Original article

Second-line therapy in Pancreatic Ductal Adenocarcinoma (PDAC) patients with germlineBRCA1-2 pathogenic variants (gBRCA1-2pv)

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Introduction

Despite its overall rarity, Pancreatic Ductal Adenocarcinoma (PDAC) is one of the leading causes of cancer-related death throughout the world, with a 5-year overall survival (OS) rate drawing near 10% in 2020 [1]. Given its increasing incidence, PDAC is expected to rank second for cancer mortality by 2030 [2]. In most cases PDAC patients present with advanced stage disease *ab initio*, either metastatic (50-55%) or locally advanced (30-35%), for the most part amenable only to systemic therapeutic approaches [3]. Phase III and II randomized controlled trials (RCTs) demonstrated a significant improvement of survival outcome of metastatic PDAC with multidrug chemotherapy regimens, including Nab-paclitaxel plus Gemcitabine (AG), FOLinic acid, Fluorouracil, IRINotecan and OXaliplatin (FOLFIRINOX) and Cisplatin, Nab-Paclitaxel, Capecitabine and Gemcitabine (PAXG) [4-6]. Conversely, recommendations on second-line therapy are largely undefined [7,8]. The PANCREOX and the CONKO-003 phase III RCTs reported either limited or no benefit from the addition of Oxaliplatin to Fluorouracil and Folinic acid upon failure of single agent gemcitabine [9,10]. Also, the more recent NAPOLI-1 RCT showed negligible survival advantage of the combination of liposomal Irinotecan (Nal-IRI) with 5-FU/LV in metastatic PDAC patients previously treated with gemcitabine-based chemotherapy (gemcitabine alone in 45% of cases) [11]. Noteworthy, 43% of these patients had received

fluorouracil-based previous anticancer therapy, thus hampering the interpretation of the true magnitude of the OS benefit of combination over single agent fluorouracil in a fluorouracil-naïve population [11]. Of note, no data from RCTs specifically addressing second-line therapy after first-line multidrug chemotherapy regimens (AG, FOLFIRINOX, PAXG) are currently available [8]. Therefore, clinical practice is based on real-word evidence, which endorses the options of either AG or gemcitabine alone after first-line FOLFIRINOX or 5-FU/LV either alone or combined with Oxaliplatin (FOLFOX) and/or Irinotecan/Liposomal Irinotecan after first-line AG-based therapy, according to patient PS [7,8,12].

GermlineBRCA1-2 pathogenic variants (gBRCA1-2pv)-related PDAC, which accounts for 5-9% of unselected patients, is emerging as a distinct clinical entity, benefitting from specific systemic treatments that exploit the defective Homologous Recombination (HR) system [13-15]. Several retrospective data support the use of platinum-based chemotherapy, inducing DNA Double Strand Breaks (DSB), in this setting [13, 16-18].

Intuitively, the scarce evidence on optimal second-line therapy for PDAC as a whole corresponds to a complete gap of knowledge in this rare subset of patients carrying gBRCA1-2pv, in which only anecdotal information is available [17,19]. As the result of the germline test is not always available at the time of treatment start and since not all patients are suitable to receive upfront FOLFIRINOX chemotherapy, it is not unusual that metastatic PDAC patients with gBRCA1-2pv are initially treated with platinum-free therapy in clinical practice. Whether platinum salts could provide the same benefit also as second-line therapy or should be introduced as early as possible in the course of treatment is an unanswered issue. Keeping in mind the rarity of gBRCA1-2pv in PDAC, which is a considerable hindrance to prospective trials, retrospective information might be reasonably useful to shed light on this topic.

In this perspective, we explored second-line therapy outcome in PDAC patients harboring gBRCA1-2pv through a multicentre survey, in an effort to provide useful insights on the therapeutic management of this specific PDAC subpopulation.

Materials and Methods

Study Design and Inclusion Criteria

Clinical data of metastatic PDAC patients of any age carrying a germline pathogenic variant of BRCA1-2 genes completing any kind of chemotherapy regimen between October 2013 and November 2021 were retrospectively retrieved by medical records of 23 Italian Oncology Departments and collected in an electronic database.

Patients who progressed on first-line therapy and completed a second-line treatment by the time of database lock (November 15th 2021) were included in the primary analysis, that focused on second-line therapy outcome evaluation. Patients receiving single-agent chemotherapy as first-line and/or second-line treatment were excluded from this analysis, to minimize the potential confounding effect of poor Performance Status (PS) on therapy outcome evaluation.

Furthermore, a secondary analysis addressing the role of timing of platinum agent introduction was performed, including all stage IV patients who received a combination chemotherapy as first-line treatment for at least six months at the time of database lock, irrespective of receiving second-line treatment. This choice allows including into this secondary analysis all those patients who had the chance to receive a platinum compound during their therapeutic management. All patients enrolled in the study had signed a written informed consent for genetic test, authorizing the use of clinical and genomic data for scientific research aims, in compliance with privacy policy.

Data collected included baseline patients and tumor characteristics (age, gender, type of germline BRCA pathogenic variant, ECOG PS, clinical stage according to AJCC/UICC TNM 8th Edition, 2017, T site, presence/absence of liver metastases), Carbohydrate Antigen 19.9 (CA19.9), first- and second-line chemotherapy regimen, duration and outcome.

A descriptive analysis of outcome was performed, covering both Response Evaluation Criteria In Solid Tumors 1.1 (RECIST 1.1) best response and survival to first-line and second-line therapies. Progression-free Survival 2 (PFS_2) and Overall survival 2 (OS_2) were calculated from second-line therapy start to second disease progression or death without disease progression and to death or last follow-up visit, respectively. Overall survival (OS) was calculated from the date of first-line therapy start until the date of death or last follow up visit. Progression -free survival 1 (PFS_1) was calculated from first-line therapy start until the first documented

disease progression. Information on CA19.9 response to first-line and second-line therapies was available for only a small subset of patients, therefore it was not included in the analysis.

Statistical Analysis

The primary endpoint of the study was the descriptive analysis of RECIST response and survival outcomes, including OS_2 and PFS_2, related to second-line therapy in a cohort of stage IV PDAC patients carrying gBRCA1-2pv. The secondary endpoint aimed at investigating the impact on the outcome of the choice of recommending platinum-based chemotherapy early and of the type of platinum regimen (3-4 drugs regimens versus 2-drug regimens) as opposed to reserving this opportunity for a later time, in terms of OS, PFS_1 and probability of receiving a second-line treatment. Survival probabilities were estimated using the Kaplan-Meier methods. Due to the descriptive nature of the investigation, no statistical design or sample size calculation were performed. All analyses were carried out using Statistica 12.0 statistical package for Windows (Statsoft Inc, 2011, Tulsa, OK. 74104, USA).

All tests were two sided and P values < 0.05 were considered statistically significant.

Results

Patients and treatment characteristics

Clinical data of 84 PDAC patients with gBRCA1-2pv, diagnosed with stage IV disease and treated with any type of chemotherapy in 23 Italian Oncology Departments between October 2013 and November 2021 were collected. Following the application of the aforementioned inclusion criteria, 43 patients were selected for the primary analysis of second-line therapy outcomes, as shown in the consort flow-chart in Figure 1. Characteristics of this subset of patients, alongside with the type of first-line and second-line chemotherapy regimens they received, are reported in Table 1. Twenty-two patients received a platinum-based first-line chemotherapy, 12 (55%) of whom were also treated with Olaparib either as a maintenance therapy (N=8) or as a subsequent line of therapy (N=4). Three further patients of this group were randomized to either Olaparib or placebo in the context of POLO trial [15]. Among the 21 patients who did not receive platinum upfront, 6 (29%) received Olaparib either as maintenance therapy of a platinum-based second-line therapy (N=3) or as subsequent line treatment (N=3).

As for the secondary analysis, 77 patients were included: 28 were treated with platinum-free first-line therapy, 40 with platinum-based 3- and 4-drugs first-line regimens and 9 with platinum-based doublets as first-line therapy. Characteristics of these patients considered for the secondary analysis are detailed in Table 2.

Olaparib was administered as maintenance therapy of a platinum-based first-line chemotherapy in 23 out of 49 patients (47%), specifically in 19/40 (48%) patients previously treated with a triplet or quadruplet and 4/9 (44%) patients that received upfront platinum-based doublet. Among these 49 patients, 5 (10%) were enrolled in the POLO trial [15] (4 treated with platinum-based triplets/quadruplets and 1 with FOLFOX) and 4 (8%) received Olaparib as subsequent line treatment. Among the 28 patients who did not receive platinum upfront, 6 (21%) received Olaparib either as maintenance therapy of a platinum-based second-line therapy (N=3) or as subsequent line treatment (N=3).

Primary analysis: second-line therapy outcomes

RECIST best response was available for 21 out 22 patients receiving platinum-free second-line therapies, entailing: 5 (24%) Partial Response (PR), 6 (28%) Stable Disease (SD) and 10 (48%) Progressive Disease (PD). Concerning the subgroup of 21 patients treated with platinum-based second-line chemotherapy, RECIST best responses were as follows: 10 (48%) PR, 5(24%) SD, and 6 (28%) PD.

Survival outcomes (PFS_2 and OS_2) of second-line therapy in relation to different stratification variables (BRCA status, gender, age, platinum-free versus platinum-based second-line therapy and PFS_1) are reported in Table 3 and Figure 2 (Kaplan Meier). In the platinum-based second-line therapy group 62% and 28.6% of patients were alive and free from disease progression at 6 months and at 1 year respectively, if compared to 45.5% and 4.5% of patients in the platinum-free second-line group. After a median follow up of 35.2 months, 66.7% of patients treated with platinum-based second-line therapy were alive at 1 year, as opposed to 43.6% of patients receiving platinum-free chemotherapy regimens as second-line (median follow-up: 30.3 months).

Among the 19 patients experiencing disease progression to platinum-free second-line therapy, 12 (63%) received a third-line treatment, that was platinum-based in 50% of cases (6/12). Notably, the Disease Control Rate in these 6 patients was 67% (i.e. 2 partial responses plus 2 stable disease) as opposed to none among the 6 who received a third-line platinum-free, with a median progression-free and overall survival from third-line chemotherapy start of 7.5 and 20.1 months (range 2.8-26 months), respectively, as opposed to 3.2 and 5.7

months, respectively, for platinum-free regimens. On the other hand, 17 out of 19 (85%) patients progressing to platinum-containing second-line therapy were furtherly treated with a third line, that was platinum-based in 5 cases (29%) and platinum-free in 12. No difference in median progression-free (2.1 and 3.3 months, respectively) and overall survival (6.6 and 8.1 months, respectively) from third-line chemotherapy start was observed.

Secondary analysis: early platinum versus no early platinum?

Concerning survival outcomes of the 77 patients included in the secondary analysis, median PFS_1 ($mPFS_1$) of the 40 patients treated with 3-4 drugs platinum-based regimens was 11.4 months (range 1.4-91.2 months), with 14 (35%) patients progression-free at 7.6-91 months (median 18.5 months), as opposed to 6.4 months (range 0.9-80.3) of the 28 patients receiving a platinum-free first-line therapy ($p = 0.007$) and 7.9 months (range 2.0-21.3) of the 9 patients that received a platinum-based first-line doublet ($p=0.01$), all experiencing disease progression (Fig. 3A -Kaplan Meier). No significant $mPFS_1$ difference was detected between platinum-based doublets and platinum-free regimens ($p=0.86$ - Fig. 3A -Kaplan Meier). 6 months PFS_1 rates were 57.1%, 55.5% and 85% for first-line therapy containing no platinum salts, platinum-based doublets and platinum-based triplets/quadruplets respectively. Accordingly, 1 year-PFS_1 rates were 14.3% vs 11.1% vs 53% in the three subgroups.

Median OS (mOS) of the 40 patients receiving platinum-based first-line triplets or quadruplets was 29.2 months (range 1.5-96.5), with 17 (42%) patients alive at 7.6-91.2 months (median 20.1 months), as opposed to 20.2 months (range 1.5-80.3) of the 28 patients treated with platinum-free first-line therapy ($p=0.19$), 6 (21%) of whom were alive at 11.1-80.3 months (median 35.2 months), and to 11.2 months (range 7.3-21.3) of the 9 patients treated with 2-drugs platinum-based first-line regimens ($p=0.017$), of whom only 1 (11%) patient was alive at 20.7 months (Fig. 3B-Kaplan Meier). Platinum-based doublets did not have a significant impact on OS if compared to no early platinum ($p=0.08$). 82.1%, 33.3% and 78.6% of patients were alive at 1 year when receiving no early platinum, platinum-based first-line doublets and triplets/quadruplets respectively. At 2 years these rates decreased to 40%, 0% and 61.9% in the three subgroups.

Among the 26 out of 28 (93%) patients who experienced disease progression to platinum-free first-line chemotherapy, 22 (85%) received a second-line therapy. Moreover, 24 of the 40 (60%) patients treated with

3-4 drugs platinum-based first-line therapy had PD and 19 out of these 24 (80%) patients received a second-line therapy. Lastly, PD was reported in 8 of the 9 (89%) patients that received a 2 drugs platinum-based first-line therapy, of whom 6 (75%) were treated with a second-line therapy.

Discussion

The primary analysis of this multicentre survey demonstrated that platinum-based second-line therapy significantly delayed disease progression when compared to platinum-free chemotherapy regimens in PDAC patients harboring gBRCA1-2pv. Indeed, the median PFS_2 of patients receiving a platinum-free second-line therapy was superimposable with that reported in RCTs, including either platinum-based combinations (FOLFOX in [9], OFF in [10]) or platinum-free regimens (Nal-IRI +5FU/LV in [11], FOLFIRI in [19]) in second-line treatment of PDAC patients, regardless gBRCA1-2 status. Similar $mPFS_2$ was also reported in many phase II trials or retrospective analyses on second-line therapy in PDAC [8]. Conversely, in our study $mPFS_2$ was longer than expected in the platinum subgroup. These figures parallel those previously reported by our group in first-line treatment of gBRCA1-2pv PDAC patients with platinum-based chemotherapy and platinum-free regimens [18].

OS_2, results are consistent with those reported for PFS_2, endorsing the benefit of platinum-based therapy use. Indeed, it must be noticed that median OS_2 in the platinum subgroup remarkably exceeded the median OS_2 to second-line treatment described in RCTs on unselected PDAC patients, ranging between 5.9 and 6.5 months [9-11, 19], that is comparable to the OS_2 reported for the platinum-free second-line therapy subgroup in our survey. To this regard, the lack of a statistically significant difference between the two subgroups seems to be due to the favorable outcome observed in the 6 patients that, after failing a platinum-free therapy, were treated with a platinum-containing third-line therapy that yielded a further sizeable benefit and shaped the tail of the Kaplan-Meier overall survival curve thus masking, in a sort of cross-over effect, the true impact of second-line platinum.

No significant differences in terms of second-line treatment survival outcomes were reported in relation to gBRCApv subtype, gender or age in our study.

Lastly, objective response rate (ORR) was doubled with platinum-based second-line therapy if compared to platinum-free chemotherapy (48% versus 24%, respectively) and higher to that reported in the literature on

second-line therapy in PDAC, both in RCTs (11-16% in [9,11,19]) and in non-randomized trials (0-23 %) [7]. Even in third-line, platinum-based chemotherapy yielded a 67% Disease Control Rate (DCR) rate versus null for platinum-free regimens in patients who received a platinum-free second-line therapy.

At best of our knowledge, overall, these findings represent the first evidence of a positive effect of platinum-based therapy in the specific setting of second (and third?)-line treatment of metastatic PDAC patients with gBRCA1-2pv, in line with the benefit demonstrated with platinum salts in the earlier phase of treatment [18]. Previously, Wattenberg et al. reported a PFS of 2.5 months for 5 PDAC patients with gBRCA1-2 pv, all receiving a platinum-based chemotherapy either as second-line (4) or third-line (1) treatment [17]. More recently, a median Time to Treatment Progression of 7.3 months and a mOS of 10.6 months were described for a subset of 4 gBRCA1-2pv PDAC patients receiving a second-line with 5-FU plus Irinotecan with (3) or without (1) the PARP-Inhibitor Veliparib as part of a randomized phase II trial [19]. Nonetheless, these data did not allow drawing any sound conclusion on second-line therapy outcome in gBRCA1-2pv-related PDAC, due to the limited number of patients and the lack of a comparison between platinum-free and platinum-based treatments.

The secondary analysis performed in our study in order to define the role of timing of platinum agent introduction in gBRCA1-2pv PDAC patients treatment revealed a positive impact of platinum-based triplets and quadruplets on extending PFS to first-line therapy. Specifically, 3-and 4-drugs chemotherapy regimens including a platinum salt significantly outperformed both platinum-free combinations and platinum-based doublets in terms of PFS, also allowing for a greater proportion of patients to be alive and free from disease progression at 6 and 12 months. On the contrary, no PFS difference was detected between platinum-based doublets and no-early platinum chemotherapy subgroups. Although this result might be partially affected by the unbalanced allocation of negative prognostic factors, namely the higher median age and percentage of patients with ECOG PS >1 and gBRCA1pv in the platinum-based doublet subgroup, it is consistent with a previous report of our group prompting a greater benefit of platinum salt-containing triplets and quadruplets over other types of regimens in this subset of patients [18]. Furthermore, the proportion of patients receiving Olaparib as maintenance therapy of a first-line platinum-containing treatment was comparable between the triplet-/quadruplet and the doublet-subgroups, thus minimizing a potential bias related to the proven effect of this drug on disease progression delay [15].

Concerning overall survival, firm conclusions cannot be drawn, due to the immature follow-up and the limited number of events, especially among the 40 patients treated with platinum-based triplets and quadruplets, 42% of whom were still alive by the time of database lock. Notwithstanding, OS of this subgroup was significantly prolonged compared to that reported for patients treated with platinum-based doublets and despite the lack of statistical significance, it numerically exceeded by 9 months survival of patients not receiving upfront platinum salts. Moreover, the proportion of patients who were alive at 2 years from therapy start with platinum-containing first-line triplets and quadruplets as opposed to the no-early platinum subgroup was increased by >20%, hinting at a possible survival benefit of these combinations that might become evident with longer follow-up.

The proportion of patients receiving a second-line treatment after disease progression to first-line therapy was comparable across the three subgroups. However, it should be highlighted that a lower percentage of patients (60%) experienced disease progression with platinum-based 3-and 4- dugs combinations as opposed to platinum-containing doublets (89%) and platinum-free regimens (93%).

The results of this multicenter survey need to be interpreted cautiously due to several drawbacks, including the retrospective and non-randomized nature of the investigation, the relatively limited sample size, alongside with the lack of a comparison with an internal control of wild-type PDAC patients. Additionally, the follow-up immaturity, especially of those patients included in the secondary analysis, hampers conclusive speculations on the impact platinum-based chemotherapy had on overall survival of this cohort.

Keeping in mind these limitations, we can conclude that our study has relevant implications for the management of PDAC patients harboring gBRCA1-2pv, as it is the first to report the beneficial role of platinum salts not only as upfront therapy but also in second- and third-line treatment setting. Moreover, our findings suggest that early platinum use provides a survival outcome advantage and raise the concern that platinum-based doublets should not be considered as a standard first-line treatment approach in this biologically distinct subgroup of patients. Overall, our findings endorse the need to screen for BRCA1-2 germ-line mutations all patients with PDAC, due to the relevance of this test to drive therapeutic recommendations that have a considerable impact of outcome.

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