Cancer Treatment Reviews 40 (2014) 118–128

Contents lists available at SciVerse ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Laboratory-Clinic Interface

# Tumour–stroma interactions in pancreatic ductal adenocarcinoma: Rationale and current evidence for new therapeutic strategies

V. Heinemann [a], M. Reni [b], M. Ychou [c], D.J. Richel [d], T. Macarulla [e], M. Ducreux [f,*]

[a] Department of Oncology, Klinikum Grosshadern and Comprehensive Cancer Center, Ludwig-Maximilians-Universität München, Germany
[b] Department of Medical Oncology, San Raffaele Scientific Institute, Milan, Italy
[c] Department of Medical Oncology, Centre Val d'Aurelle, Montpellier, France
[d] Department of Medical Oncology, Academic Medical Center, Amsterdam, The Netherlands
[e] Medical Oncology Department, Vall d'Hebron University Hospital, Barcelona, Spain
[f] Institut Gustave Roussy, Villejuif, and Paris-Sud University, Le Kremlin Bicetre, France

ARTICLE INFO

*Article history:*
Received 7 October 2012
Received in revised form 16 April 2013
Accepted 18 April 2013

*Keywords:*
Extracellular matrix
Gemcitabine
Nab-paclitaxel
Pancreatic cancer
Sonic hedgehog
SPARC
Stellate cells
Stem cells
Stroma

ABSTRACT

Most patients with pancreatic cancer present with advanced/metastatic disease and have a dismal prognosis. Despite the proven albeit modest benefits of gemcitabine demonstrated over a decade ago, subsequent advances have been slow, suggesting it may be time to take a different approach. It is thought that some key characteristics of pancreatic cancer, such as the desmoplasia, restricted vasculature and hypoxic environment, may prevent the delivery of chemotherapy to the tumour thereby explaining the limited benefits observed to-date. Moreover, there is evidence to suggest that the stroma is not only a mechanical barrier but also constitutes a dynamic compartment of pancreatic tumours that is critically involved in tumour formation, progression and metastasis. Thus, targeting the stroma and the tumour represents a promising therapeutic strategy. Currently, several stroma-targeting agents are entering clinical development. Among these, nab-paclitaxel appears promising since it combines cytotoxic therapy with targeted delivery via its proposed ability to bind SPARC on tumour and stromal cells. Preclinical data indicate that co-treatment with nab-paclitaxel and gemcitabine results in stromal depletion, increased tumour vascularization and intratumoural gemcitabine concentration, and increased tumour regression compared with either agent alone. Phase I/II study data also suggest that a high level of antitumor activity can be achieved with this combination in pancreatic cancer. This was recently confirmed in a Phase III study which showed that nab-paclitaxel plus gemcitabine significantly improved overall survival (HR 0.72) and progression-free survival (HR 0.69) versus gemcitabine alone for the first-line treatment of patients with metastatic pancreatic cancer.



## Introduction

The incidence of pancreatic cancer is rising in developed countries,[1,2] with an estimated 43,920 new cases and 37,390 deaths anticipated in the United States,[3] and 77,531 deaths predicted in the European Union in 2012.[4] Unfortunately, as this disease predominantly develops without early symptoms, more than 50% of patients have locally advanced or metastatic disease at initial diagnosis.[5] In this subgroup of patients, treatment options are limited and the 5-year survival rate is negligible.[6]

Treatment options for patients with locally advanced (unresectable) or metastatic pancreatic cancer include chemotherapy, radiotherapy or enrolment onto a clinical trial.[7,8] In terms of chemotherapy, gemcitabine became the first-line standard of care (SoC) based on the survival benefit demonstrated in a Phase III study more than a decade ago (median overall survival [OS] of 5.65 months with gemcitabine versus 4.41 months with bolus 5-fluorouracil [5-FU] [$p = 0.0025$]),[9] and the combination of a fluoropyrimidine and oxaliplatin is a second-line treatment option.

Since the introduction of gemcitabine, further advances in therapy in the advanced/metastatic setting have been extremely slow. Numerous Phase III studies have evaluated different gemcitabine-based regimens,[10–13] but in most cases, any observed benefits have been small and restricted to patients with a good performance status (PS).[14,15] Although a Phase III study showed that the addition of erlotinib to gemcitabine improved OS compared with gemcitabine alone in patients with locally advanced or metastatic disease, this OS benefit was small (0.33 months) and was accompanied by an increase in toxicities.[16]

* Corresponding author. Address: Department of Medicine, Institut Gustave Roussy, 114 rue Edouard Vaillant, 94805 Villejuif Cedex, France. Tel.: +33 1 42 11 43 08/60 17; fax: +33 1 42 11 52 29.
*E-mail address:* ducreux@igr.fr (M. Ducreux).

0305-7372/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ctrv.2013.04.004

A recent breakthrough was seen in a Phase III study which compared oxaliplatin/irinotecan/5-FU/leucovorin (FOLFIRINOX) with gemcitabine for patients with metastatic pancreatic cancer.[17] In this study, FOLFIRINOX was associated with an unprecedented 4.3 month improvement in median OS compared with gemcitabine (median OS of 11.1 months with FOLFIRINOX versus 6.8 months with gemcitabine; hazard ratio [HR] of 0.57, 95% confidence interval [CI] 0.45–0.73, $p < 0.001$). However, as patients included in this study were restricted to those with an Eastern Cooperative Oncology Group (ECOG) PS of 0–1, age ($\leqslant$75 years and bilirubin $\leqslant$1.5 times the upper limit of normal [ULN]), and comprised a lower proportion of patients with tumours in the head of the pancreas (38%) or biliary stents (14.3%) than would be expected in clinical practice,[18,19] there is much debate regarding the optimum use of this regimen. It has also been suggested that the considerable treatment burden (five components administered over 50 h every 2 weeks [Q2W]) and significantly higher rate of Grade 3/4 toxicity with FOLFIRINOX could restrict its use to specialised centres, and has raised the question of whether all components of the regimen are necessary.[18]

An additional challenge in advanced pancreatic cancer is accurate and reliable monitoring of treatment response. Although computed tomography (CT) is commonly used to measure tumours in order to assess response, in pancreatic cancer, this is complicated by the tumour's invasive growth and vigorous desmoplastic reaction.[20] Additional methods are therefore being evaluated, such as functional imaging modalities and serum biomarkers. Indeed, cancer antigen 19-9 (CA19-9) has recently been confirmed as an independent prognostic factor for survival in pancreatic cancer, suggesting it may be used as a complementary measure to improve assessment of chemotherapy activity.[21] On the other hand, no reliable predictive factors of response to chemotherapy exist and this is an area of much ongoing research.[22,23]

Collectively, these data highlight the slow progress and continued significant unmet need in advanced/metastatic pancreatic cancer. As such, new therapies that are more effective and less toxic are urgently needed. The introduction of reliable predictive factors that could guide treatment decisions would also allow us to move towards a tailored approach. However, given the limited advances seen over the past decade, it is likely that conventional therapies will not be effective, suggesting it may be time to take a different approach.

## Rationale for a different approach

### *Peculiarities of pancreatic cancer*

There are a number of key characteristics of pancreatic cancer that make it a particularly challenging and complex disease. For example, pancreatic cancer is thought to result through the successive accumulation of gene mutations,[24] including mutations in KRAS, TP53, CDKN2A, CTNNB1, DPC4 (also known as SMAD4), APC, and PIK3CA.[25] Moreover, a recent comprehensive analysis of 24 pancreatic cancers showed an average of 63 genetic abnormalities across 12 functional pathways in each tumour, with key mutations in each pathway appearing to differ from tumour to tumour.[26] These findings suggest that the genetic basis of pancreatic cancer is complex and heterogeneous, and that treatment tailored according to tumour-specific genetic aberrations is unrealistic.

Another key feature of pancreatic tumours is the critical role played by the various distinct elements, including pancreatic cancer cells, pancreatic cancer stem cells and the tumour stroma (desmoplasia).

The tumour stroma comprises abundant fibrotic tissue and is responsible for the main tumour bulk. It acts as a mechanical barrier to the tumour and also restricts the functionality of tumour vasculature, which could limit the effective delivery of anticancer agents to the pancreatic cancer cells. In addition, the tumour stroma is involved in key processes of tumour formation, progression, invasion and metastasis, and cancer stem cell maintenance.[27,28]

Pancreatic cancer stem cells are thought to make up 1-5% of pancreatic tumour cells.[27] These cells are implicated in pancreatic tumour growth since they are capable of unlimited self-renewal, produce heterogeneous lineages of cancer cells that make up the tumour, are thought to drive the development of metastases, and exhibit increased production of various important proteins, including the sonic hedgehog (SHH) ligand which activates the SHH signaling pathway to promote formation of the tumoural matrix,[29–32] suggesting it is a key driver across various cell types. In addition, cancer stem cells are resistant to chemotherapy and radiation therapy, which may help explain why these treatment approaches are associated with limited long-term benefits in pancreatic cancer.[27,30,31,33]

### *Rationale for targeting the stroma in pancreatic cancer*

The key characteristics of pancreatic cancer described above provide a strong rationale for investigating the potential for targeting additional components of pancreatic cancer in order to improve outcomes. Among these, the tumour stroma is emerging as an attractive therapeutic target.

The tumour stroma comprises fibrotic tissue composed of extracellular matrix (ECM) proteins, blood vessels, stromal fibroblasts and immuno-inflammatory cells. Although the mechanisms involved in the formation of tumour stroma are complex and only partly understood, a key player identified in this process is the pancreatic stellate cell (PSC).[34,35] Quiescent PSCs are activated by oxidative stress as well as various cytokines and growth factors produced by cancer cells, platelets and inflammatory cells, such as transforming growth factor beta-1 (TGFβ-1), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and fibroblast growth factor (FGF).[36] Upon activation, PSCs are transformed into myofibroblast-like cells which secrete growth factors and produce large amounts of ECM proteins capable of promoting growth and proliferation of cancer cells.[34,36] In the peritumoural stroma, PSCs also amplify cancer cell endostatin production via matrix metalloproteinase (MMP)-12-mediated cleavage from collagen XVIII, resulting in inhibition of endothelial proliferation and angiogenesis.[37,38] In addition, PSCs regulate ECM turnover through their ability to produce MMP-2 and MMP-9, which degrade the basement membrane collagen and bring malignant cells into direct contact with ECM proteins such as collagen type-1, thereby supporting cancer cell growth and paving the way for invasion and metastasis.[35]

Once activated, PSCs perpetuate their own activity via autocrine loops which in turn promote the continued development of the stroma beyond the tumour.[34,36] Moreover, the excessive growth of PSCs and continued production and deposition of ECM proteins into the periacinar spaces distorts the normal parenchymal architecture and increases interstitial pressure, leading to compression of the capillaries, which hinders blood perfusion and oxygen diffusion, and interferes with the terminal innervation of the pancreas.[34] This hypoxic environment also leads to the activation of various genes by hypoxia-inducible factor 1α (HIF-1α) protein to promote cell survival, progression, invasion and metastasis.[37,38]

Preclinical studies have shown that activated PSCs express several growth factors, cytokines, receptors and other proteins that are thought to contribute towards continued tumour/stroma growth.[39] Among these, SPARC (secreted protein acidic and rich