Olaparib Efficacy in Malignancies not Typically Associated with Homologous Repair Deficiency

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Abstract

Purpose: There is a strong rationale for targeting poly(ADP-ribose) polymerase (PARP), which is responsible for repairing single-stranded deoxyribonucleic acid (DNA) breaks, in tumors with HRD including deficiencies in BRCA1/2 and associated proteins. PARP inhibitors are FDA approved for use in ovarian, breast, prostate, and pancreatic cancers with BRCA1/2 germline mutations. HRD has been reported at low frequencies in a variety of other malignancies and we sought to determine the efficacy of olaparib in patients harboring these tumors.

Patients: We present three patients with BRCA1, BRCA2, and ATM mutations in malignancies not generally associated with these mutations who derived clinical benefit from olaparib monotherapy. Patient 1 with BRCA1 mutated neuroendocrine tumor achieved CR for 5 months before ultimately progressing. Patient 2 shows stable disease nine months after starting olaparib monotherapy for ATM mutated cholangiocarcinoma. Patient 3 was recently started on olaparib for BRCA1 mutated gastric carcinoma and has stable disease at his 6-month follow-up.

Conclusion: These cases demonstrate that olaparib can confer clinical benefit across a broader range of HRR altered malignancies, including those with somatic mutations.

Key Words: Autism, Neuropsychology, Neurophysiology

Abbreviations

- 5-FU: 5-fluorouracil
- ATM: ataxia-telangiectasia mutated
- BRCA: BReast CAncer gene
- CAPTEM: capecitabine plus temozolamide
- CI: confidence interval
- Cm: centimeter
- CT: computerized tomography
- DNA: deoxyribonucleic acid
- ECOG: Eastern Cooperative Oncology Group
- EGD: esophagogastroduodenoscopy
- FDA: Federal Drug Administration
- FOLFOX: folinic acid, fluorouracil, oxaliplatin
- HRD: homologous recombination deficiency
- MRCP: magnetic resonance cholangiopancreatography
- MRI: magnetic resonance imaging
- ORR: objective response rate
- OS: overall survival
- PARP: poly(ADP-ribose) polymerase
- PARPi: poly(ADP-ribose) polymerase inhibitor
- PD-L1: programmed death ligand 1
- PET: positron emission tomography
- PFS: progression-free survival
- PI-RADS: Prostate Imaging Reporting and Data Systems
- VEGF: vascular endothelial growth factor

Introduction

Breast Cancer (BRCA) genes 1 and 2 were discovered by Hall and Wooster, respectively, in the 1990s.[1,2] Mutations in BRCA1, BRCA2, and other homologous recombination deficiencies (HRDs) are associated with increased risk of developing ovarian, [3] breast, [4] prostate, [5] and pancreatic cancers [6] . These mutations have been associated with lower overall survival (OS) in breast cancer patients [7] and higher Gleason scores in prostate cancer patients [8].

There is strong rationale for targeting poly(ADP-ribose) polymerase (PARP), which is responsible for repairing single-stranded deoxyribonucleic acid (DNA) breaks, in tumors deficient in double-strand DNA repair enzymes [9] . In 2014 the Federal Drug Administration (FDA) approved olaparib, a PARP inhibitor (PARPi), for the treatment of germline BRCA-mutant ovarian cancer in the fourth-line setting. This approval was based off phase 2 results showing olaparib extended progression-free survival (PFS) from 4.3 to 11.2 months [10] . Since then olaparib has been approved for maintenance of recurrent ovarian cancer (2017;SOLO2;germline or somatic), [11] HER2-negative breast cancer (2018;OlympiAD;germline), [12] maintenance of pancreatic cancer (2019;POLO;germline), [13] prostate cancer (2020; PROfound;germline or somatic), [14] first-line maintenance of ovarian cancer (2020;PAOLA-1;germline or somatic), [15] and castrate-resistant prostate cancer in combination with abiraterone and prednisone/prednisolone (2023;PROpel;germline or somatic) (Table 1).

BRCA1/2 mutations have been reported less frequency in other malignancies such as small bowel, [16] gastric, [17] gastric neuroendocrine, [18] cholangiocarcinoma, [19] cervical, [20] and colorectal cancers [21]. Here we discuss three patients

Table 1: Timeline of Approved Indications for Olaparib.

Diagnosis	Stage	Line of Therapy	Year FDA Approved	Mutation Type	Mutation	Trial
Ovarian Cancer	Advanced/metastatic	After 3+ prior lines	2014	Germline	BRCA	Study 19 NCT00753545
Ovarian Cancer	Recurrent	Maintenance After response to platinum-based chemotherapy	2017	Germline or Somatic	BRCA or HRD	SOLO2 NCT01874353
Breast Cancer	Advanced/metastatic HER2-negative	After chemotherapy	2018	Germline	BRCA	OlympiAD NCT02000622
Pancreatic Cancer	Advanced/metastatic	Maintenance After response to platinum-based chemotherapy	2019	Germline	BRCA	POLO NCT02184195
Prostate Cancer	Advanced/metastatic	After progression on therapy including novel hormonal agent	2020	Germline or Somatic	BRCA	PROfound NCT02987543
Ovarian Cancer	Advanced/metastatic	First line maintenance Combined with bevacizumab After response to platinum-based chemotherapy	2020	Germline or Somatic	HRD or BRCA	PAOLA-1 NCT02477644
Prostate Cancer	Advanced/metastatic	After progression on therapy including novel hormonal agent	2020	Germline or Somatic	HRD	PROfound NCT02987543
Breast Cancer	Early-stage HER-2 negative	Adjuvant After neoadjuvant or adjuvant chemotherapy	2022	Germline	BRCA	OlympiA NCT02032823
Prostate Cancer	Advanced/metastatic Castrate-resistant	Combined with abiraterone and prednisone	2023	Germline or Somatic	BRCA	PROpel NCT03732820

BRCA: BReast CAncer gene; HRR: homologous recombination repair

with malignancies less commonly associated with BRCA/HRD mutations - neuroendocrine tumor, cholangiocarcinoma, and gastric cancer, who derived clinical benefit from olaparib monotherapy. Two of the three patients had somatic (acquired) mutations in these genes.

Patient Case

Patient 1

An 82-year-old male presented after noticing a left-sided abdominal lump and computerized tomography (CT) scan of the abdomen and pelvis revealed metastatic disease to the lungs, liver, and prostatomegaly. A CT-guided liver biopsy in July 2022 revealed high-grade neuroendocrine carcinoma consistent with small cell. July 2022 positron emission tomography (PET) scan noted uptake in the left posterior lateral prostate gland, lungs, liver, and nodal metastatic disease. He received 6 cycles of carboplatin, etoposide, and durvalumab.

Surveillance PET scans September 2022 and November 2022 noted a near complete resolution of his disease with only uptake in the prostate. However, PET scan March 2023 revealed new metastatic disease in the lungs, liver, and retroperitoneal pelvic lymph nodes. He received 3 cycles of combination nivolumab and ipilimumab. May 2023 prostate biopsy confirmed small cell carcinoma. Subsequent PET scan July 2023 noted progressive metastases in liver, lungs, and lymph nodes as well as new sites in the left supraclavicular fossa. He was initiated on capecitabine plus temozolamide (CAPTEM). September 2023 PET scan showed an excellent response to therapy with isolated residual uptake in the liver.

Guardant360 testing returned with a germline mutation in the BRCA1 E23fs (C.68_69delAG). Due to significant fatigue he experienced from CAPTEM, in October 2023 he was started on olaparib monotherapy. December 2023 surveillance PET showed near complete resolution with only a small focus of uptake in the prostate. Tumor markers were also stabilized on this regimen.

Follow-up PET scan in March 2024 showed progression with multifocal FDG-avid hepatic lesions and olaparib was discontinued.

Patient 2

A 64-year-old male developed a pruritus full-body rash in March 2023 and was found to have transaminitis, hyperbilirubinemia, and new moderate-to-severe intrahepatic biliary dilation. CT scan showed an ill-defined infiltrative liver mass causing severe biliary obstruction, consistent with cholangiocarcinoma. Staging MRI and magnetic resonance cholangiopancreatography (MRCP) in May 2023 showed an enhancing mass in the porta pedis with marked left intrahepatic biliary dilation suggestive of cholangiocarcinoma.

During workup for liver transplant in July 2023 he was found to have biopsy-proven peritoneal metastasis. He received six cycles of cisplatin, gemcitabine, and durvalumab. Surveillance imaging December 8, 2023 noted improvement in biliary ductal dilation without measurable lesions in the liver or porta hepatis. His periportal lymph node and metastatic implants adjacent to the right colon were stable.

Due to exacerbation of pre-existing small fiber neuropathy and presence of a non-germline ataxia-telangiectasia mutation (ATM; ATM M2728fs) he was switched to olaparib in January 2024. Surveillance CT scan September 10, 2024 found stable disease in his peritoneal implants and hilar lesion.

Patient 3

A 56-year-old male presented with 30-pound weight loss over several months. Upon presentation June 2017 workup revealed hemoglobin 8.7, platelets 575, iron saturation of 5%, and ferritin 39. CT scan showed a 7.8 centimeter (cm) exophytic mass at the gastroesophageal junction, a liver lesion, and enlarged pericardial, periaortic, and peripancreatic lymph nodes with biopsy confirming poorly differentiated gastric adenocarcinoma.

July 2017 PET scan noted a distant left para-aortic lymph node. Given that the area of disease was all within a radiation field, the decision was made to pursue concurrent carboplatin, paclitaxel, and radiation via the CROSS protocol. He completed therapy August 2017. PET scan October 2017 showed remarkable response within the treatment area, however, he developed new metastatic disease in the right cervical, right hilum, retrocrural, and retroperitoneal lymph nodes.

He completed six cycles of palliative folinic acid, fluorouracil, and oxaliplatin (FOLFOX). February 2018 CT scan was without evidence of metastatic disease. He was transitioned to 5-fluorouracil (5-FU) maintenance.

August 2018 PET scan showed further lymphadenopathy in the neck, chest, abdomen, and pelvis. He was started on pembrolizumab. PET scan January 2019 reported resolution of lymphadenopathy and was without evidence of disease. Surveillance PET scan October 2023 noted recurrence in the right supraclavicular and mediastinal area. He received 8 cycles of FOLFOX with dose-reduced oxaliplatin for persistent neuropathy. PET scan showed continued improvement and he was transitioned to maintenance 5-FU February 2024.

Subsequent imaging showed a slow progression of his disease. He was noted to have a non-germline BRCA1 deletion of exon 8-12 and in May 2024 was started on olaparib. At his clinic appointment six months later the patient reported improvement in his fatigue and CT CAP showed partial response to treatment.

Discussion

Pre-clinical and early clinical studies of olaparib suggested that responding patients required BRCA1/2 germline (inherited) mutations and loss of heterozygosity in the tumor [22,23]. Initial approvals for olaparib in ovarian, breast, and pancreatic cancer required the presence of germline BRCA1/2 mutations. However, clinical studies in ovarian (PAOLA-1) and prostate (PROfound) cancer have since demonstrated clinical activity of single agent olaparib in tumors with somatic (acquired) BRCA1/2 mutations (Table 1) [14,15]. Olaparib also conferred benefit to prostate cancers with somatic alterations in a wide range of HRR proteins leading to FDA approval for this indication (PROfound) [14].

There has been a paucity of data evaluating if olaparib clinical outcomes differ by germline or somatic mutation status. Retrospective analysis of Study 19 found that a small group of somatic BRCA mutations had a similar PFS benefit to the germline BRCA cohort [10]. The open-label, multicenter ORZORA study found the median PFS in somatic BRCA mutated ovarian cancer similar to that of the overall BRCA-mutant population [24]. In a series of seven breast cancer patients treated off-trial with olaparib for somatic BRCA1/2 mutations median PFS was 6.5 months [25]. In an exploratory analysis, somatic and germline BRCA1/2 mutated prostate cancer tumors responded in similar rates to rucaparib (ORR 52% vs 50%) although PSA response was significantly improved in the germline mutated cohort [26]. (Table 2) summaries approved PARP inhibitors grouped by malignancy.

These studies indicate that olaparib has clinical activity in somatically altered BRCA proteins among tumor types that already are known to respond to olaparib with germline BRCA mutations. Among these tumor types BRCA heterozygosity was not enough to overcome the accumulated single strand DNA damage that olaparib induces. However, it is not clear if BRCA heterozygosity in other tumor types or with somatic non-BRCA HRR protein alterations are sensitive to olaparib.

Here we present three patients with alterations in the HRR proteins BRCA1, BRCA2, and ATM in malignancies not typically associated with HRR mutations who derived clinical benefit from olaparib monotherapy. Patients reported symptomatic improvement in their disease shortly after starting therapy. Patient 1 was diagnosed with a germline BRCA1 mutation in neuroendocrine carcinoma and progressed after five months on olaparib monotherapy. Patient 2 had a somatic ATM mutation in cholangiocarcinoma and continues to have stable disease after nine months of treatment with olaparib. Patient 3 had a somatic mutation of BRCA1 in gastric cancer and had stable disease at six months after initiation of treatment. These results indicate that the clinical benefit of olaparib in somatic HRR mutations can extend to malignancies not typically associated with HRR aberrations. Olaparib also had clinical activity in a rare patient with germline BRCA1 mutated neuroendocrine tumor, again supporting the notion that efficacy of PARPi can be extended to non-traditional tumors but this time with germline BRCA alterations. We had previously reported on the first NTRK altered

Table 2: Approved PARP Inhibitors by Diagnosis.

Diagnosis	Stage	Mutation	Approved PARP Inhibitors
Ovarian Cancer	Advanced/metastatic		Olaparib +/- bevacizumab Niraparib Rucaparib
Ovarian Cancer	Recurrent		Olaparib Rucaparib
Breast Cancer	Early-stage HER-2 negative	BRCA-mutated	Olaparib
Breast Cancer	Advanced/metastatic HER2-negative	BRCA-mutated	Olaparib Talazoparib
Pancreatic Cancer	Advanced/metastatic	BRCA-mutated	Olaparib
Prostate Cancer	Advanced/metastatic Castrate-resistant	BRCA or HRR mutated	Olaparib Rucaparib
Prostate Cancer	Advanced/metastatic Castrate-resistant	BRCA or HRR mutated	Olaparib + abiraterone Niraparib + abiraterone Talazoparib + enzalutamide

neuroendocrine tumor patient responsive to a TRK targeting agent reinforcing the need for genomic analysis of all advanced solid tumor malignancies as occasional actionable mutations can be found [27].

Our cohort only included patients whose tumors emanated from the gastrointestinal tract. Early phase clinical studies and case reports have reported on activity of PARPi among GI based tumors with HRR alterations, however each of these utilized PARPi in combination with other agents, including VEGF and checkpoint inhibitors [28-30]. We report on the single agent activity of olaparib in these types of patients. Another study reported the absence of PARPi activity among a range of tumors with ATM mutations [31]. Patient 2 in our study has a somatic ATM mutation and has had protracted benefit from single agent olaparib.

This case series is limited by a small cohort of patients with varying diagnoses. However, all three patients with BRCA or ATM mutations derived benefit from olaparib regardless of disease diagnosis or germline versus somatic mutation status. Taken together these findings suggest that even among tumors with heterozygous mutations of DNA repair enzymes PARPi may inhibit tumor repair and replication resulting in clinical benefit. Further research on PARPi in somatic mutations is needed to better characterize the mechanism of action and magnitude of benefit, but accumulating evidence supports use of PARPi in these patients [32].

Conclusion

Systemic genomic profiling has demonstrated that many approved and investigational biomarker targets are present across tumor types at low frequencies. Here we report a case series of single agent activity of olaparib in gastrointestinal malignancies. To our knowledge this is the first report to describe olaparib monotherapy in this patient population. Additionally while prior studies showed a lack of PARPi in ATM mutations, our patient derived clinical benefit and continues to have stable disease after nine months on therapy. This series of patients demonstrates the clinical benefit of PARPi across tumor types regardless of mutation inheritance pattern of their targetable mutation.

Declarations

Ethics approval and consent to participate: This report did not meet institutional criteria for IRB approval. The patient whose images are included provided consent for photo release.

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Authors' Contributions

DB provided clinical review, data interpretation, and drafted and reviewed all versions of the manuscript

DS conceptualized the study, provided data interpretation, editing, oversight, and reviewed all versions of the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Context Summary

Key objective: Is olaparib effective in malignancies not typically associated with homologous repair deficiency (HRD)?

Knowledge generated: This case series demonstrates clinical benefit of olaparib in malignancies not typically associated with BRCA or other homologous recombinant repair (HRR) mutations, including neuroendocrine tumors, cholangiocarcinoma, and gastric carcinoma. Patients whose tumors only had somatic mutations also derived clinical benefit from single agent olaparib.

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