How I Use Single Agent PARP Inhibitors and Combination Therapies for Pancreatic Cancer

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INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is responsible for 3% of all cancers in the US and about 7% of all cancer deaths [1]. Even though it has a lower prevalence compared to other malignancies, it still is the third-leading cause of cancer-related death in the United States is projected to become the second-leading cause of death by 2030 [2]. Currently, advanced disease has a median overall survival (OS) of 6.7-11.1 months and early-stage disease 25-28 months [3, 4, 5]. Treatment options for advanced PDAC remain limited. FOLFIRINOX (5-FU, leucovorin, irinotecan, oxaliplatin) or gemcitabine plus nab-paclitaxel are still the only available choices in first line setting. These have a moderate clinical benefit and PDAC does eventually develop resistance to current conventional regimens. Understanding the mechanisms of this underlying chemoresistance in pancreatic cancer allows us to explore more treatment strategies. Tumor DNA repair mechanism (PARP), tumor metabolism pathways (mitochondrial inhibitor), focal adhesion kinase, and connective tissue growth factors are all areas of interest as far as targeted therapy research is concerned. Additionally, 27% highly actionable genomic alterations have been identified in pancreas cancer: BRCA 1/2, PALB2, ATM, CHEK 1/2, FANCA/C. PARP inhibitors are standing out as a recent story of success, especially in regards to these actionable mutations.

PARP enzymes play an important role in DNA Damage repair (DDR) by primarily repairing single-strand DNA breaks (DDR) [6, 7]. PARP inhibitors are small molecules that trap PARP enzymes on DNA hence preventing the process of DDR. When PARP inhibitors are present, accumulation of single-strand DNA breaks eventually causes formation of double-strand breaks, which are repaired by homologous recombination. If cells harbor mutations in DNA repair genes such as BRCA 1/BRCA 2 (cancer cells), they can't repair DNA using homologous recombination. They accumulate double-stranded DNA breaks over time and eventually die [7].

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At the 2019 American Society of Clinical Oncology (ASCO) meeting, data for Pancreas Cancer Olaparib Ongoing (POLO) trial was presented. This is a phase III randomized, double-blind controlled trial which looked at 3315 patients with metastatic PDAC in 10 countries. Individuals with germline BRCA 1 or BRCA 2 mutations were included in the study. They received at least 16 weeks of first line platinum-based chemotherapy, specifically FOLFIRINOX. 154 patients were randomized as follows: Olaparib 300 mg two times a day (92 patients) or matching placebo (62 patients) as maintenance therapy, within 4-8 weeks of completion of chemotherapy. Progression free survival was the primary end point. This was significantly longer in the Olaparib arm (median PFS 7.4 months *vs* 3.8 months; HR 0.53; 95% CI 0.35-0.82; p=0.004) [8]. Investigators reported an update on the study outcomes at the annual Gastrointestinal Cancers Symposium in January 2021. The median OS was not significantly different in the two arms: 19.2 months for olaparib group and 19.0 months for placebo group (HR 0.83; 95% CI 0.56–1.22; p=0.3487) [9]. There could be an inherent bias in this result as 26% of patients in the placebo group received Olaparib and multiple subsequent lines of therapies upon progression of disease (PD). The trial was also not adequately powered to report a significant difference in OS in the two groups. It should be noted that a large portion of patients in the Olaparib arm survived at or after the 2 year mark. At the 3 year mark, OS was 33.9% for the olaparib arm and 17.8% for the placebo arm. These results are very promising for the use of Olaparib in patients with BRCA mutated pancreas cancer, especially considering that 5-8% patients with pancreatic cancer have a mutation in BRCA 1 or 2.

Several other PARP inhibitors, namely rucaparib, niraparib, talazoparib, and veliparib are used to treat other tumor types, e.g. ovarian, fallopian tube, primary peritoneal and breast. They are also in early phase I/II trials as monotherapy or in combination with chemotherapies, immunotherapies or targeted therapies in patients with pancreas cancer.

ATM gene has also been implicated in hereditary PDAC. ATM (Ataxia-Telangiesctasia Mutated) serine/threonine kinase plays a role as a DNA damage checkpoint, leading to cell cycle arrest, DNA repair or apoptosis. Individuals who are heterozygous for ATM mutation have increased risk of pancreas cancer, prostate cancer, stomach cancer

and invasive ductal carcinoma of the breast [10]. ATM mutation prevalence in the general population is about 0.5-1%, leading researchers to believe that modifier genes also play a role in determining pancreatic cancer risk [11]. Currently, there are no targeted agents for ATM gene mutations but there have been case reports of some success with standard chemotherapy [12]. ATM is a large gene and specific implications of a mutation are not always immediately clear. IHC staining for protein loss is used in to help understand which alterations may be clinically relevant. ATM should not be lumped together with BRCA and PALB2 regarding clinical behavior. PARP inhibitors are also being explored with this mutation.

PALB2 means "Partner and Localizer of BRCA2". This gene, on chromosome 16, works with BRCA 2 to repair damaged DNA. Mutation in PALB2 poses an increased risk of pancreas cancer and is implicated in 3-4% cases of familial pancreas cancer [13]. PALB2 mutated pancreas cancer has a nearly identical phenotype to BRCA 2. O'Reilly et al has looked at Gemcitabine and Cisplatin with or without Veliparib in PDAC with germline BRCA/PALB2 mutation. Median progression-free survival was 10.1 months for Gem/Cis arm (95% CI, 6.7 to 11.5 months) and 9.7 months for Gem/Cis plus Veliparib arm (95% CI, 4.2 to 13.6 months; P=0.73). Response rate (RR) for Gem/Cis arm was 74.1% and 65.2% for Gem/Cis plus Veliparib arm (P=0.55). Addition of Veliparib did not significantly change response rate [14]. Reiss et al has also reported on the use of Rucaparib in patients with mutated PALB2 [15]. More research needs to be done looking into PALB2 mutated PDAC and the ideal maintenance treatment, but data so far looks promising for the use of PAPPi.

FDA approved Olaparib as maintenance therapy for germline BRCA mutated pancreas cancer in December 2019 due to the success of the POLO trial. Patient's eligible for this remain small as prevalence of BRCA mutations in the general population is still low. PARP inhibitors have also been shown to have a role in germline and somatic DDR mutations such as PALB2, ATM and CDK12 [16].

For the longest times, only cytotoxic chemotherapy was the only choice for PDAC. Now the future of treatment looks more promising, and all oncologists should make germline testing a part of care of PDAC patients.

REFERENCES

1. https://www.cancer.org/cancer/pancreatic-cancer/about/key-statistics.html

2. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: The unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res 2014; 74:2913-2921. [PMID: 24840647].

3. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 2013; 369:1691-1703. [PMID: 24131140].

4. Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011; 364:1817-1825. [PMID: 21561347].

5. Neoptolemos JP, Palmer DH, Ghaneh P, Psarelli EE, Valle JW, Halloran CM, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): A multicentre, open-label, randomised, phase 3 trial. Lancet 2017; 389:1011-1024.

6. Fisher AEO, Hochegger H, Takeda S, Caldecott KW. Poly(ADP-ribose) polymerase 1 accelerates single-strand break repair in concert with poly(ADP-ribose) glycohydrolase. Mol Cell Biol 2007; 27:5597-5605. [PMID: 17548475].

7. Lord CJ, Ashworth A. BRCAness revisited. Nat Rev Cancer 2016; 16:110-120. [PMID: 26775620].

8. Golan T, Hammel P, Reni M, Cutsem EV, Macarulla T, Hall MJ, et al. Maintenance Olaparib for germline BRCA-mutated metastatic pancreatic cancer. N Engl J Med 2019; 381:317-327. [PMID: 31157963].

9. Golan T, Hammel P, Reni M, Cutsem EV, Macarulla T, Hall MJ, et al. Overall survival from the phase 3 POLO trial: Maintenance Olaparib for germline BRCA-mutated metastatic pancreatic cancer. J Clin Oncol 2021: 39.

10. Hall MJ, Bernhisel R, Hughes E, Larson K, Rosenthal ET, Singh NA, et al. Germline pathogenic variants in the Ataxia Telangiectasia Mutated (ATM) gene are associated with high and moderate risks for multiple cancers. Cancer Prev Res (Phila) 2021; 14:433-440. [PMID: 31157963].

11. Bakker JL, Winter JP de. A role for ATM in hereditary pancreatic cancer. Cancer Discov 2012; 2:14-15. [PMID: 22585162].

12. Martino C, Pandya D, Lee R, Levy G, Lo T, Lobo S, et al. ATM-Mutated Pancreatic Cancer: Clinical and Molecular Response to Gemcitabine/Nab-Paclitaxel After Genome-Based Therapy Resistance. Pancreas 2020; 49:143-147. [PMID: 31856090].

13. Hofstatter EW, Domchek SM, Miron A, Garber J, Wang M, Componeschi K, et al. PALB2 mutations in familial breast and pancreatic cancer. Fam Cancer 2011; 10:225-231. [PMID: 21365267].

14. O'Reilly EM, Lee JW, Zalupski M, Capanu M, Park J, Golan T, et al. Randomized, multicenter, phase ii trial of gemcitabine and cisplatin with or without Veliparib in patients with pancreas adenocarcinoma and a germline BRCA/PALB2 mutation. J Clin Oncol 2020; 38:1378-1388. [PMID: 31976786].

15. Reiss KA, Mick R, O'Hara MH, Teitelbaum U, Karasic TB, Schneider C, et al. Phase II study of maintenance Rucaparib in patients with platinum-sensitive advanced pancreatic cancer and a pathogenic germline or somatic variant in BRCA1, BRCA2, or PALB2. JCO 2021; 39:2497-2505. [PMID: 33970687].

16. Mateo J, Porta N, McGovern UB, Elliott T, Jones RJ, Syndikus I, et al. TOPARP-B: A phase II randomized trial of the poly(ADP)-ribose polymerase (PARP) inhibitor olaparib for metastatic castration resistant prostate cancers (mCRPC) with DNA damage repair (DDR) alterations. J Clin Oncol 2021: 37.