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Management of metastatic pancreatic cancer: Current treatment options and potential new therapeutic targets

Francesco Sclafani, Ridhima Iyer, David Cunningham, Naureen Starling *

The Royal Marsden NHS Foundation Trust, London and Surrey, UK

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Abstract

Pancreatic ductal adenocarcinoma is a malignancy with a poor prognosis, with the majority of patients diagnosed with advanced disease on presentation. Treatment options remain limited with little progress over the last 40 years. This review will focus on the current management of metastatic pancreatic ductal adenocarcinoma, with a discussion of new and future treatment strategies based on an improved understanding of tumour biology and mechanisms of pathogenesis.

Keywords: Pancreatic cancer; Pancreatic adenocarcinoma; Stroma; Gemcitabine; Nab-paclitaxel; FOLFIRINOX; Nanoliposomal irinotecan

1. Introduction

Pancreatic ductal adenocarcinoma (PDA) is a relatively uncommon malignancy with 337,872 estimated new cases worldwide in 2012 and the highest incidence seen in North America and Central and Eastern Europe [1]. In the UK, approximately 8773 new cases were diagnosed in 2011 and

* Corresponding author at: Department of Medicine, The Royal Marsden NHS Foundation Trust, Downs Road, Sutton, Surrey SM2 5PT, UK. Tel.: +44 0208 6426011; fax: +44 0208 643 9414.
E-mail address: naureen.starling@rmh.nhs.uk (N. Starling).

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PDA was the tenth commonest malignancy [1]. Incidence rises steeply with age, with 96% of cases diagnosed in patients over 50 years and 47% in those above 75 years. There are no major differences in incidence between the two sexes with the lifetime risk of developing PDA estimated as 1 in 73 in men and 1 in 74 in women [1].

Despite its relatively low incidence, PDA is one of the tumour types with the highest mortality rate. According to the GLOBOCAN 2012 statistics, 330,372 patients were estimated to have died of this disease worldwide [2]. In the UK, 8320 deaths from PDA were registered in 2011 and PDA was the fifth most common cause of cancer death [1]. These figures and especially the close correspondence between incidence rate and mortality rate, dramatically reflect the poor prognosis associated with this condition.

The 5-year overall survival (OS) rate for PDA has been reported to be approximately 6% [3]. Although the poor outcome is largely secondary to the high proportion of patients who are diagnosed with advanced disease, the prognosis of PDA is also influenced by the inherent biological aggressiveness and the high metastatic potential of this malignancy. In the vast majority of cases, PDA patients are diagnosed with locally advanced, inoperable tumours (approximately 40% of cases) or metastatic disease (approximately 40–45% of cases) and the 5-year OS rates reported for these groups are 9% and 2%, respectively [3,4]. Only a minority of patients (approximately 10–20% of cases) present with early stage tumours which may be potentially treated with surgical resection [4]. However, even in this circumstance, the prognosis of PDA is significantly poor with only 21% of patients being alive 5 years after curative surgery and adjuvant chemotherapy [5].

PDA is characterised by few early 'red flag' symptoms but is often associated with debilitating cytokine mediated symptoms in the advanced setting [6,7]. In addition, the pancreas may represent a sanctuary site, avoiding the cytotoxic potential of therapeutics. Over the last few decades, very little progress has been made in the systemic treatment of this disease. Major advances include a better understanding of the role of the peritumoural stroma and the introduction of more effective combination chemotherapy regimens for the treatment of advanced tumours. However, the survival figures have not substantially changed and, in contrast to most tumour types, no improvement in mortality rate has been recently predicted for this malignancy [8]. Therefore, PDA remains a significant challenge for clinicians and an important focus of research for biologists and clinical scientists.

In this article we provide an overview of the pathogenesis and biological characteristics of PDA and discuss the currently available management options for the treatment of patients with metastatic disease. Moreover, we summarise the data from some of the most relevant clinical studies investigating new potential therapeutic targets in this malignancy.

2. The genetic basis of pancreatic ductal adenocarcinoma and potential risk factors

The genetic basis of PDA is highly complex and heterogeneous [9]. In contrast to other human malignancies, a single, targetable molecular alteration driving tumour growth and proliferation has not been identified and genetic heterogeneity is one of the key features likely to account for the aggressiveness of this tumour and its poor responsiveness to treatment. A range of mutations has been identified in pancreatic adenocarcinoma, affecting oncogenes, tumour suppressors, and genes involved in apoptosis and the cell cycle [10].

PDA usually develops from a benign precursor lesion (PanIN) with the commonest and earliest mutations predominantly within the *RAS* proliferative pathway. *K-RAS* mutation is found in the vast majority of pancreatic tumours while *B-RAF* mutation occurs in only a minority of cases [11]. After an initial *RAS* pathway mutation, a step-wise progression of mutations has been suggested which mark the genetic progression of precursor lesions into PDA and include other genes such as *APC*, *p16/CDKN2*, *PI3KCA*, *PTEN* and *TP53* [12–14]. For example, simultaneous alteration of *KRAS* and *PTEN* (i.e. *KRAS* mutation and *PTEN* loss) has been reported to facilitate activation of NF-KB, which in turn induces inflammation, initiates stromal development and promotes local and metastatic spread. *p16INK4A/CDKN2* is a tumour suppressor gene which is essential in cell cycle checkpoint control at G1/S and has been shown to be inactivated through mutations/deletions/epigenetic alterations in approximately 90% of PDAs [14,15]. Inactivation of p16 has also been reported to correlate with a more aggressive phenotype and poorer prognosis [16]. In a minority of cases PDA arises from precursor cystic lesions including intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs) [17]. The molecular alterations of these tumours are overall similar to those observed in PDAs which develop from PanIN. However, it is worth noting that an increased incidence of *GNAS* mutation have been reported for IPMNs with invasive carcinoma [18].

While the molecular events that occur during pancreatic carcinogenesis have been well characterised, those that underlie tumour progression still remain to be elucidated. However, tumour proliferation, invasiveness and metastatic potential may be promoted by the activation of a variety of intracellular signalling axes (i.e. the NF-KB, src, and Stat3 pathways) and mutations of additional genes [11,14]. Other pathways which may play a role are the Hedgehog and Notch signalling cascades which are up-regulated both in tumour and stromal cells and the SMAD-4 pathway [19–22].

Little is known about the aetiology of PDA. However, several risk factors for development of this malignancy have been identified and include increasing age, cigarette smoking and alcohol abuse [23–26]. Moreover, higher rates have been observed in patients with diabetes mellitus, chronic pancreatitis, gastric ulcers, ulcerative colitis and chronic hepatitis B and hepatitis C infection [26–31]. A positive