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State of the art and future directions of pancreatic ductal adenocarcinoma therapy

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ABSTRACT

Pancreatic ductal adenocarcinoma (PDAC) is expected to become the second cause of cancer-related death in 2030. PDAC is the poorest prognostic tumor of the digestive tract, with 80% of patients having advanced disease at diagnosis and 5-year survival rate not exceeding 7%.

Until 2010, gemcitabine was the only validated therapy for advanced PDAC with a modest improvement in median overall survival as compared to best supportive care (5–6 vs 3 months). Multiple phase II–III studies have used various combinations of gemcitabine with other cytotoxics or targeted agents, most in vain, in attempt to improve this outcome.

Over the past few years, the landscape of PDAC management has undergone major and rapid changes with the approval of the FOLFIRINOX and gemcitabine plus *nab*-paclitaxel regimens in patients with metastatic disease. These two active combination chemotherapy options yield an improved median overall survival (11.1 vs 8.5 months, respectively) thus making longer survival a reasonably achievable goal. This breakthrough raises some new clinical questions about the management of PDAC. Moreover, better knowledge of the environmental and genetic events that underpin multistep carcinogenesis and of the microenvironment surrounding cancer cells in PDAC has open new perspectives and therapeutic opportunities.

In this new dynamic context of deep transformation in basic research and clinical management aspects of the disease, we gathered updated preclinical and clinical data in a multifaceted review encompassing the lessons learned from the past, the yet unanswered questions, and the most promising research priorities to be addressed for the next 5 years.

Contents

1. Introduction 81
2. Development of pancreatic ductal adenocarcinoma 81

Abbreviations: ^{18}FDG-PET, ^{18}F-fluorodeoxyglucose-positron emission tomography; 5FU, 5-fluorouracil; α-SMA, α-smooth muscular actin; AA, amino acid; APA, adapted physical activity; ATP, adenosine triphosphate; BCAA, branched-chain amino acid; CA 19-9, carbohydrate antigen 19-9; CRT, chemoradiotherapy; dCK, deoxycytidine kinase; ctDNA, circulating tumor DNA; Dclk1, doublecortin like kinase-1; DFS, disease-free survival; ECM, extracellular matrix; ECOG, Eastern Cooperative Oncology Group; EGF, epidermal growth factor; ERCP, endoscopic retrograde cholangio-pancreatography; EUS, endoscopic ultrasonography; FDR, fixed dose rate; GDH, glutamate dehydrogenase; GOT, glutamic–oxaloacetic transaminase; HE, hematoxylin and eosin; hENT-1, human equilibrative nucleoside transporter 1; HRQoL, health-related quality of life; IGF, insulin-like growth factor; LDH, lactate dehydrogenase; MDCT, multiple detector-computed tomography; MRI, magnetic resonance imaging; MSC, mesenchymal stem cells; OS, overall survival; PanIN, pancreatic intraepithelial neoplasia lesion; PARP, poly-(ADP-ribose) polymerases; PDAC, pancreatic ductal adenocarcinoma; PFS, progression-free survival; PSC, pancreatic stellate cell; RR, relative risk; TCA, tricarboxylic acid.

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3. Diagnosis and staging . . . 87
4. Therapeutics . . . 89
5. Unanswered clinical questions . . . 93
6. Research pathways for the future of pancreatic ductal adenocarcinoma management . . . 93
7. General conclusion: from benchside to bedside . . . 98
Conflict of interest . . . 98
References . . . 98

1. Introduction

Pancreatic cancer is the 12th most frequent malignancy and the seventh leading cause of cancer-related death in men and the eighth in women worldwide (Torre et al., 2015). In developed countries, it is the fourth cause of cancer-related death (Siegel et al., 2015). Its incidence is dramatically increasing worldwide; it is expected to become the second cause of cancer death in the United States in 2030 (Rahib et al., 2014).

The vast majority of malignant pancreatic tumor cases (85%) are pancreatic ductal adenocarcinoma (PDAC). PDAC has the poorest prognostic among digestive tract malignancies with a 5-year survival rate of 5%–7%, with no significant change in death rate in 1997–2007 (National Cancer Institute. Cancer Statistics, 1975–2007 (SEER 9)). Complete surgical resection is the only treatment that can provide prolonged survival. However, due to lack of initial symptoms at early stage and high invasive potential, diagnosis is made at an advanced stage in 80% of cases, when patients already have metastases or locoregional extension (Rhim et al., 2012; Ryan et al., 2014a). Moreover, most patients with an apparently localized disease who may undergo a curative-intent resection will promptly develop metastatic and/or local relapses. The median survival after curative resection is about 20–24 months, 9–15 months in patients with locally advanced PDAC, and 6–9 months in those with metastatic disease (Ryan et al., 2014a).

Advanced PDAC remains a challenging, non-curable disease attracting attention of medical and surgical specialists, as well as pharmacologists. Over a decade (1997–2010), gemcitabine was the only validated chemotherapy regimen for advanced PDAC, yet the improvement obtained with this drug in terms of median overall survival (OS) was only of about 3 months as compared with best supportive care (BSC) (5–6 months vs 3 months). Several phase II and III studies have been designed as add-on benefit using various combinations of gemcitabine with other cytotoxics or targeted agents such as tyrosine kinase inhibitors and monoclonal antibodies. However, most of these doublets failed to demonstrate a superiority over gemcitabine monotherapy (Ryan et al., 2014a).

The landscape of PDAC management has undergone major changes during the 5 past years with the approval of two active combinations of cytotoxics: the FOLFIRINOX (5-fluorouracil [5FU], irinotecan, and oxaliplatin) and the gemcitabine plus *nab*-paclitaxel regimens. These combination regimens were shown to be superior to gemcitabine in patients with metastatic PDAC, yielding median OS of 11.1 and 8.5 months, respectively (Conroy et al., 2011; Von Hoff et al., 2013). After advent of these chemotherapy regimens, longer survival for patients with advanced PDAC has turned to a reasonably achievable goal, while before median life expectancy rarely got beyond one year. This breakthrough has raised some new specific clinical questions about the management of PDAC patients. Moreover, better knowledge of the environmental etiological factors (particularly, obesity/insulin resistance and nicotine exposure), the molecular and genetic events that underpin multistep carcinogenesis, and the microenvironment surrounding cancer cells (pancreatic stellate cells [PSC], immune cells, neural cells, abundance and composition of stroma) has opened new perspectives of therapeutic opportunities in PDAC. Accumulation of preclinical data, especially in recent years, provides a strong rational for the development of news drugs and strategies aiming to better control disease progression.

In this dynamic context of deep changes in both the basic research and clinical management aspects of a disease that is becoming a major health issue, it appears crucial to gather updated preclinical and clinical data on PDAC. In this review, we summarize the lessons learned from the past, the yet unanswered questions, and the most promising research pathways to draw up a state of the art and the future directions in PDAC management.

2. Development of pancreatic ductal adenocarcinoma

2.1. Cell of origin (acinar vs ductal cell)

Activating *KRAS* mutations are present in more than 90% of PDAC and represent one of the earliest oncogenic events driving pancreatic carcinogenesis (Hezel et al., 2006). It has long been a matter of controversy which pancreatic cell type(s) can give rise to PDAC when mutant *KRAS* is expressed. Although PDAC displays ductal characteristics, it may not necessarily emerge from the ductal compartment. Moreover, there is some preclinical evidence for its non-ductal origin, i.e. acinar, centroacinar, or insulin-positive cells (Morris et al., 2010). Mouse models harboring mutant *KRAS* in specific populations of adult pancreatic cells showed that aberrant *KRAS* signaling can convert differentiated acinar pancreatic cells into duct-like lineages capable of progressing through pre-malignant pancreatic intraepithelial neoplasia (PanIN) to PDAC (Hezel et al., 2006). The process preceding PanIN formation is also known as acinar-to-ductal metaplasia (ADM): following pancreatic injury or *KRAS* activation acinar cells gradually lose their acinar features and acquire a ductal phenotype. Recent studies have unraveled the underlying mechanisms involved in this process. The ductal differentiation factor SOX9 has been identified as a critical mediator of ADM and tumor initiation in acinar cells (Kopp et al., 2012). Ectopic SOX9 induction promotes the expression of ductal genes in acinar cells and has been shown to be necessary for *KRAS*-mediated formation of PanIN. Moreover, rather than mimicking normal pancreatic ducts, metaplastic cells harboring oncogenic *KRAS* acquire a proliferative biliary progenitor phenotype and form tuft cells. Commonly found in the biliary tract, tuft cells are normally absent from murine pancreas, but have been identified as PanIN initiating cells. These are chemosensory cells and respond to signals from the extracellular environment by the production of effector molecules, leading to inflammation and collagen deposition (Delgiorno et al., 2014). Metaplastic cells co-express the transdifferentiation SOX17 promoter and PDX1 suppressor, which control tuft cell formation and early PDAC carcinogenesis (Takeuchi et al., 2014). Co-expression of these developmental transcription factors with opposing roles may account for cellular heterogeneity within early pre-malignant pancreatic lesions (Lafaro et al., 2014). By contrast, centroacinar-specific or ductal-specific activation of *KRAS* rarely results in PanIN formation, despite the histological resemblance of PanIN to pancreatic ducts. The refractory nature of ductal cells to *KRAS* activation suggests that tumor suppressive pathways may be active in these cells and that a cooperating “second hit” leading to the downregulation of these suppressor genes is required to induce cellular transformation. Indeed, conjunction of *KRAS* activation and reduced expression of the tumor suppressor gene *PTEN* induces malignant transformation through another type of premalignant lesion, intraductal papillary and mucinous neoplasm (IPMN) (Sander et al., 2014). Overall, preclinical models