Cancer Treatment Reviews 40 (2014) 1039–1047

Contents lists available at ScienceDirect

Cancer Treatment Reviews

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

Tumour Review

Progress in the knowledge and treatment of advanced pancreatic cancer: From benchside to bedside

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ARTICLE INFO

Article history:
Received 28 May 2014
Received in revised form 9 July 2014
Accepted 10 July 2014

Keywords:
Advanced pancreatic cancer
Palliative chemotherapy
Clinical trial
Tumor microenvironment
Tumor stroma

ABSTRACT

Ever since a pivotal study in 1997 demonstrated superiority of gemcitabine over 5-FU, gemcitabine monotherapy has, until recently, comprised the standard of care in patients with advanced pancreatic cancer. However, the emerging recognition of the pancreatic cancer microenvironment, including the particularly abundant stroma, as playing a key role in disease progression and resistance to chemotherapy has marked somewhat of a paradigm shift in the way treatment of advanced pancreatic cancer is viewed, with these very same biological defenses conversely offering an Achilles heel with which to combat this aggressive disease. Recently, this approach was validated for the first time in a pivotal phase III trial in which patients received nab-paclitaxel, a stroma-targeted drug, with gemcitabine. Overall survival was significantly ($p < 0.001$) prolonged in the combination arm, compared with gemcitabine alone, and thus these convincing results pave the way forward for future treatment regimens that employ a multipronged approach, targeting not only the primary tumor but the surrounding microenvironment as well.

Introduction

Of all the solid tumors, pancreatic cancer carries one of the most dismal prognoses, with a median overall survival duration of approximately 6 months following diagnosis and an overall survival rate at 5 years of less than 5% [1]. Reasons for this include marked tumor resistance to chemotherapy and radiotherapy, lack of specific early symptoms resulting in advanced disease upon diagnosis and the ability of pancreatic cancer cells to metastasize early in disease development [2]. Indeed, for the approximately 15–20% of patients with seemingly operable disease at presentation, micrometastases have usually already been established [3] and 85% of these patients will eventually experience relapse and subsequent cancer-related death [4]. However, the majority of patients are diagnosed at a late stage in disease development, with approximately 30% and 50% having locally-advanced unresectable and metastatic disease, respectively, upon presentation [5].

Currently, definitive risk factors for pancreatic cancer remain largely unknown. Of several environmental agents possibly associated with increased risk, only tobacco use has been established as having a causative role, with smokers experiencing a 2.5–3.6-fold higher risk of disease [1]. Other possible environmental causes are nitrites which are used as preservatives in processed meats [6]. Overweight or obesity was confirmed as a risk factor in a large case-control study in which it was shown that subjects who were overweight from 14 to 39 years of age or who were obese from 20 to 49 years of age had a statistically significant increased risk of pancreatic cancer (highest odds ratios of 1.67 [95%CI: 1.20–2.34] and 2.58 [95%CI: 1.70–3.90], respectively), regardless of whether or not they had concomitant diabetes mellitus, another possible risk factor. Additionally, overweight or obesity resulted in earlier onset of disease [7].

Diabetes is associated with pancreatic cancer but whether or not it is a causative factor, an effect due to pancreatic cancer or both has yet to definitively determined. In a population-based cohort study conducted in Taiwanese patients, diabetes mellitus for less than 2 years was found to be significantly correlated with increased risk of pancreatic cancer, with the incidence being approximately 4 times higher than that observed in non-diabetic patients (27.81 vs. 6.96 cases per 10,000 patient-years). However, an increased risk of pancreatic cancer was not found in patients with long-term diabetes [8].

Familial mutations are important risk factors for pancreatic cancer, with 7–10% of pancreatic cancer patients having a family history of this disease. A first-degree relative of an individual with familial pancreatic cancer has a 9-fold higher risk of developing this neoplasm and those with 3 or more affected first-degree relatives have a 32-fold higher risk. Moreover, familial pancreatic

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http://dx.doi.org/10.1016/j.ctrv.2014.07.003
0305-7372/

cancer is associated with an increased incidence of precancerous lesions and extra-pancreatic malignancies.

Other possible risk factors that have yet to be validated include a high-fat diet or a diet that contains few vegetables, non 'O' blood type, African-American ethnicity, older age and male gender [9].

Treatment for early-stage pancreatic cancer comprises surgery followed by adjuvant chemotherapy which is usually gemcitabine or 5-FU (fluorouracil) [10]. Recently, a long-term analysis was published of the pivotal CONKO-001 study which compared adjuvant gemcitabine with observation alone in patients with resected pancreatic cancer. After a median follow-up period of 11.3 years, disease-free survival, the primary endpoint, was significantly longer in the gemcitabine arm (median of 13.4 vs. 6.7 months; $p < 0.001$) as was survival (median of 22.8 months vs. 20.2 months; $p = 0.01$). Moreover, the 5-year overall survival of 20.7% vs. 10.4% and 10-year overall survival of 12.2% vs. 7.7% was prolonged [11].

With respect to administration of neoadjuvant therapy, results so far have been inconclusive in patients with primarily resectable disease [10]. In patients with borderline resectable/unresectable pancreatic cancer, administration of chemotherapy may increase the chance of resection and, consequently, improve survival outcomes [12]. Regarding the value of radiotherapy in the treatment of locally advanced pancreatic cancer, addition of radiotherapy is not superior to continuing chemotherapy after four months of induction therapy, with the final results of the international phase III LAP 07 study showing no significant differences in efficacy between chemotherapy and chemoradiotherapy arms [13].

Unfortunately, due to the majority of patients presenting with disease that is already unresectable and/or metastatic, treatment is usually palliative, with the main goals being to ameliorate symptoms and extend survival.

Ever since gemcitabine was confirmed as the standard of care for advanced pancreatic cancer in 1997 [14], progress in improving survival outcomes has been painfully slow, with many different gemcitabine-based combinations demonstrating no more efficacy than gemcitabine alone, aside from when administered in patients with good performance status [15].

Regarding predictive biomarkers for pancreatic cancer treatment, human equilibrative nucleoside transporter 1 (hENT-1) has been identified as a predictor of response to gemcitabine. A multivariate analysis of the ESPAC-1 and -3 trials showed that increased intratumoral hENT-1 was significantly correlated to response to gemcitabine ($p = 0.008$) but not fluorouracil [16]. Similar outcomes were seen in another multivariate analysis of the RTOG 9704 trial, in which higher hENT-1 levels in gemcitabine recipients were associated with significantly ($p = 0.018$) longer overall survival, compared with those patients with lower hENT-1 levels (median of 24.2 vs. 14.8 months) [17]. Presently, a phase II trial (NCT01726582) is being conducted in patients with borderline resectable/unresectable pancreatic cancer which is assessing 6 biomarkers considered to be predictive of treatment response-secreted protein acidic and rich in cysteine (SPARC; nab-paclitaxel), ribonucleotide reductase M1 (RRM1; gemcitabine), excision repair cross-complementation group 1 (ERCC1; platinum analogs), topoisomerase 1 (TOPO1; irinotecan), hENT-1 (gemcitabine) and TYMS (fluorouracil) [18].

Genetics

Over the last decade our understanding of pancreatic cancer genetics has increased substantially, with a number of germline and somatic mutations being identified and mapped. KRAS-activating mutations, a somatic mutation found in approximately 90% of pancreatic cancers, and its downstream signaling pathways MAPK and PI3K have been the focus of intense efforts to develop targeted therapies [19]. Unfortunately, success so far has been thwarted due to the difficulty in developing a protein that precisely matches the active site in the KRAS protein. As KRAS only becomes fully activated once it is transported and embedded in the cell membrane, a new approach has been taken in which KRAS itself is not targeted but instead the target is its transport protein PDE-δ. Preclinical results appear promising thus far but have yet to be validated in clinical trials [20].

Other common somatic mutations in pancreatic cancer include inactivation of tumor suppressor genes such as CDKN2A, BRCA2, TP53 and SMAD4, with the latter three mutations occurring in advanced-stage disease. Epigenetic dysregulation is also implicated in the pathogenesis of pancreatic cancer and in neoplasms without genetic inactivation of tumor suppressor genes, gene silencing can occur via promoter methylation [9]. Currently, a demethylation agent, azacitidine, is being assessed in combination with gemcitabine in a phase I clinical trial in 30 patients with advanced disease (NCT01167816) and trial completion is scheduled for July 2014.

It is also becoming clear that pancreatic cancer tumors are highly heterogeneous, with results from a global landmark genomic analysis of 24 advanced pancreatic adenocarcinomas showing that tumors contain on average 63 genetic alterations. This heterogeneity may partially explain the notorious resistance of pancreatic cancer to chemotherapy and, unfortunately, it may also render the idea of targeted therapies to specific tumor mutations as largely unrealistic [21].

The pancreatic cancer microenvironment

Epithelial-mesenchymal transition

Characterized by multiple biochemical changes resulting in loss of cell polarity and transformation of an epithelial cell into a mesenchymal cell phenotype, the epithelial-mesenchymal transition (EMT) is a pivotal process in tumor progression. EMT enables cancer cells to become unanchored from the primary tumor and to subsequently disseminate into the bloodstream [22], thus initiating the first steps in the establishment of micrometastases and the ability of pancreatic cancer to undergo this process at a particularly early stage in disease development is one of the major reasons for its dismal prognosis [23]. Tumor growth factor-beta (TGF-ß) is one of the key induction agents of EMT [24], as well as being a mediator of fibrosis within the stroma. Recently, trabedersen, an inhibitor of TGF-ß receptor-2, demonstrated activity in a phase I trial in patients with advanced TGF-ß overexpressing solid tumors, with a median overall survival duration of 9.2 months being observed in the subgroup of patients with pancreatic cancer [25].

As well as contributing to disease progression, EMT also plays a role in the development of drug resistance. In a recent study which aimed to characterize the resistance of pancreatic cancer cell lines to 3 different classes of cytotoxic chemotherapy (gemcitabine, 5-FU and cisplatin), high levels of transcriptional factor Zeb-1, an EMT activator, and low levels of E-cadherin, a cell adhesion protein, were associated with increased resistance to all 3 drugs; subsequent silencing of Zeb1 increased E-cadherin levels and restored drug sensitivity [26]. Similar results have been observed with targeted biologics as well [27]. Inhibition of Notch-2 has been found to downregulate Zeb1 expression and recently a clinical trial was conducted that assessed the preliminary efficacy and pharmacodynamic effects of a notch signaling pathway inhibitor, RO4929097 (RG-4733), in patients with metastatic disease (NCT01232829). However, results from this trial have yet to be published.