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ORIGINAL RESEARCH

Chemotherapy toxicity and activity in patients with pancreatic ductal adenocarcinoma and germline BRCA1-2 pathogenic variants (gBRCA1-2pv): a multicenter survey

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Background: Germline BRCA1-2 pathogenic variants (gBRCA1-2pv)-related pancreatic ductal adenocarcinoma (PDAC) showed increased sensitivity to DNA cross-linking agents. This study aimed at exploring safety profile, dose intensity, and activity of different chemotherapy regimens in this setting.

Patients and methods: gBRCA1-2pv PDAC patients of any age and clinical tumor stage who completed a first course of chemotherapy were eligible. A descriptive analysis of chemotherapy toxicity, dose intensity, response, and survival outcomes was performed.

Results: A total of 85 gBRCA1-2pv PDAC patients treated in 21 Italian centers between December 2008 and March 2021were enrolled. Seventy-four patients were assessable for toxicity and dose intensity, 83 for outcome. Dose intensity was as follows: nab-paclitaxel 72%, gemcitabine 76% (AG); cisplatin 75%, nab-paclitaxel 73%, capecitabine 73%, and gemcitabine 65% (PAXG); fluorouracil 35%, irinotecan 58%, and oxaliplatin 64% (FOLFIRINOX). When compared with the literature, grade 3-4 neutropenia, thrombocytopenia, and diarrhea were increased with PAXG, and unmodified with AG and FOLFIRINOX. RECIST responses were numerically higher with the three- (81%) or four-drug (73%) platinum-containing regimens that outperformed AG (41%) and oxaliplatin-based doublets (56%). Carbohydrate antigen 19.9 (CA19.9) reduction >89% at nadir was reported in two-third of metastatic patients treated with triplets and quadruplets, as opposed to 33% and 45% of patients receiving oxaliplatin-based doublets or AG, respectively. All patients receiving AG experienced disease progression, with a median progression-free survival (mPFS) of 6.4 months, while patients treated with platinum-containing triplets or quadruplets had an mPFS >10.8 months. Albeit still immature, data on overall survival seemed to parallel those on PFS.

Conclusions: Our data, as opposed to figures expected from the literature, highlighted that platinum-based regimens provoked an increased toxicity on proliferating cells, when dose intensity was maintained, or an as-expected toxicity,

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when dose intensity was reduced, while no change in toxicity and dose intensity was evident with AG. Furthermore, an apparently improved outcome of platinum-based triplets or quadruplets over other regimens was observed.
Key words: germline BRCA, pancreatic cancer, chemotherapy toxicity, chemotherapy dose intensity, chemotherapy activity

INTRODUCTION

In the past decades, DNA damage repair systems have caught the attention of researchers as potential therapeutic targets in oncology.[1] Of special interest is the homologous recombination (HR) system, which is responsible for DNA double-strand break repair and pivots on BRCA1 and BRCA2 proteins.[2,3] Historically, inheritance of germline BRCA1 and/or BRCA2 pathogenic variants (gBRCA1-2pv) has been associated with increased risk of breast and/or ovarian cancer.[4] In addition, it has been demonstrated that, as a result of their increased genomic instability due to defective HR system, BRCA1-2-deficient cancers show higher sensitivity to DNA damaging agents inducing double-strand breaks, such as cross-linking agents, especially platinum compounds, and alkylating agents.[5-9] Poly (ADP-ribose) polymerase (PARP) inhibitors have further enriched the therapeutic armamentarium against these neoplasms.[10-12]

More recently, a significant correlation between gBRCA1-2pv and the risk of developing other malignancies, including prostate and gastrointestinal cancers, especially pancreatic ductal adenocarcinoma (PDAC), has been highlighted.[13,14] PDAC is a highly challenging neoplasm, still burdened with low survival rates, mainly due to late stage at diagnosis, early spread of micrometastatic disease, and poor response to cytotoxic agents, which represent the unique therapeutic option in most cases.[15] For carriers of gBRCA2 pathogenic variants, the lifetime risk of developing PDAC is estimated between 5% and 10%, while gBRCA1 pathogenic variants are associated with a two to four times increased risk of PDAC.[13] Overall, prevalence of these germline pathogenic variants varies from 5% to 9% in unselected PDAC populations to 15%-20% in familial PDAC.[16-18] Despite the low quality of clinical evidence, many studies have confirmed that PDAC patients carrying gBRCA1-2pv could benefit from platinum-based treatments, that are, however, hampered by toxicity.[19-21] Moreover, the PARP inhibitor olaparib has been recommended for maintenance treatment of metastatic PDAC patients with gBRCA1-2pv, not progressing on first-line platinum-based chemotherapy, on the basis of the results of the randomized phase III POLO trial.[22]

Despite an increasing interest in the efficacy of specific chemotherapy and chemo-free strategies in gBRCA1-2-mutated tumors, few studies have investigated chemotherapy toxicity in this subset of patients, often leading to inconsistent results. Indeed, it might be hypothesized that the defective allele that germline BRCA1-2pv carriers harbor in all healthy cells could lead to a partial impairment of the BRCA-related HR system and increased susceptibility to DNA damage also in non-neoplastic haploinsufficient cells, ultimately resulting in enhanced chemotherapy-related toxicity.[23] Different and controversial data are available on chemotherapy toxicity in breast and ovarian cancer patients with gBRCA1-2pv,[23-26] while no reports have addressed this topic in PDAC patients with gBRCA1-2pv.

For this reason, in this multicentric study we aimed at exploring the safety profile, alongside the activity, of different chemotherapy regimens in a cohort of chemo-naïve PDAC patients carrying gBRCA1-2pv, in order to achieve a deeper understanding of this clinical open and unexplored issue.

PATIENTS AND METHODS

Study design and inclusion criteria

This retrospective multicenter study involved 21 Italian oncology departments and was based on clinical—pathological data retrieved from medical records and collected in an electronic database. Patients of any age with documented germline pathogenic variants of BRCA1-2 genes were eligible for this analysis if they had a pathologically confirmed diagnosis of PDAC, had received a first course of chemotherapy by the time of database lock (March 2021), irrespective of the type (adjuvant, primary/neoadjuvant, metastatic first line) and regimen, and had available data on treatment toxicity and/or outcome. All patients enrolled in the study provided a written informed consent for germline BRCA1-2 test, which included the authorization for the use of clinical—pathological and genomic data for scientific purposes, in full compliance with privacy policy.

Patients and tumor characteristics included type of germline BRCA pathogenic variant, age, ECOG Performance Status, clinical stage (AJCC/UICC TNM 8th Edition, 2017), T site, grading, and presence/absence of liver metastases at diagnosis.

Concerning the first chemotherapy administered, we collected information on baseline value of carbohydrate antigen 19.9 (CA19.9), type of chemotherapy (adjuvant, neoadjuvant/primary, first line metastatic), regimen, number of cycles and duration (in weeks), dose intensity, toxicity, and outcome.

Treatment toxicity was evaluated considering the maximum grade of toxicity observed for each regimen and for each patient during the first chemotherapy, referring to the Common Terminology Criteria for Adverse Events 5.0 (CTCAE 5.0). Concurrently, analysis of the dose intensity of each drug was also performed and reported as the percentage of the ratio between the real weekly average dose and the ideal weekly average dose.

Outcome analyses based on RECIST version 1.1 and CA19.9 best response were performed for each first-line

metastatic or primary/neoadjuvant chemotherapy regimen subgroup including at least nine patients. The percentage of surgically resected patients among those treated with primary/neoadjuvant chemotherapy was also recorded. Overall survival (OS) was calculated from the date of chemotherapy start until the date of death or last follow-up visit for patients receiving first-line metastatic chemotherapy, while the date of surgery was the starting time-point for those receiving adjuvant chemotherapy. Progression-free survival (PFS) was calculated from the date of chemotherapy start until the date of documented disease progression or death in patients without disease progression or last follow-up visit for patients receiving first-line metastatic chemotherapy. Disease-free survival (DFS) was calculated for patients receiving adjuvant chemotherapy, starting from the date of surgery until the date of disease relapse or last follow-up visit.

Statistical analysis

All patients were followed up until death or the time of database lock (March 2021). The primary endpoint of the study was to perform a descriptive analysis of treatment toxicity in PDAC patients carrying gBRCA1-2pv and compare the results with the safety profile of the different chemotherapy regimens reported in the literature. The secondary endpoints were the descriptive analysis of objective response rate, disease control rate, and survival outcomes, including PFS, DFS, and OS. For this reason, no statistical design or sample size calculation was performed.

Patient consent

Before testing, all patients signed an informed consensus statement that was revised and approved by a local ethics committee and allowed for genetic testing and data collection, analysis, and elaboration. Data were irreversibly anonymized before entering into the database.

RESULTS

Patients and treatment characteristics

The final analyses of this multicenter survey encompassed 85 PDAC patients with gBRCA1-2 pathogenic variants, who received at least a first course of chemotherapy in 21 Italian oncology departments, between December 2008 and March 2021, and for whom data on treatment toxicity and/or outcome were available. Specifically, data on chemotherapy toxicity were available for 74 of 85 patients, while treatment outcomes were assessable in 83 cases.

Patients and treatments characteristics are presented in Table 1. No relevant difference was detected between the general study population and the subsets of patients evaluable for toxicity (toxicity cohort) and for outcome (outcome cohort). Characteristics of the four largest first-line chemotherapy regimen subgroups ($n \geq 9$), including the 53 metastatic patients who were assessed for outcome, are reported in Table 2.

Treatment toxicity and dose intensity

Treatment toxicity and dose intensity of the four most commonly used ($n \geq 9$) chemotherapy regimens, including nab-paclitaxel plus gemcitabine (AG);[27] folinic acid, fluorouracil, irinotecan, and oxaliplatin (FOLFIRINOX);[28] modified FOLFIRINOX (mFOLFIRINOX);[29] and cisplatin, nab-paclitaxel, capecitabine, and gemcitabine (PAXG),[30] are summarized in Tables 3 and 4, respectively. Grade 3-4 toxicities occurring in >10% of patients were neutropenia (39%) and anemia (11%) for AG; neutropenia (47%) for FOLFIRINOX; neutropenia (30%), anemia (20%), and fever (20%) for mFOLFIRINOX; and neutropenia (66%), diarrhea (25%), thrombocytopenia (17%), anemia (17%), fatigue (17%), and nausea (17%) for PAXG.

No peculiar toxicity has apparently emerged with other less commonly recommended chemotherapy regimens, such as gemcitabine, gemcitabine plus oxaliplatin (GEMOX);[31] cisplatin, epirubicin, capecitabine, and gemcitabine (PEXG);[32] folinic acid, fluorouracil, and oxaliplatin (FOLFOX);[33] folinic acid, fluorouracil, oxaliplatin, and irinotecan (FOLFOXIRI),[34] including ≤5 patients each.

Treatment outcomes

RECIST and CA19.9 response of metastatic patients receiving a first-line and a primary/neoadjuvant therapy as upfront treatment within one of the four largest chemotherapy regimen subgroups ($n \geq 9$) is shown in Table 5.

Concerning survival outcomes of metastatic patients treated with first-line chemotherapy, median follow-up was 17.8 months (range 8.1-148.1 months). Median PFS (mPFS) of the (m)FOLFIRINOX/FOLFOXIRI subgroup ($n = 16$) was >12.9 months (not reached; range 4.8-24.3 months), with five (31%) patients who were progression free at 10.7-24.3 months (median 15 months). Conversely, all 17 patients treated with AG experienced disease progression, with an mPFS of 6.4 months (range 2.0-17.2 months). In the FOLFOX/GEMOX subgroup ($n = 9$) mPFS was 8.0 months (range 2.1-127.5 months), with only one (11%) patient progression free at 17.8 months. Lastly, the 11 patients receiving a four-drug cisplatin-based regimen (PAXG/PEXG) had an mPFS of 11.4 months (not reached; range 4.4-20 months), with two (18%) progression free at 10.8-12.7 months (median 11.7 months).

Median OS (mOS) of the 16 patients treated with (m)FOLFIRINOX/FOLFOXIRI was >17.3 months (not reached; range 7.1-84.7 months), with nine (56%) patients alive at the time of database lock, at 10.7-84.7 months (median 20.4 months). Median OS of the AG subgroup ($n = 17$) was 16.0 months (range 3.1-45.8 months), with three (18%) patients alive at 13.9-33.4 months (median 22.6 months). An mOS >10.5 months (not reached; range 8.5-148 months) was reported for the nine patients receiving FOLFOX/GEMOX, four (44%) of whom were alive at 8.5-148 months (median 12.2 months). Finally, the 11 patients treated with PAXG/PEXG had an mOS of >12.7

Table 1. Patients and treatment characteristics

	All patients (n = 85)	Toxicity cohort (n = 74)	Outcome cohort (n = 83)
Age at diagnosis (years), median (range)	60 (34-84)	61 (34-84)	61 (34-84)
Sex, *n* (%)			
Female	46 (54)	39 (53)	44 (53)
Male	39 (46)	35 (47)	39 (47)
ECOG PS at diagnosis, *n* (%)			
0	57 (67)	47 (63)	55 (66)
1	24 (28)	23 (31)	24 (29)
2	4 (5)	4 (6)	4 (5)
Clinical stage at diagnosis, *n* (%)			
I	7 (8)	5 (7)	7 (8)
II	11 (13)	10 (13)	10 (12)
III	10 (12)	9 (12)	10 (12)
IV	57 (67)	50 (68)	56 (68)
T site, *n* (%)			
Head/uncinate	40 (49)	33 (47)	39 (49)
Body	23 (29)	19 (27)	23 (29)
Tail	14 (17)	14 (20)	14 (18)
Diffuse	4 (5)	4 (6)	3 (4)
NA	4	4	4
Grading, *n* (%)			
1	3 (8)	3 (8)	3 (8)
2	20 (51)	18 (49)	19 (50)
3	16 (41)	16 (43)	16 (42)
NA	46	37	45
Liver metastases at diagnosis, *n* (%)	$n = 57$	$n = 50$	$n = 56$
Yes	45 (79)	39 (78)	44 (79)
No	12 (21)	11 (22)	12 (21)
Baseline CA19.9, *n* (%)	$n = 71$	$n = 65$	$n = 69$
0-37 U/ml	15 (21)	14 (21)	15 (22)
>37 U/ml	56 (79)	51 (79)	54 (78)
Baseline CA19.9 U/ml, median (range)	1077 (37.6-456 308)	956 (37.6-456 308)	1315 (37.6-456 308)
gBRCApv status, *n* (%)			
gBRCA1	21 (25)	18 (24)	21 (25)
gBRCA2	62 (73)	55 (74)	60 (72)
gBRCA1 + gBRCA2	2 (2)	1 (2)	2 (3)
Type of first chemotherapy, *n* (%)			
Adjuvant	10 (12)	8 (11)	10 (12)
Primary/neoadjuvant	18 (21)	16 (21)	17 (20)
First line (metastatic)	57 (67)	50 (68)	56 (68)
Regimen of first chemotherapy, *n* (%)			
AG	20 (24)	18 (24)	20 (24)
(m)FOLFIRINOX/FOLFOXIRI	30 (35)	26 (35)	29 (35)
PAXG	13 (15)	12 (16)	12 (14)
GEMOX	5 (6)	5 (7)	5 (6)
Gemcitabine	5 (6)	4 (6)	5 (6)
PEXG	4 (5)	4 (6)	4 (5)
FOLFOX	5 (6)	3 (4)	5 (6)
Other	3 (3)	2 (2)	3 (4)
Platinum based	58 (68)	51 (69)	56 (68)
Nonplatinum based	27 (32)	23 (31)	27 (32)

AG, nab-paclitaxel plus gemcitabine; CA19.9, carbohydrate antigen 19.9; ECOG PS, Eastern Cooperative Oncology Group performance status; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; FOLFOXIRI, folinic acid, fluorouracil, oxaliplatin, and irinotecan; gBRCA, germline BRCA; GEMOX, gemcitabine plus oxaliplatin; (m)FOLFIRINOX, (modified) folinic acid, fluorouracil, irinotecan, and oxaliplatin; NA, not available; PAXG, cisplatin, nab-paclitaxel, capecitabine, and gemcitabine; PEXG, cisplatin, epirubicin, capecitabine, and gemcitabine; PS, performance status; pv, pathogenic variant; T, primary tumor.

months (not reached; range 4.4-41 months), with five (45%) patients alive at 8.1-41 months (median 12.7 months).

The three remaining metastatic patients who received a first-line chemotherapy were treated either within a clinical trial with napabucasin plus nab-paclitaxel with gemcitabine ($n = 1$)[35] or with gemcitabine ($n = 2$), all experiencing disease progression and death, with an mPFS of 3 months (range 1-5 months) and an mOS of 7.6 months (range 1.6-8.8).

In order to avoid the immortal time bias, we performed an additional outcome analysis, excluding those metastatic patients whose gBRCA testing was performed after first-line chemotherapy conclusion, likely due to favorable outcome. Four patients were then excluded [three treated with (m) FOLFIRINOX and one with GEMOX]. RECIST and CA19.9 responses of this second analysis are shown in Table 5. The (m)FOLFIRINOX/FOLFOXIRI subgroup encompassed 13 patients, who had an mPFS >12 months (not reached; range

Table 2. Patients and treatment characteristics of the 53 metastatic patients assessed for outcome

	AG ($n = 17$)	(m)FOLFIRINOX/FOLFOXIRI ($n = 16$)	FOLFOX/GEMOX ($n = 9$)	PAXG/PEXG ($n = 11$)
Age at diagnosis (years), median (range)	62 (40-76)	56 (34-71)	59 (41-73)	63 (46-72)
Sex, *n* (%)				
Female	11 (65)	7 (44)	5 (56)	4 (37)
Male	6 (35)	9 (56)	4 (44)	7 (63)
ECOG PS at diagnosis, *n* (%)				
0	13 (76)	12 (75)	3 (33)	5 (45)
1	3 (18)	4 (25)	4 (45)	6 (55)
2	1 (6)	0	2 (22)	0
T site, *n* (%)				
Head/uncinate	8 (47)	6 (37)	4 (50)	4 (37)
Body	5 (29)	6 (37)	2 (25)	2 (18)
Tail	3 (18)	4 (26)	2 (25)	5 (45)
Diffuse	1 (6)	0	0	0
NA	0	0	1	0
Liver metastases at diagnosis, *n* (%)				
Yes	13 (77)	12 (75)	6 (67)	10 (91)
No	4 (23)	4 (25)	3 (33)	1 (9)
Baseline CA19.9, *n* (%)				
0-37 U/ml	1 (6)	4 (29)	2 (25)	2 (18)
>37 U/ml	15 (94)	10 (71)	6 (75)	9 (82)
NA	1	2	1	0
Baseline CA19.9 U/ml, median (range)	956 (130-8485)	2850 (229-4518)	4099 (80-12 150)	2788 (65-456 308)
gBRCApv status, *n* (%)				
gBRCA1	3 (18)	4 (25)	3 (33)	2 (18)
gBRCA2	14 (82)	12 (75)	5 (56)	9 (82)
gBRCA 1 + 2	0	0	1 (11)	0

AG, nab-paclitaxel plus gemcitabine; CA19.9, carbohydrate antigen 19.9; ECOG PS, Eastern Cooperative Oncology Group performance status; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; FOLFOXIRI, folinic acid, fluorouracil, oxaliplatin, and irinotecan; gBRCA, germline BRCA; GEMOX, gemcitabine plus oxaliplatin; (m)FOLFIRINOX, (modified) folinic acid, fluorouracil, irinotecan, and oxaliplatin; NA, not available; PAXG, cisplatin, nab-paclitaxel, capecitabine, and gemcitabine; PEXG, cisplatin, epirubicin, capecitabine, and gemcitabine; PS, performance status; pv, pathogenic variant; T, primary tumor.

−4.8 to 24.3 months), with 6 (46%) patients who were progression free at 10.7-24.3 months (median 14.3 months). Median OS was >15 months (not reached; range 7.1-37.4 months), with eight (62%) patients alive at 10.7-37.4 months (median 18.7 months). In the FOLFOX/GEMOX subgroup ($n = 8$) mPFS was 7.2 months (range 2.1-17.8 months), with still only one (12%) patient progression free at 17.8 months. Median OS was >10.4 months (not reached; range 7.4-13.8 months) and three (37%) patients were alive at 8.5-13.8 months (median 10.5 months). In this additional analysis, we also compared outcomes of metastatic patients with gBRCA2pv ($n = 38$) versus gBRCA1pv ($n = 11$) treated with multidrug chemotherapy regimens (patients receiving single-agent chemotherapy were excluded). mPFS was 9.4 (range 2-46) versus 5.9 (range 0.9-14.2) months for the gBRCA2pv versus gBRCA1pv cohorts, with four (10%) patients progression free at 12.7-24.3 months (median 14.9 months) and two (18%) patients progression free at 10.7 months, respectively. Median OS was >14.1 months (not reached; range 3.1-47.9 months), with 15 (37%) patients alive at 8.1-41 months (median 20.4 months) in the gBRCA2pv subgroup, as opposed to >10.8 months (not reached; range 1.6-37.2 months), with three (27%) patients alive at 10.7-12.9 months (median 10.8 months) in the gBRCA1pv subgroup.

Outcome for patients receiving a primary/neoadjuvant upfront treatment ($n = 17$) is summarized in Table 5. Of note, 87% (13/15) of patients treated with platinum-based primary/neoadjuvant chemotherapy [(m)FOLFIRINOX = 8, PAXG = 3, PEXG = 1, liposomal irinotecan (nal-IRI) plus folinic acid, fluorouracil, oxaliplatin = 1], as opposed to none of the two patients receiving AG, were surgically resected.

The adjuvant chemotherapy subgroup included only 10 patients, treated with heterogeneous regimens [4 (m)FOLFIRINOX, 3 gemcitabine, 1 PEXG, 1 gemcitabine plus capecitabine, 1 AG]. DFS of the entire group was >16.8 months (not reached; range 8.9-87 months), with four (40%) patients who were disease free at 13.9-87 months (median 78.4 months), whereas OS was >50.4 months (not reached; range 13.9-90.1 months), with seven (70%) patients alive at 13.9-90.1 months (median 44.7 months).

Subsequent therapies

By the time of database lock, 82% (9/11) of metastatic patients treated with first-line (m)FOLFIRINOX/FOLFOXIRI who experienced progression of disease had started and/or completed a second-line treatment, mostly gemcitabine based (7/9, 78%). Among the 17 patients treated with first-line AG who had disease progression, 14 (82%) had started and/or completed a second-line chemotherapy, receiving a platinum-based combination in most cases (12/14, 86%). Patients treated upfront with an oxaliplatin-doublet (FOLFOX/GEMOX) received a second-line treatment in 75% of cases with disease progression (6/8), with heterogenous regimens. Finally, the nine PAXG/PEXG patients who had progression of disease started and/or completed a

Table 3. Treatment toxicity of the four most commonly used ($n \geq 9$) chemotherapy regimens

	AG ($n = 18$)			FOLFIRINOX[a] ($n = 15$)			mFOLFIRINOX[a] ($n = 10$)			PAXG ($n = 12$)		
	Grade			Grade			Grade			Grade		
	1-2	3	4	1-2	3	4	1-2	3	4	1-2	3	4
Neutropenia, *n* (%)	7 (39)	7 (39)	0 (0)	4 (27)	6 (40)	1 (7)	1 (10)	2 (20)	1 (10)	1 (8)	7 (58)	1 (8)
Anemia, *n* (%)	12 (67)	2 (11)	0 (0)	6 (40)	0 (0)	0 (0)	4 (40)	2 (20)	0 (0)	9 (75)	2 (17)	0 (0)
Thrombocytopenia, *n* (%)	10 (55)	0 (0)	0 (0)	5 (33)	0 (0)	0 (0)	8 (80)	0 (0)	0 (0)	3 (25)	2 (17)	0 (0)
Febrile neutropenia, *n* (%)	0 (0)	1 (5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (10)	0 (0)	1 (8)	0 (0)
Fatigue, *n* (%)	14 (78)	1 (5)	0 (0)	11 (73)	0 (0)	0 (0)	7 (70)	0 (0)	0 (0)	8 (67)	2 (17)	0 (0)
Nausea, *n* (%)	4 (22)	1 (5)	0 (0)	9 (60)	0 (0)	0 (0)	6 (60)	0 (0)	0 (0)	8 (67)	2 (17)	0 (0)
Vomiting, *n* (%)	4 (19)	0 (0)	0 (0)	2 (13)	0 (0)	0 (0)	1 (10)	0 (0)	0 (0)	1 (8)	1 (8)	0 (0)
Diarrhea, *n* (%)	3 (14)	0 (0)	0 (0)	5 (33)	0 (0)	0 (0)	6 (60)	0 (0)	0 (0)	2 (17)	3 (25)	0 (0)
Constipation, *n* (%)	2 (11)	0 (0)	0 (0)	3 (20)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (25)	0 (0)	0 (0)
Mucositis, *n* (%)	4 (19)	0 (0)	0 (0)	3 (20)	0 (0)	0 (0)	5 (50)	0 (0)	0 (0)	3 (25)	0 (0)	0 (0)
HFS, *n* (%)	1 (5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	6 (50)	1 (8)	0 (0)
Fever, *n* (%)	3 (17)	1 (5)	0 (0)	1 (7)	0 (0)	0 (0)	1 (10)	2 (20)	0 (0)	7 (58)	0 (0)	0 (0)
Infections, *n* (%)	2 (11)	0 (0)	0 (0)	1 (7)	0 (0)	0 (0)	0 (0)	1 (10)	0 (0)	3 (25)	0 (0)	0 (0)
CIPN, *n* (%)	6 (33)	1 (5)	0 (0)	7 (47)	0 (0)	0 (0)	6 (60)	0 (0)	0 (0)	7 (58)	0 (0)	0 (0)
Peripheral edema, *n* (%)	2 (11)	0 (0)	0 (0)	(7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (8)	0 (0)	0 (0)
Rash/allergy, *n* (%)	1 (5)	0 (0)	0 (0)	1 (7)	0 (0)	0 (0)	1 (10)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

AG, nab-paclitaxel plus gemcitabine; CIPN, chemotherapy-induced peripheral neuropathy; FOLFIRINOX, folinic acid, fluorouracil, irinotecan, and oxaliplatin; FOLFOXIRI, folinic acid, fluorouracil, oxaliplatin, and irinotecan; HFS, hand—foot syndrome; mFOLFIRINOX, modified FOLFIRINOX; PAXG, cisplatin, nab-paclitaxel, capecitabine, and gemcitabine.
[a] One patient treated with FOLFOXIRI regimen was excluded.

Table 4. Treatment dose intensity and median number of cycles of the four most commonly used ($n \geq 9$) chemotherapy regimens

Regimen	Dose intensity (%)	Number of cycles, median (range)
AG ($n = 18$)		7 (2-10)
Nab-paclitaxel	72	
Gemcitabine	76	
FOLFIRINOX[a] ($n = 15$)		8 (4-21)
Oxaliplatin	64	
Irinotecan	58	
Fluorouracil bolus	35	
Fluorouracil c.i.	63	
mFOLFIRINOX[a] ($n = 10$)		10 (1-12)
Oxaliplatin	85	
Irinotecan	79	
Fluorouracil c.i.	87	
PAXG ($n = 12$)		5.5 (1-6)
Cisplatin	75	
Nab-paclitaxel	73	
Capecitabine	73	
Gemcitabine	65	

AG, nab-paclitaxel plus gemcitabine; c.i., continuous infusion; FOLFIRINOX, folinic acid, fluorouracil, irinotecan, and oxaliplatin; FOLFOXIRI, folinic acid, fluorouracil, oxaliplatin, and irinotecan; mFOLFIRINOX, modified FOLFIRINOX; PAXG, cisplatin, nab-paclitaxel, capecitabine, and gemcitabine.
[a] One patient treated with FOLFOXIRI regimen was excluded.

second-line therapy in six cases (67%), three receiving GEMOX and three fluoropyrimidine plus irinotecan.

Considering the whole cohort of metastatic patients treated with first-line chemotherapy ($n = 57$), 23 (40%) received olaparib throughout their course of treatment.

DISCUSSION

This multicenter survey provides an extensive overview of the impact of chemotherapy combinations that are commonly used for PDAC treatment in clinical practice, focusing on toxicity, dose intensity, and outcome in a large series of patients harboring gBRCA1-2pv.

We believe that our data highlighted a potentially increased toxicity on proliferating cells, alongside an apparently enhanced activity of platinum-based regimens compared with platinum-free regimens.

Toxicity profile varied across chemotherapy regimens and we acknowledge that the limited sample size of our series hampers drawing firm conclusions on this topic, particularly on rare adverse events whose rates may consistently vary due to a single supplementary or decremental episode. In addition, under reporting of adverse events, mostly those that are either low grade or unrelated to laboratory data, is an inherent weakness of retrospective analyses and may account for the discrepancies between nonhematological toxicities rates reported in our survey and those described in the literature.[27-30] However, these limitations are likely less stringent in the case of grade 3-4 adverse events that we have considered for this analysis, and focusing on more frequent toxicities, such as neutropenia, may temperate these drawbacks. Furthermore, another strength of our series is the availability of data on dose intensity and treatment duration of the different regimens, paving the way for a more suitable interpretation of toxicity data that may provide hypothesis-generating information. In the AG platinum-free regimen, the median relative dose intensity was comparable to the pivotal phase III MPACT trial,[27] being unchanged for gemcitabine and slightly reduced for nab-paclitaxel (72% versus 81%). Consistently, neutropenia rate (39% versus 38%) and anemia (11% versus 13%) were superimposable, while a minor reduction of grade 3-4 fatigue, chemotherapy-induced peripheral neuropathy (CIPN; 5% versus 17% for both events), and thrombocytopenia (0% versus 13%) was observed. With regard to oxaliplatin-containing regimens, data on patients treated with mFOLFIRINOX are difficult to interpret in the context of prior literature due to the different populations (mainly metastatic versus adjuvant), lack of information on granulocyte

Table 5. RECIST and CA19.9 response of metastatic PDAC patients receiving a first-line or a primary/neoadjuvant upfront treatment within one of the four largest chemotherapy regimen subgroups ($n \geq 9$)

	First line (I L)	Primary/neoadjuvant (P/N)[c]	All (I L + P/N)
(m)FOLFIRINOX/FOLFOXIRI	$n = 16$[a]	$n = 9$	$n = 25$
RECIST response, *n* (%)			
CR	2 (12)	0 (0)	2 (8)
PR	11 (69)	8 (89)	19 (76)
SD	3 (19)	1 (11)	4 (16)
PD	0 (0)	0 (0)	0 (0)
CA19.9 reduction at nadir, *n* (%)	$n = 9$	$n = 6$	$n = 15$
>89%	6 (67)	2 (33)	8 (53)
≤89%	3 (33)	4 (67)	7 (47)
Median time to CA19.9 nadir, (range), months	4 (3-7)	3 (2-4)	3.6 (2-7)
AG	$n = 17$	$n = 2$	$n = 19$
RECIST response, *n* (%)			
CR	0 (0)	0 (0)	0 (0)
PR	7 (41)	1 (50)	8 (42)
SD	6 (35)	1 (50)	7 (37)
PD	4 (24)	0 (0)	4 (21)
CA19.9 reduction at nadir, *n* (%)	$n = 11$	$n = 2$	$n = 13$
>89%	5 (45)	1 (50)	6 (46)
≤89%	6 (55)	1 (50)	7 (54)
Median time to CA19.9 nadir (range), months	3 (1.5-8)	5 (2-8)	3 (1.5-8)
FOLFOX/GEMOX	$n = 9$[b]	$n = 1$	$n = 10$
RECIST RESPONSE, *n* (%)			
CR	0 (0)	0 (0)	0 (0)
PR	5 (56)	1 (100)	6 (60)
SD	1 (11)	0 (0)	1 (10)
PD	3 (33)	0 (0)	3 (30)
CA19.9 reduction at nadir, *n* (%)	$n = 3$	$n = 1$	$n = 4$
>89%	1 (33)	0 (0)	1 (25)
≤89%	2 (67)	1 (100)	3 (75)
Median time to CA19.9 nadir, (range), months	5 (2-5)	3	4 (2-5)
PAXG/PEXG	$n = 11$	$n = 4$	$n = 15$
RECIST response, *n* (%)			
CR	1 (9)	0 (0)	1 (7)
PR	7 (64)	2 (50)	9 (60)
SD	3 (27)	2 (50)	5 (33)
PD	0 (0)	0 (0)	0 (0)
CA19.9 reduction at nadir, *n* (%)	$n = 9$	$n = 3$	$n = 12$
>89%	6 (67)	2 (67)	8 (67)
≤89%	3 (33)	1 (33)	4 (33)
Median time to CA19.9 nadir, (range), months	4.5 (1-7)	5 (5-6)	5 (1-7)

AG, nab-paclitaxel plus gemcitabine; CA19.9, carbohydrate antigen 19.9; CR, complete response; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; FOLFOXIRI, folinic acid, fluorouracil, oxaliplatin, and irinotecan; GEMOX, gemcitabine plus oxaliplatin; (m)FOLFIRINOX, (modified) folinic acid, fluorouracil, irinotecan, and oxaliplatin; PAXG, cisplatin, nab-paclitaxel, capecitabine, and gemcitabine; PD, progressive disease; PDAC, pancreatic ductal adenocarcinoma; PEXG, cisplatin, epirubicin, capecitabine, and gemcitabine; PR, partial response; SD, stable disease.

[a,b] Additional outcome analysis: [a](m)FOLFIRINOX/FOLFOXIRI $n = 13$; RECIST response, *n* (%); CR, 1 (8); PR, 9 (69); SD, 3 (23); PD, 0; CA19.9 reduction at nadir, *n* (%); $n = 8$; ≥50%, 7 (87); <50%, 1 (13); median time to CA19.9 nadir (range): 4.2 (3-7) months. [b]FOLFOX/GEMOX $n = 8$ RECIST response, *n* (%); CR, 0; PR, 4 (50); SD, 1 (12); PD, 3 (38). CA19.9 reduction at nadir [*n* (%)], $n = 2$; ≥50%, 1 (50); <50%, 1 (50); median time to CA19.9 nadir (range): 3.5 (2-5) months.

[c] One patient received liposomal irinotecan (nal-IRI) plus folinic acid, fluorouracil, oxaliplatin with PR. CA19.9 was not expressed.

colony-stimulating factors used in our series, and lack of dose-intensity information in the phase III trial.[29] By contrast, patients treated with FOLFIRINOX received a median of only 8 cycles as opposed to 10 in the phase III trial[28] and also the dose intensity of 5-FU, irinotecan, and oxaliplatin (64%, 58%, and 63%, respectively) was considerably lower (82%, 81%, and 78%, respectively).[28] Despite the substantial reduction in chemotherapy total dose, grade 3-4 neutropenia rate (47%) in our series overlapped with previously reported data (46%).[28] Further grade 3-4 toxicities, such as thrombocytopenia, anemia, fatigue, diarrhea, vomiting, and CIPN, did not occur. However, these events usually occur later than neutropenia in the course of treatment and the lower rates observed may be a consequence of early dose reduction. Consistent with this interpretation, the cisplatin-based PAXG regimen, which was administered for an overlapping number of cycles and with comparable dose intensity with respect to the randomized phase II trial, paid the toll of an increased grade 3-4 neutropenia (66% versus 41%), thrombocytopenia (17% versus 7%), and diarrhea (25% versus 7%).[30] Noteworthy, toxicities that are multifactorial or less related to proliferating cells, such as anemia, fatigue, and CIPN, overlapped the previously reported rates.[30]

Other retrospective investigations including 31-150 patients addressed chemotherapy toxicity in other types of gBRCA1-2pv neoplasms.[23-26,36-39] Albeit mostly not reporting information on dose-intensity or treatment duration, these series apparently confirm our findings. Patients with breast cancer receiving anthracycline- and taxane-based chemotherapy had no difference in toxicity as opposed to wild-type patients.[24,25,36,37] Only acute (i.e. after the first

cycle) neutropenia increased without any impact on overall grade 3-4 maximum toxicity.[24,36] By contrast, in patients with ovarian cancer receiving platinum-based chemotherapy, hematological toxicity was more serious among those harboring gBRCA1-2pv in the majority of series,[26,38] with a few exceptions in smaller surveys[23] or without separately reported data for patients receiving either intravenous or intraperitoneal platinum salts.[39]

The unique data about chemotherapy toxicity in PDAC patients with gBRCA1-2pv can be derived from the phase II trial by O'Reilly and colleagues,[21] which investigated the activity of gemcitabine plus cisplatin with or without veliparib in patients with gBRCA1-2 or PALB2pv.[21] In the 23 patients treated with gemcitabine plus cisplatin, grade 3-4 neutropenia and anemia were 30% and 35%, respectively.[21] Again, these rates are higher than expected on the basis of a previous phase III trial with gemcitabine plus cisplatin in unselected PDAC patients (25% and 5%, respectively), when data are properly interpreted in the context of the mean planned weekly dose of gemcitabine that was nearly halved (400 mg/mq/week versus 750 mg/mq/week).[40]

Regarding the response rate and survival endpoints of our survey, the descriptive analysis was mainly focused on the larger group of metastatic PDAC patients. RECIST complete and partial responses were numerically higher with the three- (81%) or four-drug (73%) platinum-containing regimens that outperformed AG (41%) and oxaliplatin-based doublets (56%). Consistently, CA19.9 reduction at nadir >89% was reported in two-third of metastatic patients treated with triplets and quadruplet, as opposed to 33% and 45% of patients receiving oxaliplatin-based doublets or AG, respectively. Keeping in mind the limitations of the small sample size of any treatment subgroup and the retrospective nature of our analysis, RECIST and CA19.9 response rates were 23%-49% higher than expected based on the literature with platinum salt-based regimens.[28,30,31,41] Conversely, limited (versus 29% in[27]) or no difference at all if compared with more recent phase III data (42% in[42]; 36% in[43]) appeared with AG.

With regard to survival outcomes, the follow-up was immature and the number of events was limited, not allowing firm inferences. Furthermore, prognostic factors were heterogeneously distributed across treatment subgroups. In particular, patients receiving FOLFIRINOX were younger, had better PS, less frequent involvement of the liver, and more often a normal baseline CA19.9 as compared with other groups. Nonetheless, it is noteworthy that all patients receiving a first-line treatment with AG experienced disease progression, with an mPFS of 6.4 months, whereas the other patients treated with platinum-containing triplet or quadruplet had an mPFS ≥11.4 months. Albeit still immature, data on OS seem to parallel those on PFS and to endorse previous findings reported in the literature.[19-21,44] The 1- and 2-year actuarial survival was 76% and 18%, respectively, for the 17 AG-treated patients, as compared with 71% and 56%, respectively (75% and 56%, respectively, for the triplets; 67% and 53%, respectively, for the quadruplets) for the 24 patients treated with platinum salt-containing triplets or quadruplets (excluded those whose gBRCA testing was performed after first-line chemotherapy conclusion; data not shown).

National Comprehensive Cancer Network (NCCN) guidelines suggest that all newly diagnosed PDAC patients meet the criteria for genetic testing, regardless of age at diagnosis, family history, or tumor stage.[45] Indeed, our data suggest that the identification of a gBRCA1-2pv has a relevant impact not only on screening of patient's relatives and of other gBRCA1-2-related neoplasms but also on therapeutic decisions.

Conclusion

Overall, our findings endorse the hypothesis that BRCA1-2 haploinsufficiency, namely, mutation of a single allele, might result in increased cytotoxic effect of DNA cross-linking agents, such as platinum salts, on both cancer cells and proliferating noncancerous cell types (e.g. hematopoietic and bowel cells). Consequently, dose reductions, treatments delays, and higher risk of (hematological and gastrointestinal) toxicity encumber administration of platinum-based chemotherapy regimens. Nevertheless, this perspective efficacy is clearly superior, when compared with platinum-free therapeutic options, and low-dose cisplatin-containing regimens or oxaliplatin-containing triplets with appropriate dose reductions have manageable toxicity and must be preferred.

In conclusion, albeit caution should be exercised due to drawbacks of this analysis, including the lack of a matching internal cohort of wild-type controls, extensive gBRCA testing is recommended in all PDAC patients, irrespective of stage, to inform and drive the therapeutic choice, which should favor platinum-based triplets and quadruplets whenever a gBRCA1-2pv is detected.

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DISCLOSURE

MN reports travel expenses from Celgene; speaker honorarium from Accademia della Medicina; and consultant honoraria from EMD Serono. IG serves on the advisory board of Amgen, Takeda, and Eisai. GT reports travel expenses and personal honoraria for advisory boards from Celgene, Merck, AstraZeneca, Servier, and BMS. SC reports travel expenses and personal honoraria for the following companies: Amgen, Bayer, Eli Lilly, and Servier (as speaker); Amgen, Eli Lilly, Bayer, Baxter, Merck Sharp & Dohme (MSD), Servier (on advisory boards). Amgen, Baxter, Eli Lilly, Celgene, Novartis, and MSD (as consultant); receiving research grant from Celgene and Eisai. MM reports personal

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DATA SHARING

Data are available upon reasonable request.

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