Editorial

The Imprecision of "Precision Medicine" in Pancreatic Adenocarcinoma

Stefano Cascinu[1]

[1] Department of Oncology, Vita-Salute University, San Raffaele; IRCCS San Raffaele Hospital, Milano, Italy

Pancreatic adenocarcinoma is one of the most lethal cancers. The 5-year survival of only 10%, the presence of metastatic disease in about 60% of patients at diagnosis, as well as the recurrence and death in 80% of even radically resected patients make pancreatic cancer really a challenge for oncologists [1].

Across these 20 years, the only advancement in its treatment has been the development of chemotherapeutic regimens such as FOLFIRINOX (made up of folinic acid, fluorouracil, irinotecan, and oxaliplatin) or gemcitabine/nab-paclitaxel [2,3]. No biological agents have been demonstrated to be effective in this cancer.

Genomic studies supported the opinion that pancreatic cancer is homogeneous with mutations in 4 genes: KRAS, CDKN2A, TP53, and SMAD-4. Unfortunately, none of these genes are druggable or, as it happened with KRAS, no benefit was observed by targeting them [4].

The progress in understanding the biology of pancreatic adenocarcinoma led to the identification of other molecular alterations deemed to be responsible for cancer initiation or progression.

Recently, olaparib, a Poly (ADP-ribose) polymerase—PARP inhibitor, has been reported to improve progression-free survival—PFS in metastatic pancreatic cancer patients harboring a BRCA1/2 mutation without a progressive disease after > 16 weeks of a first-line platinum-based chemo-therapy [5]. Of 3315 screened patients, 247 (7.5%) had a BRCA mutation. 158 patients were randomized to receive olaparib (92) or placebo (62), since 38% of patients had a disease progression at the first-line chemotherapy. Median PFS was significantly better for the olaparib group: 7.4 months vs. 3.8 months, as well as response rate, 23.1% vs. 11.5%. Unfortunately, survival was not improved: 18.9 months vs. 18.1 months. This is the first positive trial of a targeted agent in pancreatic adenocarcinoma. However, the lack of a survival advantage and the results of another randomized trial with veliparib associated to gemcitabine and cisplatin, that failed to show any benefit, question the role of PARP inhibitors in pancreatic cancer [6]. Once again, pancreatic ductal adenocarcinoma—PDAC seems to remain an orphan cancer for targeted therapies.

Recently, in *Lancet Oncology* a retrospective analysis has been published on matched therapies following molecular profiling in pancreatic cancer patients [7]. Actionable molecular alterations were identified in 282 out of 1082 (26%) tumor samples. 46 patients received matched therapies, while 143 unmatched therapies. Overall survival was better in patients receiving matched therapies (HR 0.42; p = 0.0004). Although these findings are really of interest, there are some concerns about their interpretation. In fact, they could be due not only to the molecular selection of the treatment, but also

Corresponding author
Stefano Cascinu
cascinu@yahoo.com

to different patient characteristics, known as prognostic in pancreatic cancer in the two groups. In fact, 94% of patients in the matched group received a cisplatin-based regimen versus only 73% in unmatched group. Furthermore, 85% of patients received 2 or more lines of treatment in the matched group versus 58% of patients in unmatched group. These differences may explain at least in part the observed results in the two groups. Furthermore, the only clear effective matched therapies are those based on MSI (immunotherapy), BRCA1/2 mutations, and NTKR fusions.

Why is precision medicine so imprecise in pancreatic cancer?

There are some possible explanations. The first one is that pancreatic cancer is not only a KRAS mutated tumor, as believed for a long time. There are 10-15% of pancreatic tumor with a non-mutated KRAS. These tumors are really different and probably a targeted therapy may be already an option. In fact, they present MSI, BRCA1/2; PALB2 mutations or NTRK fusions. For all these alterations there are molecularly-based treatments. The issues concern the about 90% of pancreatic tumors harboring the classical pancreatic mutations: KRAS, TP53; CD-KN2A and SMAD-4, for whom, actually, we do not have target agents.

A small step forward in the interpretation of KRAS mutated tumors has been done when transcriptomic and genomic analyses have shown that these tumors present two different subtypes: basal-like and classical [8]. More recently, it has been shown that basal-like exists at two states: basal-like A and basal-like-B and their expression is different in resectable or metastatic tumors, suggesting that basal-like phenotype is acquired and it is a hallmark of progression

[9]. This may be relevant because when and where we obtain tumor samples may be not irrelevant for the tumor-profiling assay and the treatment decisions.

Another critical aspect is that many tumors harbor more than one actionable molecular alterations and some of them are not drivers. The knowledge of this aspect matters for improving the therapy.

Finally, in pancreatic cancer there are two other critical aspects: the relationship of tumor cells with stroma and the presence of epithelial-mesenchymal transition (EMT). The interaction of tumor cells and stroma may be not the same even in the presence of a similar pattern of molecular alterations. It may depend on the features of the host and this gets more difficult the interpretation of tumor profiling. EMT may modify continuously the genomic profile of the tumors and make useless or problematic a molecularly-guided treatment [10]. Furthermore, this phenomenon may be induced or promoted even by chemotherapy by adding further variables in the interpretation of the molecular profile [11].

In conclusions, the availability of multiplatform tumor profiling may open new room for the treatment of pancreatic cancer. Nevertheless, before designing and carrying out new clinical trials based on matched therapies following molecular profiling, our first task should be to improve the knowledge about the biology of this tumor. Pancreatic cancer may be compared to Proteus, the ancient god of the rivers and the oceans, who was capable of assuming many forms. He could foretell the future, but he changed his shape to avoid doing so. He answered only to those who were capable of capturing him. Pancreatic will be captured only if we are able to catch its biology.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram J, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; 68: 394-424; https://doi.org/10.3322/caac.21492

2. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011; 364: 1817-25; https://doi.org/10.1056/NEJMoa1011923

3. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* 2013; 369: 1691-703; https://doi.org/10.1056/NEJMoa1304369

4. Aguirre AJ, Nowak JA, Camarda ND, et al. Real time genomic characterization of advanced pancreatic cancer to enable precision medicine. *Cancer Discov* 2018; 8: 1096-111; https://doi.org/10.1158/2159-8290.CD-18-0275

5. Golan T, Hammel P, Reni M, et al. Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer. *N Engl J Med* 2019; 381: 317-27; https://doi.org/10.1056/NEJMoa1903387

6. O'Reilly EM, Lee JW, Zalupski M, et al. Randomized multicenter Phase II trial of gemcitabine and cisplatin with or without veliparib in patients with pancreas adenocarcinoma and a germline BRCA/PALB2 mutation. *J Clin Oncol* 2020; [published online ahead of print, 2020 Jan 24]; https://doi.org/10.1200/JCO.19.02931

7. Pishvaian MJ, Brody JR, Lyons E, et al. Overall survival in patients with pancreatic cancer receiving matched therapies following molecule profiling: a retrospective analysis of the Know Your Tumor registry trial. *Lancet Oncol* 2020; S1470-2045(20)30074-7; [published online ahead of print, 2020 Mar 2]; https://doi.org/10.1016/S1470-2045(20)30074-7

8. Bailey P, Chang DK, Nones K, et al. Genomic analyses identify molecular subtypes of pancreatic cancer. *Nature* 2016; 531: 47-52; https://doi.org/10.1038/nature16965

9. Chan-Seng M, Jaeseung C, Kim L, et al. Transcription phenotypes of pancreatic cancer are driven by genomic events during tumor evolution. *Nature Gen* 2020; 52: 231-40; https://doi.org/10.1038/s41588-019-0566-9

10. Rhim AD, Mirek ET, Aiello NM, et al. EMT dissemination precede pancreatic tumor formation. *Cell* 2012: 148: 349-61; https://doi.org/10.1016/j.cell.2011.11.025

11. Porter RL, Magnus NKC, Thapar V, et al. Epithelial to mesenchymal plasticity and differential response to therapies in pancreatic ductal adenocarcinoma. *Proc Natl Acad Sci U S A* 2019; 116: 26835-45; https://doi.org/10.1073/pnas.1914915116