

The personalized medicine for pancreatic ductal adenocarcinoma patients: The oncologist perspective

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INTRODUCTION

Over the past 15 years, therapeutic strategies have evolved toward a personalized approach, leading to significant clinical benefit in many tumors. Early diagnosis, progress in surgical and radiotherapy techniques and the availability of more effective chemotherapy agents, targeted therapies, and better management strategies led to longer survival in cancer patients, reducing mortality of at least 1%/year since the early 2000s.^[1,2] Unfortunately, this was not the case for pancreatic cancer, which is still the malignant tumor with the highest mortality rate and remains one of the most challenging oncological issues. Furthermore, over the last decades, its incidence has progressively increased compared to the other tumors, and the estimated incidence curves show a further increase in the near future. Moreover, since no remarkable therapeutic improvements have been reported since the early 2000s, also its mortality rate has alarmingly grown.^[3]

A consistent number of chemotherapeutic agents have been individually tested in the setting of advanced disease, without any significant survival benefit, and until few years ago, single-agent gemcitabine was considered the gold standard.^[4] Recently, association

among chemotherapy and molecular targeted drugs has been tested, but so far only the combination of erlotinib with gemcitabine has improved patients survival, albeit not in a clinically meaningful way.^[5] To date, three combination chemotherapy associations (nab-paclitaxel-gemcitabine, FOLFIRINOX, and PEFG) have shown superiority in terms of activity and survival in patients with advanced disease as compared to single-agent gemcitabine, yielding median survival to 8.6–11 months, with a different spectrum of toxicity.^[6–8] These results justified the substitution of gemcitabine as standard of care in the fit population.

Several key challenges justify the limited outcome improvement and hinder therapeutic progress in pancreatic adenocarcinoma.

GENETIC HETEROGENEITY

Pancreatic adenocarcinomas are characterized by considerable genetic heterogeneity across individuals. Furthermore, it has been demonstrated that several different cell clones with over 60 genetic alterations and 12 pathway alterations exist in the same tumor as well. The presence of multiple pathway alterations at

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the same time could explain the presence of multiple resistance mechanisms, especially to molecular-targeted agents.^[9]

GENETIC INSTABILITY

It is still unclear whether the increase in the number of genetic aberrations occurs gradually and simultaneously to carcinogenesis and tumor progression or if pancreatic tissue early accumulates a number of critical genetic mutations conferring characteristics of invasion, metastatic migration, and treatment resistance, from the onset.^[10] This lack of knowledge does not allow to properly identify relevant molecular targets.

MOLECULAR CLASSIFICATION

The availability of tumor tissue for molecular profiling is very limited in pancreatic cancer because the vast majority of patients are diagnosed by fine-needle aspirate and only cytological samples are obtained. Attempts to classify this disease based on molecular analysis have been performed.

Pancreatic cancer has been described as a complex molecular landscape, where four main common critical mutations (KRAS, TP53, SMAD4, and CDKN2A) are accompanied by a milieu of minor gene mutations at low prevalence aggregating into core molecular pathways (DNA damage repair, cell cycle regulation, transforming growth factor-beta signaling, and chromatin regulation). Thus, this classification can identify four main clusters: stable (<50 genetic events), focal (between 50 and 200 events, 50% on a single chromosome), scattered (between 50 and 200 widespread mutations), and unstable (>200 widespread mutations).^[11]

Another classification has been proposed based on a combination of genetic alterations and histotype. An analysis from 453 pancreatic adenocarcinomas revealed 32 recurrent genetic mutations linked to 10 meaningful pathways. The expression of these mutations showed a correlation with cancer histotype (squamous, pancreatic progenitor, immunogenic, aberrantly differentiated endocrine/exocrine).^[12]

These proposals witness the remarkable economic and intellectual effort currently ongoing worldwide to deepen the knowledge of the disease and provide a molecular classification, which could more precisely drive clinical research toward a personalized therapeutic approach.

Nevertheless, to date, no prospectively validated or clinically useful classification has yet been identified.

PHENOTYPIC HETEROGENEITY

Molecular inhomogeneity is paralleled by phenotypical variability. No predominant pancreatic cancer phenotype has been recognized that could account for specific prognostic and predictive features, such as for breast and lung cancer. A number of alterations of several molecular pathways that may consider druggable have been reported, each of which, however, affect a limited percentage of patients with pancreatic adenocarcinoma. Accordingly, the rarity of disease and phenotypical subsets represents a major challenge for clinical trial conduction.

MICROENVIRONMENT

A peculiar aspect of pancreatic adenocarcinoma is the desmoplastic reaction that occurs in the tumor tissue consisting of a poorly vascularized area of altered extracellular stroma with infiltrating macrophages and fibroblasts that renders hypoxic the peritumoral microenvironment and hampers the arrival of drugs and host immunological reaction. In such conditions, the role of pharmacological agents which activates in hypoxic tissues was assessed. TH-302 showed promising results in terms of responses and PFS in a Phase II randomized trial.^[13] Unfortunately, the results of the subsequent Phase III trial were disappointing and did not confirm preliminary results.^[14] The role of other drugs targeting tumor stroma, such as PEGPH 20 which regulates the expression of hyaluronic acid and ibrutinib that inhibits stroma-producing cells, is currently explored in Phase III clinical trials (ClinicalTrials.gov Identifier: NCT02715804 and NCT02436668).

Considering also immunity as part of microenvironment, a Phase III trial currently underway is AM0010, which is evaluating in second-line setting, the association between FOLFOX and pegylated recombinant human interleukin-10 (ClinicalTrials.gov Identifier: NCT02923921).

CANCER STEM CELLS

Cancer stem cells account for 1%–5% of the totality of tumor cells; they are capable of self-renewal, chemical, and radiation resistance and drive the process

of tumorigenesis, progression, invasion, and metastasis. Among tumor stem cell regulatory agents, tarextumab initially showed encouraging results in a Phase I study; however, an interim analysis of a Phase II study showed a strong trend to a lack of benefit, and the trial was discontinued due to futility (ClinicalTrials.gov Identifier: NCT01647828;^[15]).

Another potential target is STAT3, for which a Phase III study is currently underway, evaluating napabucasin in association with gemcitabine and nab-paclitaxel (ClinicalTrials.gov Identifier: NCT02993731).

DEVELOPMENT STRATEGIES

The disappointing results of several trials after enthusiastic reporting of preliminary data may have their roots in some strategic, methodological, or interpretation biases. For instance, among other methodological mistakes, the addition of a novel experimental molecule to an outdated chemotherapy backbone is not necessarily the best way for assessing its efficacy. Similarly, to address the efficacy of targeted agents in the absence of a validated molecular target appears unwise. Moreover, the choice of not validated or inadequate surrogate end points (such as resectability rate or R0 resection rate), the use of limited samples of patients, the nonrandomized design of Phase II trial, and the use of nonstandard calibration arms in randomized trials are some of the most frequent pitfalls in clinical research leading to unjustified and premature enthusiasm based on misinterpretation of preliminary results and to embarking in large resource-consuming Phase III trials with very limited success probability. Finally, drug development strategies are still based on an outdated scheme that addresses the role of the addition of the experimental agent to standard backbone chemotherapy (strategy that obtained uncountable failures during the past 20 years) and the assessment of new agents and regimens in first-line metastatic setting or, very rarely, in second-line metastatic setting. Conversely, potential new and more original investigation fields, such as maintenance therapy or neoadjuvant treatment in resectable disease or unresectable disease, are almost completely ignored by large trials. Furthermore, trials driven by basic research and translational research generated hypotheses are rare.

CONCLUSION

No evidence-based personalized treatment for pancreatic adenocarcinoma is currently available for clinical practice. While new agents or combinations are extensively explored in the hope of improving disease outcome, new development strategies and better research methodology are eagerly needed to foster therapeutic progress in pancreatic cancer.

REFERENCES

1. Lorenzoni L, Belloni A, Sassi F. Health-care expenditure and health policy in the USA versus other high-spending OECD countries. *Lancet* 2014;384:83-92.
2. Boffetta P. The Decrease in Global Cancer Mortality AACR 106th Annual Meeting. 18-22 April, 2015. Philadelphia, PA: AACR; 2015.
3. Ilic M, Ilic I. Epidemiology of pancreatic cancer. *World J Gastroenterol* 2016;22:9694-705.
4. Burris HA 3rd, Moore MJ, Andersen J, *et al.* Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: A randomized trial. *J Clin Oncol* 1997;15:2403-13.
5. Moore MJ, Goldstein D, Hamm J, *et al.* Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: A phase III trial of the national cancer institute of Canada clinical trials group. *J Clin Oncol* 2007;25:1960-6.
6. 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.
7. Conroy T, Desseigne F, Ychou M, *et al.* FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011;364:1817-25.
8. Reni M, Cordio S, Milandri C, *et al.* Gemcitabine versus cisplatin, epirubicin, fluorouracil, and gemcitabine in advanced pancreatic cancer: A randomised controlled multicentre phase III trial. *Lancet Oncol* 2005;6:369-76.
9. Samuel N, Hudson TJ. The molecular and cellular heterogeneity of pancreatic ductal adenocarcinoma. *Nat Rev Gastroenterol Hepatol* 2011;9:77-87.
10. Notta F, Chan-Seng-Yue M, Lemire M, *et al.* A renewed model of pancreatic cancer evolution based on genomic rearrangement patterns. *Nature* 2016;538:378-82.
11. Waddell N, Pajic M, Patch AM, *et al.* Whole genomes redefine the mutational landscape of pancreatic cancer. *Nature* 2015;518:495-501.
12. Bailey P, Chang DK, Nones K, *et al.* Genomic analyses identify molecular subtypes of pancreatic cancer. *Nature* 2016;531:47-52.
13. Borad MJ, Reddy SG, Bahary N, *et al.* Randomized phase II trial of gemcitabine plus TH-302 versus gemcitabine in patients with advanced pancreatic cancer. *J Clin Oncol* 2015;33:1475-81.
14. Van Cutsem E, Lenz H-J, Furuse J, *et al.* MAESTRO: A randomized, double-blind phase III study of evofosfamide (Evo) in combination with gemcitabine (Gem) in previously untreated patients (pts) with metastatic or locally advanced unresectable pancreatic ductal adenocarcinoma (PDAC). *J Clin Oncol* 2016 Annual meeting proceedings; 34:abstract 4007.
15. OncoMed Provides Update on Tarextumab Phase 2 Pancreatic Cancer ALPINE Trial. Source. OncoMed Pharmaceuticals, Inc.; 25 January, 2016.