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HIGHLIGHT ARTICLE

BRCA and Pancreatic Cancer

Highlights from the "2013 ASCO Annual Meeting". Chicago, IL, USA; May 30 - June 4, 2013

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Summary

Germline mutations in BRCA genes have been associated with pancreatic cancer. Laboratory and clinical data suggest that patients with BRCA mutations may be more responsive to therapy consisting of conventional chemotherapy with a poly(ADP-ribose) polymerase inhibitor (PARPi). The most recent data from the 2013 American Society of Clinical Oncology (ASCO) Annual Meeting will be reviewed (Abstracts #11024 and #TPS4144).

Introduction

There are approximately 45,000 new cases of pancreatic adenocarcinoma diagnosed in the USA annually. Pancreatic cancer is considered incurable, with the expectation that all newly diagnosed cases will succumb to the disease [1]. Eighty-five percent of malignant tumors arise in the exocrine pancreas and are ductal adenocarcinomas. While there are many risk factors for pancreatic cancer, hereditary factors, such as the breast cancer early onset (BRCA1 and 2) tumor suppressor genes, have become increasingly studied due to the potential of targeted therapy. It is well known that germline mutations in the BRCA genes are associated with breast and ovarian cancer [2]. Patients with BRCA2 mutations have also been reported to have an overall 3.5-fold risk of pancreatic cancer as compared to the general population [3]. Among patients with a family history of pancreatic cancer, 17% were found to have a BRCA2 mutation [4]. Ashkenazi Jews are one population that has been shown to carry the BRCA mutations in the setting of pancreatic cancer. The importance of BRCA1 mutations has been demonstrated as well. One study showed a 2.4-fold increased incidence of pancreatic cancer in women with a BRCA1/2 mutation, with both having similar increased incidence [5].

The BRCA tumor suppressor gene products are proteins involved in the repair of DNA cross-linking damage via homologous recombination [6]. Given this function, it has been shown that pancreatic cancer cell lines with BRCA mutations are sensitive to cross-linking agents such as mitomycin C (MMC), and cisplatin [7]. Other pre-clinical data suggest that targeting poly(ADP-ribose) polymerase may be effective in killing BRCA mutated cells. Poly(ADP-ribose) polymerase inhibitors (PARPi) disrupt repair of single stranded DNA breaks by the poly(ADP-ribose) polymerase enzyme [8]. In tumor cells, the inhibition of PARP results in the development of DNA lesions that require intact BRCA for repair; however, tumor cells with defective BRCA1 or BRCA2 lack the ability to repair DNA rendering the cells more susceptible to cell death [9] (Figure 1). Thus combining PARPi with DNA damaging chemotherapy is a strategy for targeting tumors with BRCA mutations [10].

The PALB2 gene, like BRCA, is also associated with pancreatic cancer [11]. It encodes a BRCA2 binding protein. Given its intimate molecular relationship with BRCA, this may also be a potential candidate for targeted therapy [12]. Because this gene acts on the same pathway, it is hypothesized that therapy that is effective in BRCA mutations should also be efficacious in PALB2 mutated cancers.

Key words 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 Did We Know Before the 2013 American Society of Clinical Oncology (ASCO) Annual Meeting?

Because the proportion of pancreatic cancers caused by mutations in BRCA and related genes like PALB2 are small, substantial clinical data is lacking. However, there have been numerous studies aimed at finding optimized treatments for this population. A case report by James *et al.* followed the treatment of a man with a common Ashkenazi Jewish BRCA2 mutation and a dual diagnosis of pancreatic and prostate cancer. He was treated with cross-linking agents as well as the topoisomerase inhibitor, irinotecan. The patient had prolonged survival (56 months) after initial diagnosis [13].

A retrospective analysis presented at the 2012 ASCO Gastrointestinal Cancers Symposium by Tran *et al.* identified 5 pancreatic cancer patients with BRCA mutations (4 BRCA2 and 1 BRCA1) who were treated with platinum based regimens [14]. The Ontario Pancreatic Cancer Study and pharmacy databases were used to identify one patient with resectable disease, one with locally advanced, and three with metastatic disease. It is intriguing that the patient with locally advanced disease (T4N0) was downstaged after receiving a platinum based regimen and eventually went on to resection. The resectable patient (T1N0) remained disease free after almost 3 years. The three metastatic patients had strong response to platinum based regimen as well, with progression free survival of 12 and 45 months in two of the patients. Even though the number of patients in this case series was small, it supports previous cases that found potential benefits of using platinum based regimens for pancreatic cancer. Because the size of this subgroup of patients with BRCA mutations and pancreatic cancer is small as well, platinum based chemotherapy should be studied further as a possible form of targeted therapy.

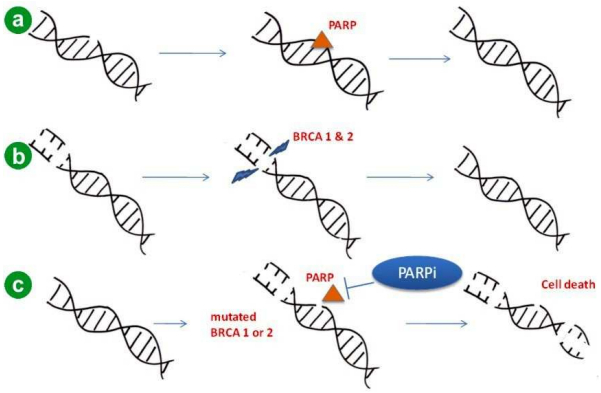

Figure 1. Effect of PARP, BRCA and PARP inhibition on DNA replication. **a.** PARP binds single strand DNA breaks and helps repair damage via base excision repair. **b.** BRCA1 and BRCA2 are important in double strand break repair and at replication forks through homologous replication. **c.** Inhibition of PARP in combination with mutated BRCA leads to double stranded DNA breaks and cell death.

As with platinum based therapy, the published clinical data for the support of the use of PARPi's is limited. However, a relatively large sample of 15 patients with BRCA1 (n=4) or BRCA2 (n=11) mutations and pancreatic adenocarcinoma was studied at the Memorial Sloan-Kettering Cancer Center, New York, NY, USA [15]. Four patients received a PARPi alone or in combination with chemotherapy. Of these, three demonstrated a radiographic partial response by Response Evaluation Criteria in Solid Tumors (RECIST) and the remaining patient had stable disease for six months. Six patients had metastatic disease and received platinum-based chemotherapy. Five of those patients had a radiographic partial response. The median survival of this cohort was 27.6 months.

What Have We Learned from the 2013 American Society of Clinical Oncology (ASCO) Annual Meeting?

Olaparib Monotherapy in Patients with Advanced Cancer and a Germ-Line BRCA1/2 Mutation: An Open-Label Phase II Study (Abstract #11024 [16])

Kaufman *et al.* presented the results of their phase II, multicenter, non-comparative study which evaluated the response of patients, with BRCA germline mutations, to the PARPi, olaparib [16]. Two-hundred and ninety-eight patients with advanced, refractory solid tumors and a BRCA1/2 mutation were enrolled and received olaparib 400 mg orally twice daily until disease progression. The primary objective was tumor response as evaluated by RECIST 1.1. Twenty-three patients enrolled on this study had pancreatic cancer; all patients had progressed after treatment with gemcitabine based therapies. In the 23 patients, the response rate was 21.7%, (complete or partial response). Thirty-six percent had progression free survival at 6 months and 41% were alive at 12 months. The olaparib was well tolerated, with the major adverse events being fatigue and nausea/vomiting. This small study showed the potential effectiveness of PARPi in BRCA mutated pancreatic cancer.

Randomized Phase II Study of Gemcitabine (G), Cisplatin (C) with or without Veliparib (V) (arms A, B) and a Phase II Single-Arm Study of Single-Agent Veliparib (arm C) in Patients with BRCA or PALB2-Mutated Pancreas Adenocarcinoma (PC) (Abstract #TPS4144 [17])

Another abstract presented at ASCO 2013 deals with the treatment of pancreatic cancer in BRCA positive patients. O'Reilly *et al.* present the design of a phase II study addressing the uses of PARPi's compared to standard chemotherapy agents in patients with either BRCA or PALB2-mutated

pancreatic adenocarcinoma. Arms A and B, are a randomized phase II study comparing gemcitabine and cisplatin with or without a PARPi, veliparib, in untreated stage III/IV pancreatic cancer. The primary endpoint will be the RECIST 1.1 response rate. Secondary endpoints will include progression-free survival, safety, disease-control rate, and overall survival. Arm C, is a phase II single-arm study of single-agent veliparib in previously-treated pancreatic cancer (with 2 lines of therapy or less) with similar end points. The trial is currently enrolling patients (NCT01585805).

Conclusions

Germline mutations in BRCA and related genes, such as PALB2, are associated with pancreatic cancer. Although this represents a small subset of pancreatic cancer patients, they may benefit from targeted therapy. Basic research and limited clinical data suggest that certain therapeutic agents, such as platinum based cross-linking chemotherapy as well as PARPi's, have increased activity against this small subset of pancreatic cancers. Multiple trials (Table 1) are actively recruiting patients with BRCA mutations to further delineate the role of PARPi's and chemotherapy in this population. The Abstract #TPS4144 presented at the 2013 ASCO Annual Meeting is particularly interesting because it will be the first to provide randomized controlled clinical data addressing the treatment of BRCA (and PALB2) mutated pancreatic adenocarcinoma with platinum based chemotherapy and PARPi's.

Take Home Message

Identifying patients with pancreatic cancers that express mutations in BRCA1, BRCA2, and PALB2 allows for the use of chemotherapy which targets the DNA repair defect in these cells. Alkylating agents, such as cisplatin, that affect DNA crosslinks, may be more beneficial in these patients. Platinum based therapies (i.e., gemcitabine plus cisplatin) should be considered. Early data also suggests that combining PARPi's with conventional chemo-therapy may be of added benefit. Enrollment on a clinical trial for patients who fit these criteria would be favored.

Table 1. Clinical trials actively recruiting with PARP inhibitors for solid tumors (http://www.clinicaltrials.gov).

Study of BMN 673, a PARP Inhibitor, in Patients with Advanced or Recurrent Solid Tumors (NCT01286987)	Phase I
A Study of Poly (ADP-Ribose) Polymerase Inhibitor PF-01367338 in Combination with Several Chemotherapeutic Regimens (NCT01009190)	Phase I
Veliparib and Dinaciclib with or without Carboplatin in Treating Patients with Advanced Solid Tumors (NCT01434316)	Phase I
A Study of Oral Rucaparib in Patients with gBRCA Mutation Breast or Ovarian Cancer, or Other Solid Tumor (NCT01482715)	Phase I/II

Conflicts of interest The authors have no potential conflicts to disclose

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