Outcomes in patients with DNA-damage repair related pancreatic cancer

Sarah Macklin
Mayo Clinic Florida https://orcid.org/0000-0001-5141-3321
Stephanie L. Hines
Mayo Clinic Florida
Pashtoon M. Kasi (pashtoon-kasi@uiowa.edu)
https://orcid.org/0000-0002-5169-7085

Research article

Keywords: Hereditary cancer; pancreatic cancer; platinum chemotherapy; PARP inhibitors; BRCA1/2; genetic testing

Posted Date: June 3rd, 2019

DOI: https://doi.org/10.21203/rs.2.10012/v1

Abstract

Background: Patients with DNA-damage response genes (DDR)-related pancreas cancer (BRCA1/2 or other DNA-damage related genes) may have improved outcomes secondary to increased sensitivity to DNA-damaging drugs (platinum chemotherapy/ poly ADP ribose polymerase (PARP)-inhibitors). However, data is scarce pertaining to outcomes in this subset of patients. Our objective was to retrospectively identify DDR-related pancreas cancer patients and report on clinical outcomes. Methods: Pancreas cancer patients with either a somatic or germline BRCA1/2 or other DDR genes were identified retrospectively through review of medical records (medical genetics/oncology), germline and tumor-based genetic testing results at our institution. Data regarding clinical outcomes, therapy received, and survival was subsequently extracted. Results: A total of 11 patients with pancreas cancer were identified. Pathogenic DDR-variants detected were within BRCA1 (3), ATM (4), BRCA2 (2), PALB2 (1) and FANCC (1). Five of these individuals had prior history of other cancers. Clinically these tumors were localized (4), locally advanced (3), and metastatic (4) at diagnosis. Seven out of 11 patients were still alive at time of data review. Survival in the 3 patients who had died in the metastatic/advanced cohort was 23.5, 25.8 and 111.5 months. All patients with advanced disease had exposure to platinum chemotherapy. Conclusions: Historical survival in patients with advanced and metastatic pancreas cancer is poor. Results of this DDR-subset of patients do show significantly superior outcomes, likely secondary to exposure to platinum drugs. This data, alongside other similar cohorts, would favor the DDR-genes being a predictive marker with improved survival if exposed to these drugs and the new class of drugs, PARP-inhibitors.

Background

For years, germline testing for hereditary cancer syndromes was completed largely to provide guidance for future surveillance and consideration of risk reduction measures, such as chemoprevention and/or prophylactic surgery. Developments in cancer pathology understanding opened additional applications for genetic results. Individualized approaches for pancreatic adenocarcinoma receive keen attention as survival rates are among the poorest, with 5-year survival around 8%[1]. Germline and somatic results can influence management recommendations and possibly general prognosis as well.

Treatment alterations can be considered if a cancer shows mismatch repair (MMR) or DNA damage repair (DDR) deficiency[2-4]. Tumors with high microsatellite instability (MSI) due to MMR deficiency have been shown to respond to immunotherapy[2]. MMR deficient tumors can be found in individuals with Lynch syndrome, but are not limited to this population. One study reported disease control in over 75% (66/88) of the patients with an MMR deficient cancer with immunotherapy, regardless of tumor origin[2]. Pembrolizumab was approved by the FDA for tumors with high MSI and/or MMR deficiency[5].

Individuals with a DDR-related cancer can include those with a pathogenic, germline or somatic *BRCA1/2* variant and other genes within the homologous recombination and Fanconi anemia pathways. This population appears to have better outcomes compared to the general pancreatic cancer population. Median all stage overall pancreatic cancer survival has been reported as 14 months for those with a pathogenic *BRCA1/2* variant[6]. For reference, those with metastatic pancreatic cancer generally have an estimated median survival below 6 months[7,8]. Following clear margin removal of a pancreatic tumor, median survival time increases to around 23 months[8,9]. Prognosis between those with a *BRCA1/2*-related pancreatic cancer and those with an apparently sporadic cancer may be more similar if both tumors are resectable[10].

DDR-related pancreatic tumors also appear to have a better response to platinum- based regimens and/or PARP inhibitors[3,6,11]. Stage 3 or 4 pancreatic cancer survival increased from 9 to 22 months for those with a *BRCA1/2* mutation (P=0.039) if a platinum-based chemotherapy was introduced into their care[6]. Another study reported median time of survival of 11 months in the *BRCA1/2*- population (95% CI, 1.5-12) and 23.3 months in *BRCA1/2*+ group (95% CI, 3.8-30.2) with cisplatin, gemcitabine and veliparib[3]. Others found median survival was 46.6 months for those with a pathogenic *BRCA1/2* or *PALB2* variant following platinum exposure compared to 23.3 for those without a variant detected[12].

Methods

This clinical review was approved by the Mayo Clinic Florida Institutional Review Board (ID:18-006620). The clinical histories of patients with pancreatic adenocarcinoma and a germline pathogenic variant in a hereditary cancer gene were retrospectively reviewed. Patients were identified by the Mayo Clinic Florida Clinical Genomics and the Division of Oncology between 2016 and 2018. Patients underwent germline genetic testing through various commercial genetic testing companies.

Results

Eleven patients were identified, and the average age of diagnosis of this population was 60.3 years (SD = 15.9). Five patients had prior history of cancer. Patients 3, 4, and 11 had a breast cancer diagnosis prior to age 50. Patients 2-6, 8, 9, and 11 had at least 1 first degree relative with pancreatic, breast, ovarian or prostate cancer, and 5 of those patients had at least 2 first degree relatives with 1 of those cancers. Patient 1 had a first degree relative with colon cancer and second degree relatives with breast and prostate cancer. Patient 10 had family history of cholangiocarcinoma and glioblastoma. Patient 7 had history of breast and colon cancer in second degree relatives. Pathogenic variants detected were within *BRCA1* (3), *ATM* (4), *BRCA2* (2), *PALB2* (1) and *FANCC* (1). Three individuals had variants of uncertain significance (VUSs) reported. Patient 11 had a VUS in *PMS2*, and Patient 5 had 1 in *POLE*. Patient 3 had a VUS in *RAD50*, *RAD51C*, and *SDHB*.

Four tumors were initially localized, 3 locally advanced, and 4 metastatic. At time of diagnosis, 5 of the tumors discovered were resectable, and 2 were deemed resectable only following chemotherapy. All patients that had died at the time of clinical review had either metastatic or advanced disease initially and survival measured 23.5, 25.8 and 111.5 months. All patients with advanced disease had exposure to platinum chemotherapy. Patient 4 had the longest treatment period. Initially, she presented as locally advanced and later had recurrence/metastatic disease for which she received systemic therapy with multiple lines. She passed from fatal pneumonitis secondary to immunotherapy.

Conclusions

Patients with DDR-related pancreatic cancer had significantly improved survival in our cohort. This contrasts sharply with historical landmark studies of pancreatic cancer where survival ranges between of 6-11 months[13]. Response duration was also significantly longer compared to what has been reported, likely secondary to increased sensitivity to

DNA-damaging drugs. The increased survival is comparable to previous research on DDR-related pancreatic cancer cohorts[3,12].

Patient 11 was the only individual in this population to pass away before the general population median survival time for a similarly staged tumor. Unfortunately, at the time of her pancreatic cancer diagnosis, she had other significant co-morbidities, including end-stage renal disease requiring dialysis. At the time of her passing, there was no evidence of cancer recurrence on MRI or CT.

Estimates vary, but around 5-15% of all patients with pancreatic cancer have a detectable pathogenic DDR-related gene variant, and around 5% have a *BRCA1/2* variant specifically[14-16]. The National Comprehensive Cancer Network (NCCN) recommends *BRCA1/2* analysis for all diagnosed with pancreatic adenocarcinoma[17]. The significant, potential impact for the patient has led to this approval.

Even with potential, personal benefit, cost can still be a prohibitive factor. Patient 2 had not been able to complete germline testing initially due to high personal cost despite young diagnosis and family history of pancreatic, prostate and uterine cancer in first degree relatives. Results of circulating tumor DNA (ctDNA) testing and an additional testing platform that reported somatic/ germline status confirmed his *BRCA1* variant.

It is less well studied whether other DDR-related gene variants would respond to platinum based chemotherapies and/or PARP-inhibitors in same way as *BRCA1/2*. *BRCA1/2* and *PALB2* are known to be associated with an increased risk for pancreatic cancer[18-21]. Evidence supports that risk for pancreatic cancer may be elevated as well in those with a pathogenic *ATM* variant[22], and *BRCA1* is a downstream target of the *ATM* gene[23]. *FANCC* is less well characterized and associated with lower penetrance for hereditary cancer risk[17]; limited research suggests an association with pancreatic cancer[24,25]. The *FANCC* gene is a DDR-related gene in the Fanconi anemia pathway[26]. Decisions regarding chemotherapy should be weighed and discussed on an individual basis preferably in a molecular tumor board setting. Further research should include these other DDR-related cohorts to explore if they derive similar benefit. It is also important to note that most experts would suggest that cisplatin may be superior as compared to other platinum drugs. Furthermore, irinotecan, which is part of FOLFIRINOX combination chemotherapy, is a DNA-damaging drug (topoisomerase inhibitor). Therefore, the benefit derived in patients who are exposed to FOLFIRINOX is likely from both the irinotecan and the platinum part of the combination chemotherapy.

The relatively small sample size, large number of resectable tumors, and the retrospective, single-institutional nature of this study with selection bias are all limitations. However, our study corroborates previous studies and expands the literature with inclusion of non-*BRCA1/2* genes.

This case series does suggest that patients with pancreatic cancer due to DDR-related genes may have better overall outcomes than the general population with pancreatic cancer. Their response to platinum based or other DNA-damaging chemotherapies may be the driving factor. Similar results are being reported from pooled large cohorts from other major academic centers. With universal germline testing now endorsed for pancreatic cancer, data regarding DDR-related pancreatic cancer will significantly increase. For the time being, with platinum-based therapies already approved for these patients, if there is a choice, it would be reasonable to choose a DNA-damaging based therapy and/or participation in some of the PARP-inhibitor trials.

Abbreviations

MMR: mismatch repair

DDR: DNA damage repair

MSI: microsatellite instability

PARP: poly ADP ribose polymerase

VUS: variant of uncertain significance

NCCN: National Comprehensive Cancer Network

ctDNA: circulating tumor DNA

Declarations

Ethics Approval and consent for publication: This clinical review was approved by the Mayo Clinic Florida Institutional Review Board (ID: 18-006620). It was approved by expedited review procedures (45 CFR 46.110, item 5). The Reviewer conducted a risk-benefit analysis, and determined the study constitutes minimal risk research.

Availability of data and materials and competing interests funding authors: The dataset generated/ analyzed during the current study are not publicly available as individual privacy could be compromised but are available from the corresponding author on reasonable request. The authors declare that they have no competing interests. No sources of funding to report.

Authors' contributions and Acknowledgements: All authors participated in the design of the study. SM reviewed and analyzed the patient data regarding the oncologic disease and genetic testing. All authors were major contributors in writing the manuscript. All authors read and approved the final manuscript.

References

1. Siegel RL, Miller KD, and Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018;68:7-30; doi: 10.3322/caac.21442.

2. Le DT, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science. 2017;357:409-413; doi: 10.1126/science.aan6733.

3. O'Reilly EM, Lee JW, Lowery MA, Capanu M, Stadler ZK, Moore MJ, et al. Phase 1 trial evaluating cisplatin, gemcitabine, and veliparib in 2 patient cohorts: Germline BRCA mutation carriers and wild-type BRCA pancreatic ductal adenocarcinoma. Cancer. 2018;124:1374-1382; doi: 10.1002/cncr.31218.

4. Piklak R, Valle JW, and McNamara MG. Germline mutations in pancreatic cancer and potential new therapeutic options. Oncotarget. 2017;8:73240-73257; doi: 10.18632/oncotarget.17291.

5. Release P. FDA approves first cancer treatment for any solid tumor with a specific genetic feature; https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm560167.htm (2017). Accessed 6 December 2018.

6. Golan T, Kanji ZS, Epelbaum R, Devaud N, Dagan E, Holter S, et al. Overall survival and clinical characteristics of pancreatic cancer in BRCA mutation carriers. Br J Cancer. 2014;111:1132-8; doi: 10.1038/bjc.2014.418.

7. Golan T, Sella T, Margalit O, Amit U, Halpern N, Aderka D, et al. Short and long-term survival in metastatic pancreatic adenocarcioma, 1993-2013. J Natl Compr Cancer Netw. 2017;1022-1027; doi: 10.6004/jnccn.2017.0138.

8. Vincent A, Herman J, Schulick R, Hruban RH, and Goggins M. Pancreatic Cancer. Lancet. 2011;378: 607–620; doi: 10.1016/S0140-6736(10)62307-0.

9. Konstantinidis IT, Warshaw AL, Allen JN, Blaszkowsky LS, Castillo CF, Deshpande V, et al. Pancreatic ductal adenocarcinoma: is there a survival difference for R1 resections versus locally advanced unresectable tumors? What is a "true" R0 resection? Ann Surg. 2013;257:731-6; doi: 10.1097/SLA.0b013e318263da2f.

10. Golan T, Sella T, O'Reilly EM, Katz MH, Epelbaum R, Kelsen DP, et al. Overall survival and clinical characteristics of BRCA mutation carriers with stage I/II pancreatic cancer. BR J Cancer. 2017;116:697-702; doi: 10.1038/bjc.2017.19.

11. Waddell N, Pajic M, Patch AM, Chang DK, Kassahn KS, Bailey P, et al. Whole genomes redefine the mutational landscape of pancreatic cancer. Nature. 2015; 518: 495–501; doi: 10.1038/nature14169.

12. Yu S, Agarwal P, Mamtani R, Symecko H, Spielman K, and O'Hara M, et al. Retrospective Survival Analysis of Patients With resected Pancreatic Ductal Adenocarcinoma and a Germline BRCA or PALB2 Mutation. JCO Precision Oncology. 2019; https://doi.org/10.1200/PO.18.00271.

13. Conroy T, Desseigne F, Ychou M, Bouche O, Guimbaud, Becouarn Y, et al. FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer. N Engl J Med. 2011; 364:1817-1825; doi: 10.1056/NEJMoa1011923.

14. Hu C, Hart SN, Bamlet WR, Moore RM, Nandakumar K, Eckloff BW, et al. Prevalence of pathogenic mutations in cancer predisposition genes among pancreatic cancer patients. Cancer Epidemiol Biomarkers Prev. 2016;35:207-211; doi: 10.1158/1055-9965.EPI-15-0455.

15. Ryan DP, Hong TS, and Bardeesy N. Pancreatic adenocarcinoma. N Engl J Med. 2014;371:1039-1049; doi: 10.1056/NEJMra1404198.

16. Shi C, Hruban RH, and Klein AP. Familial pancreatic cancer. Arch Pathol Lab Med. 2009;133:365-374; doi: 10.1043/1543-2165-133.3.365.

17. Daly MB, Pilarski R, Berry MP, Buys SS, Friedman S, Garber JE, et al. Genetic/ Familial High-Risk Assessment: Breast and Ovarian: Version 3.2019. National Comprehensive Cancer Network (2019). https://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf. Accessed 9 December 2019.

18. Thompson D, Easton DF, and Breast Cancer Linkage Consortium. Cancer incidence in BRCA1 mutation carriers. J Natl Cancer Inst. 2002;94:1358-1365.

19. van Asperen CJ, Brohet RM, Meijers-Heijboer EJ, Hoogerbrugge N, Verhoef S, Vasen HF, et al. Cancer risks in BRCA2 families: estimates for sites other than breast and ovary. J Med Genet. 2005;42:711-719; doi: 10.1136/jmg.2004.028829.

20. Borecka M, et al. Mutation analysis of the PALB2 gene in unselected pancreatic cancer patients in the Czech Republic. Cancer Genet 2016;209(5):199-204; doi: 10.1016/j.cancergen.2016.03.003.

21. Jones S, Hruban RH, Kamiyama M, Borges M, Zhang X, Parsons DW, et al. Exomic Sequencing Identifies PALB2 as a Pancreatic Cancer Susceptibility Gene. Science. 2009;324:217; doi: 10.1126/science.1171202.

22. Roberts NJ, Jiao Y, Yu J, Kopelovich L, Peterson GM, Bondy ML, et al. ATM mutations in hereditary pancreatic cancer patients. Cancer Discov. 2012; 2:41–46; doi: 10.1158/2159-8290.CD-11-0194.

23. Lavin MF, Delia D, and Chessa L. ATM and the DNA damage response. Workshop on ataxia-telangiectasia and related syndromes. EMBO Rep. 2006;7:154-160; doi: 10.1038/sj.embor.7400629.

24. van der Heijden MS, Yeo CJ, Hruban RH, and Kern SE. Fanconi anemia gene mutations in young-onset pancreatic cancer. Cancer Res. 2003;63:2585–2588.

25. Rogers CD, van der Heijden MS, Brune K, Yeo CJ, Hruban RH, Kern SE, and Goggins M. The genetics of FANCC and FANCG in familial pancreatic cancer. Cancer Biol Ther. 2004;3:167–169.

26. Donahue SL and Campbell C. A DNA double strand break repair defect in Fanconi Anemia fibroblasts. J Biol Chem. 2002;277:46243-46247; doi: 10.1074/jbc.M207937200.

Tables

Table 1: Clinical History of Patients with a DDR- related Pancreatic Cancer

Patient ID	Sex	Prior cancer	Dx. Age	Clinical stage at diagnosis	Gene	Variant	Survival (mo.)	Surgery	Chemotherapy	
									Drug	Duration (mo.)
1	M	-	30-35	metastatic	*BRCA1*	c.34C>T	25.8	No	FOLFIRINOX	5
									Erlotinib	1
									Gemcitabine, Nab-Paclitaxel	6
2	M	-	55-60	metastatic	*BRCA1*	c.212+3A>G	23.5	Yes[b]	FOLFIRINOX	3
									Gemcitabine, Nab-Paclitaxel	2
									Gemcitabine	2
									Gemcitabine, Cisplatin	7
3	F	breast	40-45	metastatic	*ATM*	c.2921+1G>A	8.9[a]	No	FOLFIRINOX	8[c]
4	F	bilateral breast	50-55	locally advanced; later recurrent/ metastatic	*BRCA1*	c.2722G>T	111.5	Yes	Gemcitabine	6
									FOLFIRINOX	6
									Gemcitabine, Nab-Paclitaxel	1
									Gemcitabine	8
									FOLXFOX	6
									Irinotecan	3
									Nivolumab	13
									Nivolumab, Gemcitabine, Carboplatin	1
									Nivolumab, Gemcitabine	2
									Nivolumab	1
									PARP inhibitor	1
5	F	-	60-65	metastatic	*ATM*	c.7630-2A>C	6.3[a]	No	FOLFIRINOX	6[c]
6	M	-	60-65	locally advanced	*BRCA2*	c.9435_9436del	20.1[a]	Yes[b]	FOLFIRINOX	2
									Gemcitabine, Capecitabine	5
7	M	basal cell carcinoma	70-75	locally advanced	*FANCC*	c.1642C>T	8.6[a]	No	Gemcitabine, Nab-Paclitaxel	4
									FOLFIRINOX	2[c]
8	F	-	40-45	localized	*PALB2*	c.487_488delGT	70.2[a]	Yes	Gemcitabine	5
9	F	melanoma, bladder	80+	localized	*ATM*	c.6975+2T>C	42.4[a]	Yes	Gemcitabine	3
10	M	-	80+	localized	*ATM*	c.2921+1G>A	29[a]	Yes	Gemcitabine	2
11	F	breast	75-80	localized	*BRCA2*	c.1976_1977insSVA	14.0[d]	Yes	Gemcitabine	3

[a]These patients have not passed away. [b]Resectable following chemotherapy. [c]Chemotherapy ongoing. [d]Died due to comorbidities (no recurrence).

Figures

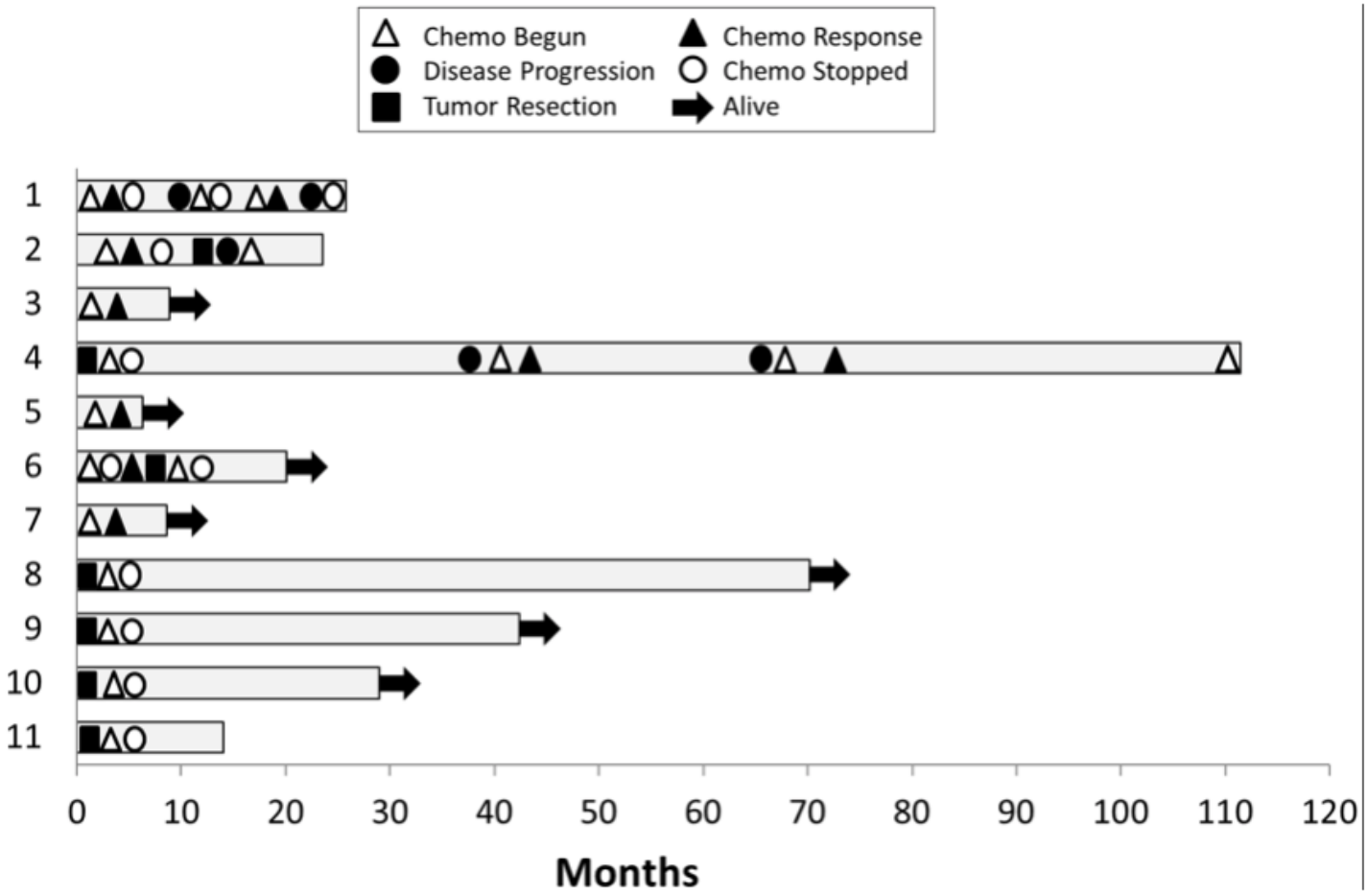

Figure 1

Timeline of survival following diagnosis of pancreatic adenocarcinoma.