HIGHLIGHT ARTICLE

PARP-Inhibitors in BRCA-Associated Pancreatic Cancer

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ABSTRACT

Recent data suggests that treating patients with pancreatic cancer that express mutations in BRCA1, BRCA2, and PALB2 with chemotherapy which targets the DNA repair defect in these cells, such as platinum based therapies or PARPi [poly (ADP-ribose) polymerase inhibitor], may be more beneficial in these patients. Moreover, further data also indicates the promise of combining PARPi with conventional chemotherapy. Authors summarize the data related to PARPi in BRCA-associated pancreatic cancer that was presented at the annual meeting of ASCO 2014. Enrolment on a clinical trial for patients who fit these criteria should be encouraged.

Introduction

American Cancer Society estimates that more than 46000 people will be diagnosed with pancreatic cancer in 2014, 85% of which will die of pancreatic cancer. The incidence rates have slowly been increasing for the past 10 years with a 1.3% lifetime risk of developing pancreatic cancer [1]. There is a significant genetic component contributing to the risk of developing pancreatic cancer with hereditary cancers being 2% of total pancreatic cancers. The genetic mutation most commonly involves the tumor suppressor genes, BRCA1 and BRCA2, with their incidence varying between 5-10% [2-4]. BRCA2 mutation carriers have a 3.5-fold risk of developing pancreatic cancer [5, 6]. Women with BRCA 1/2 mutation have been shown to have a 2.4 fold increase in incidence of pancreatic cancer [7].

The BRCA1 and BRCA2 genes encode large proteins that coordinate the homologous recombination repair double strand breaks (DSBs) pathway. Poly-ADP ribose polymerases (PARP) are a family of nuclear enzymes that regulates the repair of DNA single-strand breaks (SSBs) through the base-excision repair (BER) pathway. In the presence of BRCA mutation, the BER rescue pathway for DNA repair not affected and thus can be utilized for DNA repair [8-10]. Synthetic lethality is a concept ofcellular condition in which simultaneous loss of two nonessential mutations results in cell death, which does not occur if either gene products is present and functional [11]. Using the same principle, inhibitors of PARP (PARPi) can be used to target tumor cells in patients with BRCA1/2-mutated tumors who cannot utilize homologous recombination to repair DSBs, to shut down their BER rescue pathway thus leading to accumulation of DNA damage, genomic instability and cell death (Figure 1) [12].

Key words Drug Therapy; gemcitabine; Genes, BRCA1; Genes, BRCA2; Mutation; PALB2 protein, human; Pancreatic Neoplasms; Poly(ADP-ribose) Polymerases

Abbreviations PARPi, poly (ADP-ribose) polymerase inhibitor; RECIST, Response Evaluation Criteria in Solid Tumors

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What We Knew Before 2014 ASCO Annual Meeting?

There has been a considerable interest in recent years on evaluation of therapies for pancreatic cancers associated with BRCA-mutations. Data from limited preclinical (Table 1), clinical (Table 2) studies and abstracts published at 2013 ASCO meeting (Table 3) has demonstrated that PARPi are efficacious.

What Have We Learned from the 2014 ASCO Annual Meeting?

Combination of Cisplatin, Gemcitabine, and Veliparibin Patients with Known or Potential BRCA or PALB2-Mutated Pancreas Adenocarcinoma

O'Really *et al.* presented the results of their Phase 1B study to assess the toxicity and recommend dose of Veliparib for phase II studies in combination with a fixed dose of Gemcitabine and Cisplatin in patients with pancreatic adenocarcinoma with BRCA and PALB2 mutations [21]. In addition, primary endpoints also included safety. Secondary end points assessed response rate by RECIST 1.1, duration of response, progression-free and overall survival and evaluated the sensitivity and resistance to the regimen.

17 patients were enrolled between 02/2012 and 10/2013, out of which 53% had BRCA mutations. All patients received a fixed dose of platinum based therapy with increasing doses of Velirapib. 56% of the BRCA mut positive patients had partial responses to the treatment and the rest had stable disease. Fatigue and hematologic side effects

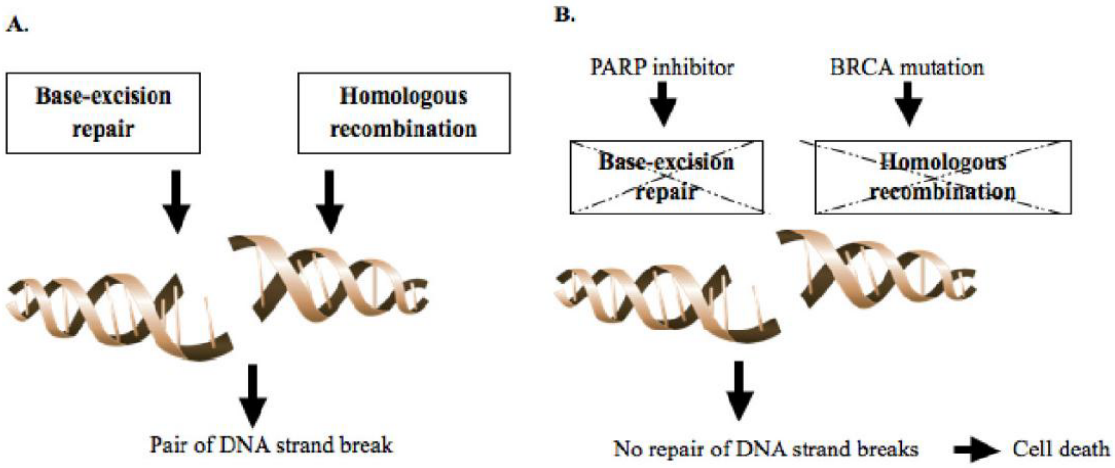

Figure 1. Schematic representation of PARP and BRCA mediated DNA repair in cells without exposure to PARP inhibitor and BRCA mutation (A), and synthetic lethality in cells with BRCA mutation exposing to PARP inhibitor (B) [12].

Table 1. Published preclinical Studies.

Combination therapy of poly (ADP-ribose) polymerase inhibitor 3-aminobenzamide and gemcitabine shows strong antitumor activity in pancreatic cancer cells [13].	Better tumor growth suppression with combination therapy as compared to gemcitabine alone.
Combination of AZD2281 (Olaparib) and GX15-070 (Obatoclax) results in synergistic antitumor activities in preclinical models of pancreatic cancer [14].	Demonstrate antitumor activities of the (Olaparib) and Obatoclax, pan-Bcl-2 inhibitor in 6 pancreatic cancer cell lines.
PARP-1 regulates resistance of pancreatic cancer to TRAIL therapy [15].	PARP inhibition sensitized PANC-1 and Suit2 cells to TRA-8-induced apoptosis in a dose-dependent manner.
Optimize radiochemotherapy in pancreatic cancer: PARP inhibitors a new therapeutic opportunity [16].	For the first time, the rationale of using a PARP inhibitor as chemoradiosensitizer in pancreatic cancer models was hypothesized and demonstrated.

Table 2. Published clinical studies.

An emerging entity: pancreatic adenocarcinoma associated with a known BRCA mutation: clinical descriptors, treatment implications, and future directions [17].	3/4 patients who received a PARP inhibitor alone or in combination with chemotherapy demonstrated an initial radiographic PR by RECIST and stable disease in the 4th patient.
Evidence for the efficacy of Iniparib, a PARP-1 inhibitor, in BRCA2-associated pancreatic cancer [18].	Case report showing a complete pathologic response.

Table 3. ASCO 2013 abstracts.

Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation: An open-label phase II study [19].	Clinical benefit seen in prostrate and pancreatic cancer and activity confirmed in ovarian and breast cancer.
A phase I/II study of ABT-888 in combination with 5-fluorouracil (5-FU) and oxaliplatin (Ox) in patients with metastatic pancreatic cancer (MPC) [20].	The combination of ABT-888, 5-FU, and Ox is safe and well tolerated. The combination has demonstrated promising efficacy in MPC, particularly in pts with BRCA2 gene mutations.

including anemia, neutropenia, and thrombocytopenia were the major dose limiting toxicities noted at 80 mg bid continuous (21 day) dosing regimen. Thus, they concluded that the recommended dose for phase 2 study (RP2D) for Velirapib should be 80 mg bid 1-12 days q3 weeks along with fixed dose of platinum based therapy and has shown evidence of high activity in BRCA mutated PC. This would form the basis of a randomized phase II trial currently enrolling patients with valuating the abovementioned regimen in patients with BRCA/PALB2 mutated pancreatic cancer.

Rucaparib in Patients with Pancreatic Cancer and a Known Deleterious BRCA Mutation

Domchek *et al.* presented the design of a Phase II study addressing the use of rucaparib, an oral PARPi, in patients with pancreatic ductal adenocarcinoma associated with a BRCA mutation [22]. It's a single arm study where continuous rucaparib will be given to patients with BRCA mutation associated pancreatic carcinoma who have had a relapse with at least 1 but not more than 2 treatment regimens or are intolerant to chemotherapy along with no response evident on imaging. They will assess safety every 2-4 weeks, disease progression with CT scans and CA 19-9 every 4-8 weeks and survival every 4 weeks after disease progression. Primary endpoint will be RECIST1.1 response rate. Secondary endpoints will be duration of response, progression free survival, overall survival and safety. DNA analysis and gene sequencing will also be done. The trial is currently enrolling patients. NCT02042378.

Evaluation of PARP Inhibition as a Platinum Sparing Strategy in Brca2-Deficient Pancreatic Tumors

Another abstract presented at ASCO 2014 meeting was a preclinical study which assessed the efficacy of Cisplatin in combination with Olaparib (oral PARPi), Cisplatin with a non-active vehicle, Olaparib alone or vehicle alone in BRCA-2 deficient mice with pancreatic adenocarcinoma ($Kras^{G12D/+}$; $p53^{R270H/+}$; Pdx-1-Cre; $Brca2^{mut}$) [23]. MRI was done at regular intervals to detect tumor development. The results are shown in the Figure 2. They showed a

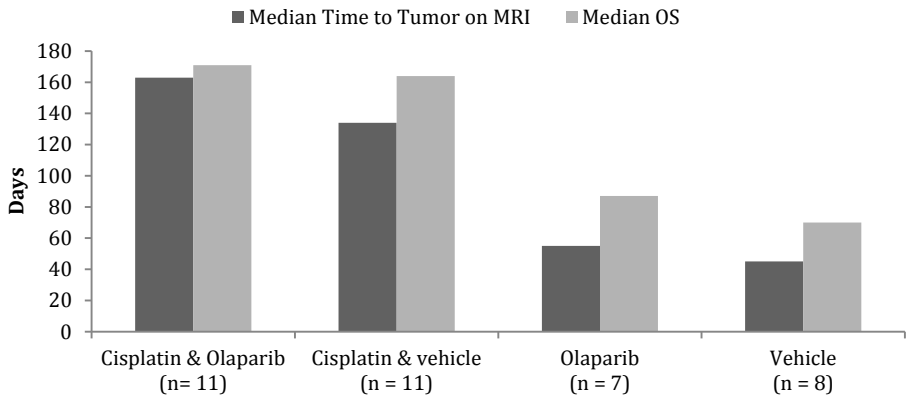

Figure 2. Cisplatin treated mice compared to Ola alone or vehicle (p<0.001).

Table 4. Ongoing Clinical Trials for PARPi for Solid tumors including pancreatic cancers. (www.clinicaltrial.gov)

Ongoing Clinical Trials for PARPi for Solid Tumors Including Pancreatic Cancers
Study of BMN 673, a PARP Inhibitor, in Patients With Advanced or Recurrent Solid Tumors (NCT01286987)
ABT-888 With Modified FOLFOX6 in Patients With Metastatic Pancreatic Cancer (NCT01489865)
Open Label Study to Assess Efficacy and Safety of Olaparib in Confirmed Genetic BRCA1 or BRCA2 Mutation Pats (NCT01078662)
Pilot Trial of BMN 673, an Oral PARP Inhibitor, in Patients With Advanced Solid Tumors and Deleterious BRCA Mutations (NCT01989546)
A Study of Rucaparib in Patients With Pancreatic Cancer and a Known Deleterious BRCA Mutation (NCT02042378)

significant prolongation of median overall survival and thus higher efficacy in Cisplatin treated mice compared to Ola alone or vehicle (p<0.001) and The benefit of adding Olaparib was increased time to tumor identification and reduced reuse of cisplatin.

Discussion

Pancreatic adenocarcinomas with germline mutations in BRCA and related genes is an important subset of pancreatic cancers diagnosed every year. Prior and ongoing preclinical and clinical research to develop targeted therapies, including PARPi, as single or combination agent has shown great promise. Nuclear PARP has been shown to be an independent prognostic marker with respect to standard clinicopathological parameters [24]. The above mentioned studies have laid a foundation based on which multiple phase II/III trials are underway and are currently recruiting patients with the exception of one which is active but not recruiting (NCT01078662) (Table4). The data from the studies will help a lot in establishing their efficacy and safety. Given the high mortality associated with these cancers, this is a step in the right direction.

Conflict of Interest

Authors declare no conflict of interest.

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