Landscape of germline Pathogenic Variants beyond *BRCA* in Pancreatic Cancer (PC) patients

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Background

Pancreatic Cancer (PC) is a lethal cancer with a 5-year survival rate of less than 10% (1). Current evidence suggest that 10 to 20% of PC may be due to germline Pathogenic Variants (PV) in high-risk genes (2-4). The impact of mutational status on overall survival is still uncertain. Most of the previous studies on PC patients were focused on BRCA1/2 mutations due to the possibility of using PARP inhibitors (5). A recent metanalysis reported a prevalence of homologous recombination deficiency (HRD) between 14.5%-16.5% (6). However, the precise contribution of additional susceptibility genes other than BRCA is still to be clarified as different panel were used among different studies. Nevertheless, international guidelines recommend multigene germline testing for all PC patients.

The purpose of our study was to evaluate the prevalence of PVs focusing on DNA Damage Repair (DDR) and other candidate susceptibility genes, and their impact on patient survival, in a prospective and retrospective series of unselected PC patients.

Methods

PVs in DNA Damage Repair (DDR) and other candidate susceptibility genes were detected through an oncologist-led Multiple Gene Panel (MGP) testing (Tab1). The germline MGP tested 53 genes, selected according to the recent literature. Only PVs and Likely Pathogenetic Variants (LPVs) were included in the analyses. We investigated the prevalence and impat of PVs/LPVs on survival on a retrospective series of unselected PC patients.

APC	ARID1A
ARID2B	ARID2
ATM	ATR
ATRX	BAP1
BARD1	BMPR1A
BRCA1	BRCA2
BRIP1	CDC73
CDK12	CDK4
CDKN2A	CHEK1
CHEK2	COL7A1
CPA1	EPCAM
ERCC4	FAM175A
FANCA	FANCB
FANCC	FANCD2
FANCE	FANCF
FANCG	FANCL
HOXB13	MLH1
MRE11	MSH2
MSH6	NBN
PALB2	PMS2
PRSS1	RABL3
RAD50	RAD51
RAD51B	RAD51C
RAD51D	RET
SDHA	SPINK1
STK11	TINF2
TP53	

Table 1. mutational panel

Results

Table 2. Patients Characteristics (N=185)

Sex	
M	90
F	95
Age (yrs)	
Median	54
Range	14-58
PC stage	
Stage I to III	89
Metastatic	96

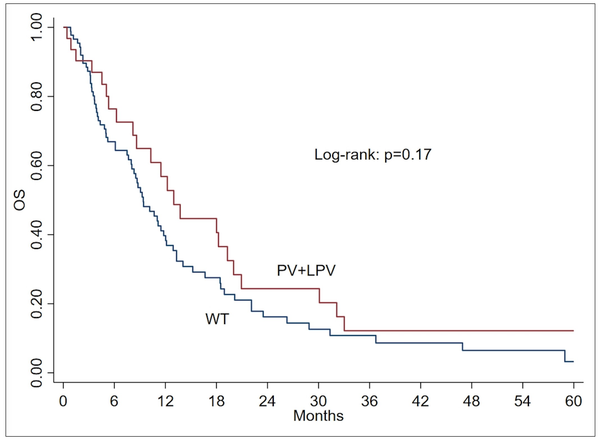

Figure 1. PC Patient survival according to PVs /LPVs

A total of 185 patients were included in the analyses. Their characteristics are reported in Tab 2.

We found either a PV or LPV in 43/185 patients, with PVs in 32 (17.3%) and LPVs in 13 (7%) of the patients. A *BRCA1/2* PV or LPV was found in 8/185 (4.3%) patients. The most frequent altered genes other than *BRCA* were *CDKN2A* (3.7%), *CHEK2* and *ATM* (2.7%), *COL7A1* (4.8%).

Median age and stage IV frequency at diagnosis did not differ in Wild-Type (WT) and PV+LPV patients. Median overall survival (mOS) was 11 months. A trend towards better survival was observed for PV+LPV (12.9 mOS) than among WT cases (9.4 mOS), although not statistically significant (p=0.17) (Figure 1).

Among the 17 patients who survived for longer than 20 months, there were one *COL7A1* LPV, 2 *CDKN2A* and 2 *ATM* PV carriers, one of whom is still alive at 57 months from diagnosis and the start of neoadiuvant treatment.

Few data available about chemotherapy regimens do not allow further analyses.

Conclusions

A high PV and LPV overall frequency was found in our unselected prospective and retrospective series of PC patients (23%), with a 4.3% of *BRCA* PV rate, in line with the literature. Interestingly, we found a 3.5 month longer mOS in PV+LPV as compared to WT patients, although not statistically significant. Encouraging good prognosis was observed for some 'outliers' with PVs and LPVs in *COL7A1, CDKN2A* and *ATM*.

Increasing knowledge in tumor biology is a critical step to develop personalized treatment and, consequently, improve therapeutical benefit.

References

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