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**How to improve metastatic pancreatic ductal adenocarcinoma patients' selection:
between clinical trials and real-world**

Improving pancreatic cancer patients' selection

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Abstract

As underlined in the minireview by Blomstrand H. *et al*, given the poor prognosis and the paucity of data on a therapeutic sequence in pancreatic ductal adenocarcinoma (PDAC), additional randomized controlled trials (RCTs) and real-world evidence studies addressing current and novel regimens are needed. The real-world outcomes of first-line chemotherapy regimens such as FOLFIRINOX and gemcitabine/nab-paclitaxel are thoroughly reviewed and seem to be largely generalizable in a real-world context. Regarding second-line chemotherapy the key question about the optimal sequence of regimens remains uncertain. Precisely in this setting it is therefore useful to encourage the implementation of clinical studies that may contribute to the scarcity of data available up to now. We report our experience with a small group of patients treated with second-line liposomal irinotecan (nal-IRI) plus 5-fluorouracil and leucovorin (5FU/LV).

To improve the treatment of patients affected by PDAC, it is useful to identify subgroups of patients who may benefit from target treatments (e.g. BRCA mutant) and it is also important to focus on any prognostic factors that may affect the survival and treatment of these patients.

Key Words: Metastatic pancreatic ductal adenocarcinoma; Palliative chemotherapy; Real-world data; Molecular selection; Biomarkers; Second-line treatment.

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Core Tip: The present letter is intended to contribute to the collection of data on PDAC treatments in second-line settings through our experience with the promising data of efficacy and safety of small group of study patients treated with second-line liposomal

irinotecan (nal-IRI) plus 5-fluorouracil and leucovorin (5FU/LV). We also focused on highlighting the subgroups of PDAC patients who might benefit from target treatments such as a small proportion of mutated BRCA and to identify comorbidities or characteristics that impact the prognosis of PDAC patients through our retrospective analysis that demonstrate a correlation between type II diabetes mellitus and improved overall survival.

TO THE EDITOR

We read with great interest the review by Blomstrand *et al*^[1], entitled “Real-world evidence on first- and second-line palliative chemotherapy in advanced pancreatic cancer”. This review provides a comprehensive overview on real-life data on metastatic pancreatic ductal adenocarcinoma (PDAC) patients treated in the first- and second-line setting. The authors critically compare the results obtained in a real-world population with those provided by randomised clinical trials (RCT), highlighting that the outcomes are consistent and similar, especially on first-line with FOLFIRINOX and gemcitabine - nab-paclitaxel.

We agree with authors that PDAC patients enrolled in RCT represent a highly selected population and that despite real-world outcomes derive from different countries, with various regulatory agencies and health care systems, all data available in literature seem to confirm the effectiveness and safety of chemotherapy regimens in real-life setting. Moreover, since no strong data on second-line setting are available, we greatly appreciate the authors’ effort to analyse this topic.

At our Centre, we conducted a retrospective analysis in a real-world population of metastatic PDAC patients treated with second-line liposomal irinotecan (nal-IRI) plus 5-fluorouracil and leucovorin (5FU/LV) in a compassionate use program at our Centre, in order to assess clinical outcome, tolerability and potential prognostic factors. Statistical analysis was performed with the MedCalc package. The association between categorical variables was estimated by chi-square test. Survival distribution was estimated by the Kaplan-Meier method and survival curves comparison was evaluated with log-rank

test. The cut off value for laboratory parameters was identified with ROC curves. The study was approved by the Ethical Committee of the Cagliari University Hospital (Prot. PG /2018/7339, 1 June 2018) and was performed in accordance with the ethical principles stated in the Declaration of Helsinki and in the International Conference on Harmonization (ICH) Note for Guidance on Good Clinical Practice (GCP, ICH E6, 1995) and all applicable regulatory requirements.

Globally, 14 patients treated with nal-IRI and 5FU/LV from June 2016 to November 2018 were included in our analysis. Baseline characteristics are shown in Table 1. Median overall survival (OS) was 9.1 (95%CI, 5.8-13.1) months. Median progression free survival (PFS) was 7.2 mo (95%CI, 3.0-33.8). 3 patients achieved a partial response, 2 stable disease and 9 developed progression. Median duration of treatment with nal-IRI plus 5FU/LV was 6 mo; treatment longer than 6 mo was related to improved OS (13.1 mo [95%CI, 9-17] vs 7.1 mo [95%CI, 2.9-13.1], $P = 0.0127$, HR=0.18) and PFS (9.1 mo [95%CI, 7.2-33.8] vs 3.1 mo [95%CI, 2.2-7.7], $P = 0.0011$, HR=0.08). Baseline haemoglobin levels equal or lower than 10 g/dL were associated with worse prognosis (OS: 11 mo [95%CI, 1-15.9] vs 3 mo, $P = 0.0384$, HR=0.005; PFS: 7.6 mo [95%CI, 3.1-33.8] vs 3 mo, $P = 0.0384$, HR=0.005). 64% of patients developed grade>2 toxicity. The occurrence of grade>2 anaemia was related to shorter OS (3 mo vs 11 mo [95%CI, 7.1-15.9], $P = 0.0384$, HR=0.005) and PFS (3 mo vs 7.6 mo [95%CI, 3.1-33.8], $P = 0.0384$, HR=0.005). As shown in Figure 1, the need for erythropoietin administration was associated with poorer OS (3 mo vs 10.7 mo [95%CI, 7.1-15.9], $P = 0.0287$, HR=0.003) and PFS (3 mo vs 7.6 mo [95%CI, 3.1-33.8], $P = 0.0287$, HR=0.003). In our real-world retrospective analysis, nal-IRI plus 5FU/LV confirmed its efficacy and tolerability, consistently with NAPOLI-1 RCT^[2,3]. Longer duration of treatment was related to improved survival, whereas lower baseline haemoglobin levels, anaemia occurrence and the necessity of erythropoietin were negative prognostic factors. These results are consistent with some findings of a previous Italian large real-world analysis^[4].

As underlined by Blomstrand *et al*, there is an urgent need for prognostic and predictive biomarkers to improve the therapeutic management of PDAC patients and to

prolong survival, as well as more effective treatment strategies. Indeed, intensive research efforts and substantial progress in the understanding of PDAC genetic background and molecular biology have not yet been matched either by the successful development of novel agents or by the identification of predictive biomarkers that could increase the effectiveness of existing therapies^[5]. In contrast to other solid tumours, immunotherapy strategies have failed to yield any notable impact in PDAC. This is likely related to the critical role of tumour microenvironment as physical barrier and its inhibitory immune signaling. The most promising therapeutic strategy seems to be combination of immunotherapeutics with other targeted treatments^[6].

To our knowledge, the only successful biomarker-driven phase III RCT so far is the POLO trial, which showed improved PFS with maintenance Olaparib, a PARP-inhibitor, *vs* placebo in germline BRCA-mutant PDAC not progressing after first-line platinum-based chemotherapy^[7]. Notably, BRCA-mutant PDAC represents a unique entity with specific disease features that are still to be fully understood and BRCA1/2 alterations are the most explored targetable mutations. Moreover, in this patients' setting, the sensitivity to platinum chemotherapy requires further research and confirmations. Recently, concept of "BRCAness" has gained increasing importance. This term refers to high-grade genomic instability of non- BRCA- mutant cancers and represents a phenotype of defective homologous recombination to which somatic mutations in genes like BRCA1/2, ATM, PALB2, CHEK1, RAD51, and FANCA, can contribute. For these reasons, "BRCAness" is under evaluation as a biomarker for DNA-damaging agents and PARP inhibitors^[8].

Finally, we believe that in a real-life focusing-approach, a particular focus should be deserved also to the assessment of the impact of comorbidities on PDAC patients' prognosis. In a retrospective analysis that we conducted on 164 advanced PDAC patients, we demonstrated a correlation between type II diabetes mellitus and improved OS, both in the exploratory and in the validation cohort at univariate analysis (16 *vs* 10 mo; $P = 0.004$ and 11 *vs* 6 mo; $P = 0.01$, respectively). Moreover, in multivariate analysis, insulin-treated patients compared with non-diabetic patients had a significantly

increased survival of 4.6 mo ($P = 0.03$). Surely, the correlation between OS and insulin-treated type II diabetes mellitus should be confirmed in prospective clinical trials^[9].

In conclusion, in the era of precision medicine, larger and prospective studies in the real-world population, with focus on specific PDAC subtypes (e.g. BRCA-mutant), would further clarify the impact of available and innovative treatment strategies on PDAC patients and help identifying potential biomarkers to improve patients' selection and prognosis.

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PRIMARY SOURCES

- 1

Eleonora Lai, Marco Puzzoni, Pina Ziranu, Chiara Cremolini et al. "Long term survival with regorafenib: REALITY (Real life in Italy) trial - a GISCAD Study", Clinical Colorectal Cancer, 2021

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Eleonora Lai, Pina Ziranu, Dario Spanu, Marco Dubois et al. "BRCA-mutant pancreatic ductal adenocarcinoma", British Journal of Cancer, 2021

Crossref

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Eleonora Lai, Marco Puzzoni, Pina Ziranu, Andrea Pretta et al. "New therapeutic targets in pancreatic cancer", Cancer Treatment Reviews, 2019

Crossref

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Andrea Pretta, Pina Ziranu, Marco Puzzoni, Eleonora Lai et al. "Retrospective survival analysis in patients with metastatic pancreatic ductal adenocarcinoma with insulin-treated type 2 diabetes mellitus", Tumori Journal, 2020

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