase II basket trial ROAR, which included 43 CCA patients and showed an ORR 47% (13); larotrectinib (14); and entrectinib for tumors harboring *NTRK* fusions (15); HER2-targeted therapies (16); targeting of *RET* mutations (17); and immunotherapy for patients with mismatch repair deficiency or an elevated tumor mutational burden (18,19).

Highlight box

Key findings

- A 79-year-old man with metastatic extrahepatic cholangiocarcinoma (CCA) harboring a somatic *BRCA1* mutation was treated in the first-line setting with the poly(ADP-ribose) polymerase (PARP) inhibitor talazoparib.
- He experienced a complete radiographic response six months into treatment and has remained on talazoparib for over three years without disease recurrence.

What is known and what is new?

- Clinical trials have shown that *BRCA* mutations predict response to PARP inhibitors in several solid tumors including breast, ovarian, prostate and pancreas. However, no similar large-scale trials have been published in CCA.
- The exceptional response to talazoparib in a patient with metastatic, *BRCA1*-mutated extrahepatic CCA reported here is the first reported use of this agent in the frontline setting.

What is the implication, and what should change now?

- This case adds to a growing list of retrospective studies supporting the utility of PARP inhibitors in *BRCA*-mutated CCA. However, prospective data are currently lacking.
- Fortunately, multiple prospective studies are underway, and their results are eagerly awaited.

Rationale and knowledge gap

BRCA1/2 mutations, identified in 3–5% of CCA patients, may be an additional target for novel treatment approaches (20). These mutations have been shown to predict response to treatment with poly(ADP-ribose) polymerase (PARP) inhibitors in several solid tumors including breast, ovarian, prostate and pancreas (21-25). However, no similar prospective data exist for the use of PARP inhibitors (PARPi) in *BRCA*-mutated CCA.

Objective

In this case report, we describe an exceptional frontline response using the PARPi talazoparib as monotherapy in an extrahepatic CCA patient harboring a somatic *BRCA1* loss-of-function mutation. We present this article in accordance with the CARE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-425/rc).

Case presentation

A 79-year-old man presented with painless jaundice and

was found to have a bile duct malignancy for which he underwent pancreaticoduodenectomy. Surgical pathology showed a stage IIB, G2 moderately differentiated adenocarcinoma of the distal common bile duct. Adjuvant therapy was deferred due to poor performance status (PS). Imaging obtained one year after surgery showed retroperitoneal lymphadenopathy (four index lesions, with the largest being an interaortocaval node measuring 13.8 mm × 40.9 mm), and a subsequent biopsy confirmed recurrent adenocarcinoma. Next-generation sequencing including a panel of 324 genes revealed a pathogenic *BRCA1* loss-of-function mutation. Additional genetic alterations included *STK11* loss of exon 1, *CDK6* amplification, *MYC* amplification, *ACVR1b* W122*, *MAP2K4* D324fs*16, RAD21 amplification, and *TP53* loss of exons 2–3. The tumor exhibited microsatellite stability and TMB was intermediate at 6 mutations per megabase. Subsequent germline testing was negative. Cytotoxic chemotherapy was offered, but the patient instead chose to pursue off-label talazoparib due to concerns about chemotherapy tolerability.

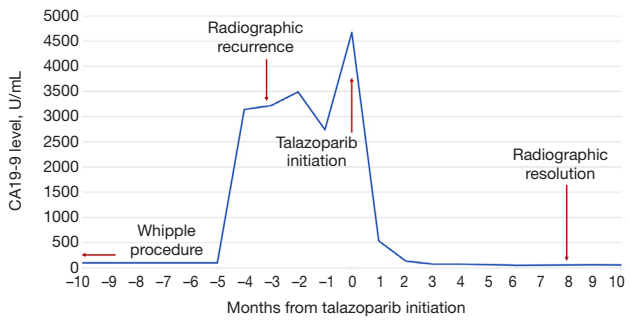

Figure 1 CA19-9 response to talazoparib. Change in CA19-9 levels in U/mL (y-axis) over time in months (x-axis) with clinically significant events denoted with red arrows. CA19-9, carbohydrate antigen 19-9.

Within a month of talazoparib initiation, his carbohydrate antigen 19-9 (CA19-9) level dropped from 4,673 to 534 U/mL (*Figure 1*). Re-staging scans at two months showed decreased retroperitoneal lymphadenopathy. CA19-9 reached a nadir of 50 U/mL six months into treatment and CT scans at that time showed a complete radiographic response (*Figure 2*). The patient has remained on talazoparib and is now over three years out from his recurrence with no evidence of disease on most recent imaging. Treatment has been well tolerated apart from grade 2 anemia requiring a dose reduction to 0.75 mg daily.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

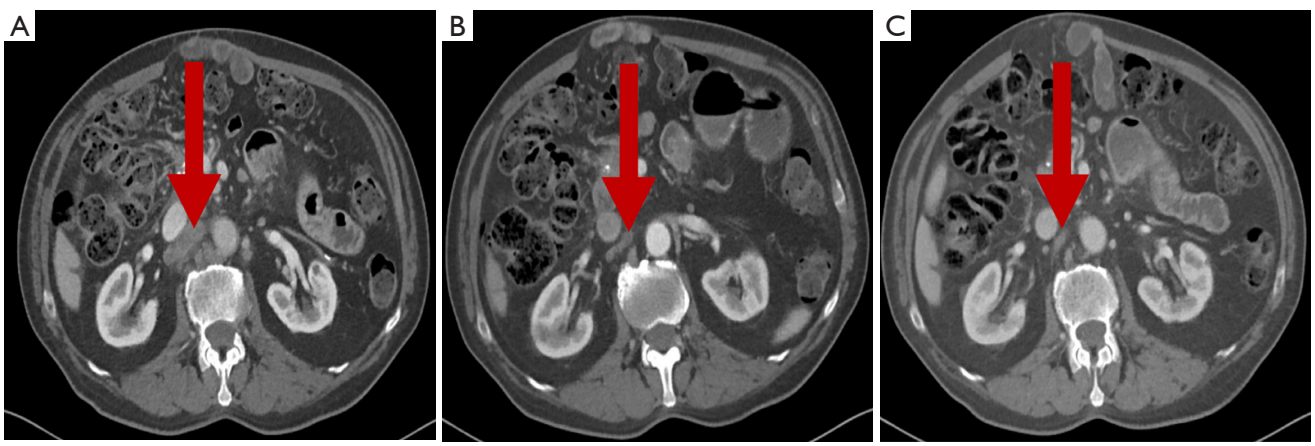

Figure 2 Radiographic response to talazoparib. Selected axial images from serial computed tomography scans demonstrating complete radiographic response. (A) Representative image of retroperitoneal lymphadenopathy (interaortocaval node measuring 13.8 mm × 40.9 mm, red arrow) 1 month prior to talazoparib. (B) Decrease in lymphadenopathy to 7.2 mm in short-axis diameter (red arrow) after 4 months of talazoparib. (C) Resolution of retroperitoneal lymphadenopathy (red arrow) without evidence of disease in the chest, abdomen, or pelvis after 8 months of talazoparib.

Discussion

To our knowledge, this is the second report of frontline PARPi monotherapy in advanced *BRCA*-mutated extrahepatic CCA, and the first reported use of the second-generation PARPi talazoparib in this setting (26). This case has significant clinical relevance as CCA frequently harbors somatic mutations in *BRCA1* and *BRCA2*. In one study of 1,292 CCA patients, *BRCA1/2* mutations were present in 3.6% of cases, with equal distribution across age groups, gender, and primary tumor site [intrahepatic (iCCA), extrahepatic (eCCA) or gall bladder] (27). Another study of iCCA patients similarly found a 4% prevalence of both *BRCA1* and *BRCA2* mutations (28). Notably, *BRCA* mutations in biliary tract cancers appear to be more commonly somatic than germline (29).

The *BRCA* tumor-suppressor genes encode proteins that are integral to repairing double-strand DNA breaks via homologous recombination repair (HRR). The PARP proteins (PARP1 and PARP2) also play a role in DNA damage response (DDR) and are thought to be necessary to maintain cell growth and division in the presence of *BRCA* mutations. PARP1 binds to single-strand DNA breaks and adds a poly(ADP-ribose) (PAR) chain, a process termed PARylation, which attracts additional DDR proteins to the lesion. PARPi, of which talazoparib is the most potent, function by binding to and trapping PARP1, preventing progression of the replication fork. Malignant cells with intact BRCA proteins can employ HRR to overcome this insult. However, *BRCA*-mutant cells must resort to alternative, less accurate DNA repair mechanisms which may introduce lethal genomic alterations; the resulting cytotoxicity is termed synthetic lethality (30). The therapeutic potential of synthetic lethality has now been evaluated in several trials. In 2015, a phase II basket trial demonstrated efficacy with the PARPi olaparib in germline *BRCA1/2*-mutated ovarian, breast, pancreatic, and prostate cancers (21). The POLO trial evaluated maintenance olaparib after platinum-based chemotherapy in germline *BRCA*-mutated advanced pancreatic cancer. Olaparib improved progression-free survival (PFS) compared to placebo (7.4 *vs.* 3.8 months; hazard ratio (HR) 0.53; 95% CI: 0.35–0.82) but failed to improve OS (25). In the SOLO-2 trial, maintenance olaparib improved PFS in *BRCA*-mutated ovarian cancer (HR 0.30; 95% CI: 0.22–0.41) (22). Similar outcomes have been shown with maintenance niraparib in ovarian cancer patients with HRR deficiency (23). Lastly, the PROfound trial led to the approval of olaparib in metastatic castration-resistant prostate cancer with alterations in HRR genes after demonstrating improvement in PFS when compared to enzalutamide or abiraterone (HR 0.34; 95% CI: 0.25–0.47) (24).

Unfortunately, no similar large-scale clinical trials of PARPi in CCA have been published to date. Evidence for the efficacy of PARPi in *BRCA*-mutated CCA remains at the level of case reports or small case series. In 2016, a report of a patient with gallbladder cancer responsive to olaparib was published (31). Another study reported four cases of *BRCA*-mutated CCA treated with a PARPi; this series was notable for an exceptional 42.5-month response in a patient with advanced CCA in the third-line setting (32). Yet another report described a partial response to olaparib in a *BRCA2*-mutated iCCA patient refractory to several courses of liver-directed therapy and chemotherapy (33). More recently, a 2019 study described the sequencing results of 357 primary liver cancers and found *BRCA1/2* mutations in 4.8% (34). Eight of these patients (seven iCCA and one combined hepatocellular carcinoma-CCA) were treated with olaparib in the third-line or greater setting. Three patients achieved a partial response and two had stable disease. Rarely has PARPi monotherapy been delivered in the frontline, with the only other described case beyond that reported here being a patient with *BRCA2*-mutated eCCA who refused adjuvant chemotherapy and was treated with olaparib monotherapy after recurrence, attaining an OS of 27 months (26).

Although the responses to PARPi in the *BRCA*-mutated patient described in this report and others are encouraging, prospective data are clearly needed. One early-phase trial has evaluated combination talazoparib and carboplatin in patients with germline *BRCA2* mutations including CCA patients; responses were observed, however the combination led to significant hematologic toxicity (35). Fortunately, multiple trials investigating novel combination therapies utilizing PARPi in CCA patients are underway (*Table 1*). These trials include combination of immunotherapy with PARPi as well as trials evaluating the use of PARPi in patients with genetic alterations other than *BRCA1/2*.

Conclusions

The case described here highlights an exceptional response to frontline talazoparib in a patient with metastatic extrahepatic CCA harboring a somatic *BRCA1* mutation for whom cytotoxic therapy was not felt to be an option. This case adds to a growing list of retrospective studies supporting the clinical activity of PARPi in this disease, and

Table 1 Ongoing trials of PARP inhibitors in cholangiocarcinoma

Trial	Phase	Treatment arms	Primary endpoint(s)	ClinicalTrials.gov identifier
Testing Olaparib and AZD6738 in *IDH1* and *IDH2* Mutant Tumors	II	Combined olaparib and ceralasertib (AZD6738) in two cohorts: CCA and other solid malignant tumors	Objective response rate	NCT03878095
Study of Olaparib and Durvalumab in *IDH*-Mutated Solid Tumors	II	Combined olaparib and durvalumab in three cohorts: *IDH*-mutated glioma, *IDH*-mutated CCA, all other *IDH*-mutated solid tumors	Objective response rate and overall disease control rate at 3 years	NCT03991832
Niraparib Combined with Anlotinib in Homologous Recombination Repair Gene-mutated Advanced Solid Tumors	I	Niraparib-anlotinib combination therapy	Dose-limiting toxicity and maximum tolerated dose	NCT04764084
A Trial of Niraparib in *BAP1* and Other DNA Damage Response Deficient Neoplasms	I	Niraparib monotherapy in two cohorts: mesothelioma, uveal melanoma, renal cell carcinoma, and CCA; and patients with known DNA damage response mutations of any malignancy except prostate	Objective response rate	NCT03207347
Olaparib in Treating Patients With Advanced Glioma, CCA, or Solid Tumors With *IDH1* or *IDH2* Mutations	I	Olaparib monotherapy in metastatic glioma, CCA, or other *IDH*-mutated solid tumors	Overall response rate	NCT03212274

IDH, isocitrate dehydrogenase; CCA, cholangiocarcinoma; *BAP1*, BRCA1 associated protein-1.

suggests PARPi may be useful for similar patients who cannot tolerate chemotherapy. The results of ongoing prospective studies confirming the effect of PARPi combination therapies in this population are eagerly awaited.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-425/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-425/coif). V.F. reports consultant/advisory roles with Deciphera and Incyte. I.G.L. reports receipt of institutional grants from Novartis, Bayer, Britsol Myers Squibb, Pfizer, MedImmune, Lilly, Incyte, GlaxoSmithKline, Tolero Pharmaceuticals, BridgeBio Pharma, Jacobio, Repare Therapeutics, Sumitomo Dainippon Pharma Oncology, Revolution Medicines, and Yingli Pharma; and consulting fees from SOTIO, Kanaph,

Jazz, and OncXer. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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