Review Article

Biliary tract cancer and genomic alterations in homologous recombinant deficiency: exploiting synthetic lethality with PARP inhibitors

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Abstract: Biliary tract cancers (BTC) are a group of rare, chemoresistant solid tumor malignancies that arise from the bile ducts. BTC are typically associated with poor outcomes. Most patients present with advanced disease, where treatment is palliative with platinum based cytotoxic therapy. Response to chemotherapy is variable with limited duration of response. A subset of patients that will receive durable and meaningful responses to platinum-based chemotherapy is deemed to be platinum sensitive. The availability and implementation of next-generation sequencing allowed genomic profiling of BTC, which have identified potential targetable somatic genetic aberrations, which include kinases (FGFR, BRAF, ALK, ERBB2), oncogenes (IDH1/2, CCND1) and tumor suppressor genes, including germline or somatic mutations involved in DNA damage response (DDR) genes. These genes include, but are not limited to: *ATM*, *ATR*, *BRCA1/2*, *RAD51*, *PALB2*, *PTEN*, *FANC*, *NBN*, *EMSY*, *MRE11*, *ARID1A*. In BTC, alterations in DDR genes are identified in up to 20% of patients, with a higher proportion identified in those with extrahepatic cholangiocarcinoma. Patients harboring mutations exhibit varying patterns of clinical behavior and response to therapy. The presence of these mutations typically predicts for susceptibility to DNA damaging chemotherapy, such as platinum agents.

Keywords: Homologous recombinant deficiency; PARP; biliary tract cancer (BTC); cholangiocarcinoma

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Introduction

Biliary tract cancers (BTC) are a group of rare, chemoresistant solid tumor malignancies that arise from the bile ducts (1-3). BTC are typically associated with poor outcomes. Most patients present with advanced disease, where treatment is palliative with platinum based cytotoxic therapy (4). Response to chemotherapy is variable with limited duration of response. A subset of patients that will receive durable and meaningful responses to platinum-based chemotherapy is deemed to be platinum sensitive. The availability and implementation of next-generation sequencing allowed genomic profiling of BTC, which have identified potential targetable somatic genetic aberrations, which include kinases (FGFR, BRAF, ALK, ERBB2), oncogenes (IDH1/2, CCND1) and tumor suppressor genes, including germline or somatic mutations involved in DNA damage response (DDR) genes (5-7). These genes include, but are not limited to: *ATM*, *ATR*, *BRCA1/2*, *RAD51*, *PALB2*, *PTEN*, *FANC*, *NBN*, *EMSY*, *MRE11*, *ARID1A*. In BTC, alterations in DDR genes are identified in up to 20% of patients, with a higher proportion identified in those with extrahepatic cholangiocarcinoma. Patients harboring

mutations exhibit varying patterns of clinical behavior and response to therapy. The presence of these mutations typically predicts for susceptibility to DNA damaging chemotherapy, such as platinum agents.

Homologous recombination deficiency and the role of PARP in DNA repair

The PARP family of proteins is comprised of 17 members that catalyze poly (ADP-ribosyl)ation of proteins by promoting the synthesis and transfer of negatively charged ADP-ribose polyes (8-10). The major role of PARP1 is in DNA repair. PARP1 is the predominant isoform of the PARP family, accounting for up to 80% of PARP activity (11). PARP2, which exhibits a high degree of structural similarity to PARP1, is also able to promote PARP activity, especially in the absence of PARP1 (12,13). PARP1 & PARP2 are the only members of the PARP family known to be involved in DNA repair (14-17). Binding to DNA strand interruptions stimulate the catalytic activity of PARP1 and PARP2 leading to poly (ADP-ribosyl)ation of key DNA repair proteins (15).

Synthetic lethality of PARP inhibition in homologous recombinant deficient (HRD) cancer cells

In order to combat the detrimental effects of DNA damage, mammalian cells have evolved a complex network of interconnected pathways, proteins as associated with DNA damage response. Homologous recombinant repair (HRR) and non-homologous end joining are the two major pathways involved in the repair of double strand breaks in eukaryotic cells (18-21). BRCA1 and BRCA2 are two DNA repair proteins that serve a critical role in DNA repair through homologous recombination, where the mutation of this gene results in HRD. Substantial pre-clinical and clinical evidence have demonstrated sensitivity of BRCA1 and BRCA2 deficient cancers to PARP1/2 inhibition. A collaborative multicenter retrospective study defined the clinical characteristics of BTC patients with somatic and/or germline BRCA mutations. Eighteen patients were identified, with 5 patients that harbored germline BRCA1/2 mutations and thirteen with somatic alterations (22). Thirteen patients received platinum-based therapy, with four who were treated with poly ADP ribose polymerase (PARP) inhibitors. The median overall survival for patients with stage I/II in this study was 40.3 months [95% confidence interval (CI), 6.73–108.15] and with stages III/IV was 25 months (95% CI, 15.23–40.57) (22). In this limited sample size, patients whose tumors expressed a BRCA1/2 mutation experienced a near doubling in survival compared to historical outcomes (4), thus representing a distinct phenotype where tumor genotype can impact treatment response and should be incorporated into treatment consideration. While DNA damaging chemotherapy represents one potential strategy aimed at targeted tumors with genetic alterations in HRR, or HRD, side effects related to chemotherapy including cytopenia, peripheral neuropathy and fatigue limits its exposure and duration.

PARP inhibition represents one approach in targeting tumors with deficiencies in DNA repair mechanisms. PARP enzymes are essential for repairing DNA single strand breaks (SSBs) (23-25). PARP1/2 inhibition suppresses base excision repair and results in the accumulation of single-strand breaks (SSBs), which are then converted to the more serious DNA double strand breaks (DSBs) during the process of DNA replication. During the process of cell division, DSBs can be efficiently repaired in normal cells by homologous recombination repair (HR). Tumors with HRD, such as ovarian cancers in patients with BRCA1/2 mutations, cannot accurately repair the DNA damage, where the accumulation of double strand breaks are either repaired by non-homologous end joining pathway or are left unrepaired, leading to genomic instability and apoptotic cell death (26). PARP1 also has a direct role in the HRR pathway at replication forks (27). This dual role of PARP1 in DNA repair and the HRR pathway has been postulated as an important factor in the profound activity of PARP1/2 inhibitors in HRD cancer cells (28). In such tumor types, PARP inhibitors may offer a potentially efficacious and less toxic cancer treatment compared with currently available chemotherapy regimens.

In 2005, two landmark pre-clinical studies showed that PARP1/2 inhibitors have profound activity in cancer cells without functional BRCA1 or BRCA2 (29,30). In subsequent phase I and II trials, PARP1/2 inhibitors were highly active in ovarian, breast and prostate cancers with germline BRCA inactivating mutations (23,25,31-33). The potency of PARP 1/2 inhibitors in BRCA-deficient cells arises from a synthetic lethality, where the combination of multiple genomic alterations result in cellular death (34). In turn, SSBs result in replication fork stalling and collapse that result in the formation of double strand breaks during DNA replication (26,28).

Thus, patients whose tumors express loss of function

of genes associated with HRD potentially may benefit most from agents aimed against DNA repair mechanisms. In gastrointestinal malignancies, recent positive data has confirmed the potential therapeutic role of PARP inhibition in HRD cancer. The POLO trial, an international randomized double-blind placebo controlled phase III trial was designed to evaluate the efficacy of maintenance therapy with olaparib, a PARP inhibitor, in patients with metastatic pancreatic adenocarcinoma whose tumors harbored germline BRCA1/2 mutations that had not progressed after at least 16 weeks of front-line platinum-based chemotherapy (35). The median progression free survival (PFS) was longer in the olaparib arm compared to the placebo group (7.4 *vs.* 3.8 months; HR 0.53, 95% CI, 0.35–0.82; P=0.004), however, no significant difference in overall survival was observed between the two groups in the planned interim analysis (median OS 18.9 versus 18.1 months; HR 0.91, 95% CI, 0.56–1.46; P=0.68) (35). Despite the observed positive results and first randomized trial to investigate the efficacy of PARP inhibitors in gastrointestinal malignancies, the modest benefit in PFS and absence of survival benefit is unlikely going to change the current standard of practice. Given the modest benefit of PARP inhibitor monotherapy, ongoing and future studies have shifted focus on enhancing the response by combining PARP inhibitors with other agents.

Future directions

In preclinical studies, PARP1 has been identified to poly(ADP-ribosyl)ates STAT3 and subsequently promotes STAT3 dephosphorylation, resulting in reduced transcriptional activity of STAT3 and expression of PD-L1. PARP inhibition enhanced programmed death ligand 1 (PD-L1) transcription in cancer cells, which was associated with the upregulation of PD-L1 in cancer cells and PD-L1 protein expression in both the cytoplasm and cell surface (36). PD-L1 induction was lessened in the absence of transcription factor STAT3. These findings suggest that PARP inhibition augments the mutational burden through increasing DNA damage and promotes immune priming by increasing neoantigen exposure and upregulating PD-L1 expression, providing the rationale for the strategy of combining PARP inhibitors with PD-1/PD-L1 inhibitors in the treatment of solid tumor malignancies.

In early phase studies, the combined therapy of PARP1/2 inhibitor with programmed cell death (PD-1) inhibitor was well tolerated and showed intriguing synergistic anti-tumor activity in heavily pretreated solid tumor malignancies. In a phase I trial of patients with treatment refractory solid tumors, the combination of pamiparib, a selective PARP inhibitor and tislelizumab, a PD-1 inhibitor was investigated in a two part phase I dose escalation study followed by expansion cohort. BRCA status was assessed locally in 25 patients, of who 14 had a germline or somatic BRCA1/2 mutation (37). Despite being heavily pretreated, a response rate of 20% including two complete responses (4%) and eight confirmed partial responses (16%) were observed. The combination was deemed to be safe with no significant adverse effects. These findings have resulted in the ongoing investigation of PARP inhibitors with the combination of various PD-1 or PD-L1 inhibitors across various solid tumors harboring HRD.

Hypoxic conditions results in the downregulation of DNA repair, resulting in genomic instability (38). Thus, the combination of anti-angiogenic agents and PARP inhibitors may result in further synergistic activity through synthetic lethality. In ovarian cancer, a phase II trial that investigated the combination of cediranib, a VEGFR inhibitor, in combination with olaparib resulted in a significant improvement in PFS (16.5 versus 5.7 months; HR 0.32, P=0.008) (38). The strategy of hypoxia induction through various anti-angiogenic agents in combination with PARP inhibitors represents one potential strategy for those with *de novo* or secondary resistance to PARP inhibitors. An ongoing study in ovarian cancer is investigating the combination of cediranib with olaparib in patients with advanced ovarian cancer after disease progression on a PARP inhibitor (ClinicalTrials.gov, NCT02681237).

Mitogen signaling pathways (e.g., *PI3k/Akt* and *MAPK* pathways) have been associated with a reduction in HR repair and implicated as a mechanism of secondary resistance to PARP inhibition (39,40). In BTC, The MAPK and PI3k pathway are often constitutively activated and represent a mechanism for tumor cell growth, proliferation and metastases (41,42). Preclinical and early clinical studies have demonstrated synergistic activity from the combination of PARP inhibitors with PI3k and MEK inhibitors and represent another potential strategy in the treatment for BTC.

Mutations in IDH1 are common in intrahepatic cholangiocarcinoma, occurring in approximately 15–20% of patients (43-45). IDH1 normally convert isocitrate to α-ketoglutarate, but if mutated, they transform α-ketoglutarate into 2-hydroxyglutarate (2HG), which may promote tumor progression (46). Preclinical studies

have identified alterations in the homologous recombinant pathway in tumors that harbor IDH1 mutations (47). Preclinical models have mutant IDH1-dependent PARP inhibitor sensitivity (48), suggesting a potential treatment strategy targeting the 2HG-dependent HR deficiency with PARP inhibition in this subgroup of BTC.

Conclusions

BTC are a rare, heterogenous disease group that have limited treatment options and are associated with poor outcomes. Recent advances in next generation sequencing have allowed for the further understanding of the genomic alterations in BTC, and understand the variances present in the genomic makeup of this disease, including the identification of HRD. Further understanding of HRD and the recognition of the "BRCAness" phenotype could result in the identification of a larger or broader group of patients benefiting from PARP inhibition.

While PARP inhibitors have demonstrated meaningful clinical activity across various solid tumors, the optimal strategy at targeting BTC tumors that harbor HRD alterations remains undefined. This includes identifying which genomic alterations are most likely to benefit from strategies aimed at targeting synthetic lethality as well the investigation of the combination of various agents including cytotoxic chemotherapy, anti-angiogenic agents and small molecule inhibitors targeting various signaling pathways.

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Footnote

Conflicts of Interest: The 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.

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