Review Article

Emerging therapies in pancreas cancer

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ABSTRACT

Pancreas cancer has a grave prognosis and treatment options remain limited despite advancement in anti-cancer chemotherapeutics. This review provides an overview of the emerging therapies for pancreas cancer, focusing on novel signal transduction inhibitors (insulin-like growth factor receptor, hedgehog/Smo, PI3k/Akt/mTOR) and cytotoxics (nab-paclitaxel) that are currently in clinical development. Despite the impact molecularly targeted agents have on other tumor types, their application without cytotoxics in pancreas cancer remains limited. In addition, recent report of the superiority of an intensive cytotoxic regimen using fluorouracil, irinotecan and oxaliplatin (FOLFIRINOX) over gemcitabine reminded us of the importance of cytotoxics in this disease. As such, the future of pancreas cancer therapy may be combination regimens consisting of cytotoxics and molecularly targeted agents.

KEY WORDS

Pancreas cancer, chemotherapy, target therapy

Introduction

Pancreas cancer is a lethal disease with mortality closely mirroring the incidence. Approximately 43,410 new cases will be diagnosed in the United States and 36,800 will die from the disease in 2010 (1). The mortality rate has not improved since the 1970s. A number of genetic mutations, such as KRAS, p16/CDKN2A, TP53, and SMAD4/DPC4, have been linked to aberrant cell proliferation, signaling, and reduced apoptosis in the disease (2). Recent genome-wide analysis showed that the genetic makeup of pancreas cancer is highly complex, with each tumor harboring more than 60 mutations (3). These aberrancies may be broadly categorized into 12 core cell-signaling pathways involved in the initiation and maintenance of malignant phenotype with each tumor harboring more than 60 mutations (3). These aberrancies may be broadly categorized into 12 core cell-signaling pathways involved in the initiation and maintenance of malignant phenotype, with each tumor harboring more than 60 mutations. These aberrancies may be broadly categorized into 12 core cell-signaling pathways involved in the initiation and maintenance of malignant phenotype, with each tumor harboring more than 60 mutations (3). These aberrancies may be broadly categorized into 12 core cell-signaling pathways involved in the initiation and maintenance of malignant phenotype, with each tumor harboring more than 60 mutations (3). These aberrancies may be broadly categorized into 12 core cell-signaling pathways involved in the initiation and maintenance of malignant phenotype, with each tumor harboring more than 60 mutations (3). These aberrancies may be broadly categorized into 12 core cell-signaling pathways involved in the initiation and maintenance of malignant phenotype, with each tumor harboring more than 60 mutations (3). These aberrancies may be broadly categorized into 12 core cell-signaling pathways involved in the initiation and maintenance of malignant phenotype, with each tumor harboring more than 60 mutations (3). These aberrancies may be broadly categorized into 12 core cell-signaling pathways involved in the initiation and maintenance of malignant phenotype, with each tumor harboring more than 60 mutations (3). These aberrancies may be broadly categorized into 12 core cell-signaling pathways involved in the initiation and maintenance of malignant phenotype, with each tumor harboring more than 60 mutations (3). These aberrancies may be broadly categorized into 12 core cell-signaling pathways involved in the initiation and maintenance of malignant phenotype, with each tumor harboring more than 60 mutations (3). These aberrancies may be broadly categorized into 12 core cell-signaling pathways involved in the initiation and maintenance of malignant phenotype, with each tumor harboring more than 60 mutations (3). These aberrancies may be broadly categorized into 12 core cell-signaling pathways involved in the initiation and maintenance of malignant phenotype, with each tumor harboring more than 60 mutations (3). These aberrancies may be broadly categorized into 12 core cell-signaling pathways involved in the initiation and maintenance of malignant phenotype, with each tumor harboring more than 60 mutations (3). These aberrancies may be broadly categorized into 12 core cell-signaling pathways involved in the initiation and maintenance of malignant phenotype, with each tumor harboring more than 60 mutations (3). These aberrancies may be broadly categorized into 12 core cell-signaling pathways involved in the initiation and maintenance of malignant phenotype, with each tumor harboring more than 60 mutations (3). These aberrancies may be broadly categorized into 12 core cell-signaling pathways involved in the initiation and maintenance of malignant phenotype, with each tumor harboring more than 60 mutations (3). These aberrancies may be broadly categorized into 12 core cell-signaling pathways involved in the initiation and maintenance of malignant phenotype, with each tumor harboring more than 60 mutations (3). These aberrancies may be broadly categorized into 12 core cell-signaling pathways involved in the initiation and maintenance of malignant phenotype, with each tumor harboring more than 60 mutations (3). These aberrancies may be broadly categorized into 12 core cell-signaling pathways involved in the initiation and maintenance of malignant phenotype, with each tumor harboring more than 60 mutations (3). These aberrancies may be broadly categorized into 12 core cell-signaling pathways involved in the initiation and maintenance of malignant phenotype, with each tumor harboring more than 60 mutations (3).
target in pancreas cancer due to its frequency, higher grade and that increased expression associated with a worse prognosis (10,11). In a randomized trial of erlotinib plus gemcitabine versus gemcitabine alone, patients receiving the combination has a statistically significant improvement in overall survival (0.82 HR, 6.24 months vs 5.91 months) (5). However, the improvement is marginal and many oncologists consider the 2 weeks survival improvement unsatisfactory. The inhibitor is being evaluated in the adjuvant setting, and in combination with other targeted agents such as insulin-like growth factor (IGF) pathway targeting drugs.

Cetuximab is a monoclonal antibody (MoAb) against the ligand-binding domain of the EGFR evaluated in combination with gemcitabine in a randomized phase III trial. However, the study failed to demonstrate the superiority of the combination over the gemcitabine control arm (12). Subset analysis showed that tumor EGFR expression does not predict benefit to the cetuximab-containing regimen. A phase II trial with cetuximab +/- gemcitabine and cisplatin showed similar negative results (13). The objective response rate was 17.5% for the combination arm versus 12.2% in control, and median progression-free and overall survivals were 4.2 months vs 3.4 months, and 7.8 months vs 7.5 months respectively.

**Anti-angiogenesis**

Pancreas cancer was thought to thrive on neovascularization and dependent on a rich blood supply as the tumors grow (14). The importance of vascular endothelial growth factor (VEGF) pathway was shown in preclinical pancreas cancer studies (15). Though the exact mechanism in patients is unclear, anti-angiogenic therapies are thought to interrupt tumor neovascularization and normalize existing inefficient tumor vasculature, thereby enhancing drug delivery and synergize the effects of cytotoxic agents.

Bevacizumab, a MoAb to VEGF ligand was studied in multiple trials. Recently published CALGB 80303 (gemcitabine +/- bevacinumab) treated 535 patients and overall response rates, median OS and PFS were 13%, 5.8 months, and 3.8 months for the gemcitabine/bevacizumab arm and 10%, 5.9 months, and 2.9 months for the gemcitabine/placebo arm, respectively (16). When bevacizumab was evaluated in combination

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with gemcitabine and erlotinib, the phase III trial failed to demonstrate significant improvement by the bevacizumab-containing arm compared to control (median OS 7.1 months vs 6.2 months respectively) (8). Bevacizumab failed to improve survival when evaluated in combination with gemcitabine and capecitabine in a phase II trial (6). Despite the initial excitement, bevacizumab failed to improve survival in advanced pancreas cancer patients when evaluated in combination with standard of care.

A number of small molecular tyrosine kinase inhibitors against VEGFR2, including sorafenib, sunitinib and vatalanib, have being evaluated in the disease but none showed positive efficacy signal so far (6-9). Combination therapies targeting VEGFRs and other signaling pathways are under investigation.

**Insulin-like growth factor pathway**

The IGF axis comprises multiple circulating ligands, such as IGF-1, IGF-II and insulin, interacting with membrane bound receptors, such as type I IGF receptor (IGF-1R). The PI3k-Akt pathway is one main downstream mediator of IGF-1R signaling and plays a potentially important role in anticancer drug resistance (17). IGF-1R has been shown in preclinical studies to mediate resistance to EGFR inhibition, and co-targeting of both receptors enhances the abrogation of PI3k-Akt activity and reduces survivin expression (18,19). Transgeneic mouse models of pancreas cancer expressing high levels of IGF-1R showed increased...
invasive carcinomas and lymph node metastases (20). Targeting of IGF-1R expression by siRNAs achieved growth inhibition in many gastrointestinal malignancies, suggesting potential importance of the pathway in pancreas cancer (21-24). In concert, changing IGF-1R copy number by cDNA plasmid augmented mitogenic response in mouse embryo. Treatments with MoAb seemed to lead to IGF-1R internalization and degradation, and enhanced cytotoxic chemotherapy effects (25). DNA repair pathways are other downstream effectors of IGF-1R axis and provide the rationale for combining IGF-1R inhibitors with cytotoxics (30,31).

A number of agents targeting IGF-1R, both MoAbs and TKIs, are being evaluated clinically and we are just starting to understand their clinical role and potential mechanisms of resistance to this class of drugs (26).

**Anti-IGF-1R monoclonal antibodies**

AMG-479 is a fully humanized MoAb that blocks the binding of IGF-I and IGF-II to IGF-1R (IC$_{50}$ < 0.6 nmol/L), and does not cross-react with the insulin receptor (IR) (27). AMG-479 completely inhibited ligand-induced dimerization and activation of IGF-1R/IGF-1R and IGF-1R/IR in two pancreas cancer cell lines. The antibody reduced IGF-1R-mediated downstream Akt phosphorylation with pro-apoptotic and anti-proliferative effects in the cancer cell lines. The agent demonstrated additive effects with gemcitabine in preclinical studies (27). In a randomized phase II trial, AMG-479 in combination with gemcitabine demonstrated a trend to improvement in median survival when compared to the placebo/gemcitabine control arm (8.7m vs 5.9m; HR 0.67, $P=0.12$) in previously untreated metastatic pancreas cancer patients. The median PFS was 5.1 months and 2.1 months respectively (HR 0.65, $P=0.07$). The investigators conclude that there was sufficient efficacy signal to warrant further evaluation in a phase III trial.

IMC-A12 (cixutumumab) (29) and MK-0646 (dalotuzumab) are other anti-IGF-1R MoAb that are being evaluated in untreated metastatic pancreas cancer patients. MK-0646 enhanced gemcitabine induced apoptosis in preclinical studies and is being evaluated clinically. This phase I/II trial is enrolling patients to 3 treatment arms; A: gemcitabine 1000mg/m2 weekly × 3 with MK-0646 weekly × 4, Arm B: gemcitabine + MK-0646 + erlotinib 100mg daily, Arm C: gemcitabine 1000mg/m2 weekly × 3 + erlotinib 100mg daily. MK-0646 achieved 6 partial responses (PR), 1 hepatic complete response (CR) and 8 stable disease (SD) out of 22 patients (32). Grade 3 or dose-limiting toxicities were rare and included hyperglycemia, hepatic transaminitis, and febrile neutropenia. The demonstrated responses confirm the hypothesis of cross-talk between EGFR and IGF axis signaling and the importance of adding cytotoxic therapy.

**Small molecule IGF-1R/IR kinase inhibitors**

Compensatory activation of IR signaling following inhibition of IGF-1R is emerging as a pathway of resistance to IGF-1R MoAbs. TKIs against IGF axis thus have a theoretical advantage over MoAbs given the IR cross-reactivity (33). OSI-906 is a potent and highly selective inhibitor of IGF-1R, with 14 times greater selectivity for IGF-1R over IR.34 OSI-906 alone did not show significant efficacy in pancreas cancer cell lines and was further evaluated in other tumor types preclinically (35). IGF-1R pathway has been reported as potential resistance mechanism to EGFR inhibition and it seems logical to expect increased efficacy when an IGF-1R inhibitor is combined with gemcitabine and erlotinib in pancreas cancer patients. Clinical trials evaluating OSI-906 with gemcitabine and erlotinib combination have yet to be initiated. However, the dosing regimen and toxicity profile of the combination of OSI-906 and erlotinib were reported at 2010 American Society of Clinical Oncology Annual Meeting: OSI-906, administered daily at 50mg and 100mg, combined with erlotinib 100mg daily yielded stable disease in 4 out of 7 (57%) patients, including adrenocortical carcinoma, Ewings sarcoma, chordoma and adenocarcinoma of unknown primary (36). Toxicities included fatigue (31%) gastrointestinal side effects diarrhea (31%) nausea (15%); grade ≥3 hyperglycemia.

**Hedgehog/smoothened pathway**

Smoothened (Smo) is a transmembrane receptor with seven domains, and the activity is repressed by Patched (Ptc). The repression is relieved when ligands bind to Ptc or when there is activating mutations in Ptc, leading to increased transcription and up-regulation of GlI-1 to 3, thereby modulating cell cycle and adhesion, angiogenesis, and apoptosis. In a comprehensive genomic analysis of pancreas cancers, mutations in at least one Hedgehog (Hh) signaling component has been reported in all samples analyzed, indicating the importance of Hh pathway in pancreas tumorgenesis (3). In addition, Hh signaling may be an important modulator of tumor-stromal interaction in the disease (37,38). Preclinically, Olive et al. evaluated IP-926, a Smo inhibitor, with gemcitabine which the combination improved survival of tumor-bearing mice and reduced metastasis in a transgenic model (39). The anti-cancer
effect seems to be related to a decrease in tumor-associated stromal tissue and improve drug delivery by stimulating VEGF-independent angiogenesis. In this study, the tumor-bearing mice eventually adapted to chronic Smo inhibition and became resistant to the treatment, thus raising the importance in identifying potential resistant mechanisms. Hh signaling is also implicated as an important mediator of cancer stem cell (CSC) phenotype in pancreas cancer. Several groups have reported on the cellular markers of CSCs in pancreas cancer and the CSCs may be identified by the co-expression of CD133/CXCR4, or CD44/CD24/ESA. Extractions enriched in cancer cells expressing these markers is highly tumorigenic in in vitro and in vivo experiments and re-capitulate the characteristics of parent tumors (40,41). Analysis of the CSCs found increased activation of Hh signaling and other self-renewal signaling pathways. Mueller et al reported anti-CSC effects when pancreas tumors were treated with a combination of cyclopamine or CUR199691 (Smo inhibitors), rapamycin (mTOR inhibitor) and gemcitabine, and treated tumor-bearing mice survived longer than control (40). This was associated with elimination of CD133-expressing CSCs. As such, approaches targeting CSC signaling pathways are worth exploring clinically.

GDC-0449 (Vismodegib), XL139 (BMS-833923), and LDE225 are oral agents with anti-Smo activities in single-agent phase I trials conducted so far (43,44). The former study with temsirolimus was halted due to toxicities and no objective response was observed, and the median PFS was 19 days and survival 44 days. The everolimus and erlotinib combination was better tolerated, but no response was observed and median PFS and survival was 49 days and 87 days respectively. The everolimus and erlotinib combination was better tolerated, but no response was observed and median PFS and survival was 49 days and 87 days respectively. These trials demonstrate that mTOR inhibition as a single agent is ineffective and combining inhibitors of multiple steps and the role for these inhibitors may lie in combination regimens.

PI3K/AKT/mTOR pathway

The phosphoinositide 3'-kinase (PI3k)/Akt/mammalian target of rapamycin (mTOR) pathway acts as a cellular sensor for nutrients and growth factors, and integrates signals from multiple receptor kinases to regulate cellular growth and metabolism (4). The pathway is regulated by a number of upstream proteins including KRas, which activating mutations are found in the majority of pancreas cancer (48). In addition, Akt2 activation, associated with the development of human cancers, is detected in about half of the tumors (49). PI3K/Akt/mTOR activation was associated with early carcinogenesis and interruption of the pathway achieved anti-proliferation, -survival, -angiogenic and pro-apoptotic effects (50-58). Other activating events include PTEN loss and Akt amplification (59-61). Activation of this pathway was associated with poor prognosis and contributed to chemoresistance in many cancers (62-66). Thus, the PI3k/ Akt/mTOR pathway is an attractive pathway to target in pancreas cancer.

Akt inhibitors

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mTOR signaling. MK-2206, an allosteric Akt1-3 inhibitor, was evaluated in a phase I trial of 70 patients with advanced cancers (69). Interestingly, tumor shrinkage (23%) was observed in a patient with PTEN-negative pancreas cancer and was associated with a 60% decrease in CA19-9. MK-2206 is being evaluated as weekly (300mg) and every other day (75mg and 90mg) dosing schedules. MK-2206 is also being evaluated in combination with cytotoxic chemotherapy agents and inhibitors of c-Met and EGFR (70,71).

RX-0201 is an antisense oligonucleotide against Akt1 mRNA, thereby interrupting the pathway’s activation. The anti-sense oligonucleotide demonstrated activity against pancreatic cancer cell lines in low nanomolar range, reducing the expression of Akt1 mRNA and protein. In in vivo studies, RX-0201 treatment led to complete response in 2 out of 3 pancreas tumor-bearing mice (72). As such, RX-0201 in combination with gemcitabine is currently being evaluated in a phase II trial for metastatic pancreas cancer patients (73). Given the short half-life typical of anti-sense agents, RX-0201 is being administered by continuous infusion for 14 days of a 21-day cycle and presents a potential obstacle to patient accrual. Liposomal formulations are in development (74).

**PI3K inhibitors**

XL147 and BKM120 are oral class I PI3k inhibitors that are being evaluated in phase I trials, alone and in combination with cytotoxic chemotherapy agents and inhibitors of c-Met and EGFR (75-77). These trials have focused on lung, colorectal and breast cancers given the higher frequency of pathway aberrations in these tumor types. XL765 is a novel selective inhibitor that interrupts the pathway at various nodes: PI3K, TORC1 and TORC2. The efficacy of such agents in pancreas cancer is to be evaluated (78).

**Cytotoxics**

Gemcitabine has been the chemotherapy backbone for the treatment of newly diagnosed advanced pancreas cancer (79,80). Various other cytotoxic drugs have been tested in combination with gemcitabine, including fluoropyrimidines, platinum derivatives, and taxanes (80-84). Meta-analysis of various cytotoxic trials over the last one-and-a-half decades suggest improved survival with doublet or triplet gemcitabine-based therapy among patients with good performance status, who can, supposedly, better withstand the toxicities (85).}

Final results from the interim analysis of the PRODIGE 4/ACCORD 11 trial were presented at 2010 European Society for Medical Oncology annual meeting, which randomized 342 patients with previously untreated metastatic pancreas cancer to receiving FOLFIRINOX (oxaliplatin 85 mg/m² Day 1 + irinotecan 180 mg/m² Day 1 + leucovorin 400 mg/m² Day 1 followed by S-fluorovorin 400 mg/m² bolus Day 1 and 2,400 mg/m² 46 hours continuous infusion biweekly) or gemcitabine alone. The study was stopped on recommendation by the independent monitoring committee during preplanned interim analysis when FOLFIRINOX was determined to be superior to gemcitabine alone, making the fluoropyrimidine-based regimen first non-gemcitabine based regimen to show significant improvement in overall survival. The objective response rate for FOLFIRINOX, compared to gemcitabine alone, was 31.6% vs 9.4% (P=0.0001), median PFS 6.4 vs 3.3 months (P<0.0001) and median survival 11.1 vs 6.8 months (HR=0.57, 95% CI =0.45-0.73; P<0.001) respectively. However, there were significantly more grade 3 and above toxicities in the FOLFIRINOX arm, including diarrhea, nausea, vomiting, neutropathy, neutropenia, neutropenic fever. Given the higher frequency of clinically significant toxicities, FOLFIRINOX cannot be accepted as the standard first-line treatment for all newly diagnosed advanced pancreas cancer patients. The choice of FOLFIRINOX in advanced patients needs to be personalized according to factors such as performance status, treatment aim, physiological reserve and patient preference, and the role in adjuvant setting is being evaluated.

Nab-paclitaxel (Abraxane®; Abraxis) is a nano-particle preparation in which paclitaxel is bound to albumin as compared to sb-paclitaxel (Taxol®, Bristol Meyers Squibb), which is dissolved in poloxynethylated castor oil (Cremaphor EL®) and ethanol. The absence of castor oil renders nab-paclitaxel clinically advantageous since this avoids the infusion and hypersensitivity reaction characteristics of sb-paclitaxel. In the initial phase I clinical trial of nab-paclitaxel, there was no hypersensitivity reaction typical of sb-paclitaxel and was well tolerated up to 300mg/m² administered as a 30-minute infusion (86). The recommended dosing for nab-paclitaxel is 260mg/m² compared to 175 mg/m² for sb-paclitaxel (87). In a crossover pharmacokinetik study to limit patient variability, nab-paclitaxel had higher peak plasma and unbound concentrations (88). Greater unbound fraction of paclitaxel has been hypothesized to lead to greater efficacy seen in many clinical trials.

One possible mechanism of efficacy by the albumin-bound agent may be related to enhanced tumor uptake through interaction with the SPARC (secreted protein acid rich in cysteine) molecule. The SPARC gene, highly conserved among vertebrates, regulates the assembly, organization, and turnover of the extracellular matrix by binding and modulating the deposition of multiple
structural components and attenuating the activity of extracellular proteases. SPARC is expressed in cancer-associated stroma and in malignant cells of some types, affecting tumor development, invasion, metastases, angiogenesis and inflammation. SPARC-induced changes in the tumor microenvironment can suppress or promote progression of different cancers depending on the tissue and cell type. SPARC expression is related to tumor aggressiveness though the exact mechanism is unclear. The molecule regulates the effects of bFGF and VEGF on MAPK signaling and increased expression of SPARC in pancreas tumors has been related to poorer survival (91,92). Infante et al. characterized SPARC expression in peritumoral fibroblasts and pancreas cells from 299 patients with resectable pancreas cancer. Median survival was halved in patients’ tumors that expressed SPARC (15 months vs 30 months) and when cases were controlled for other prognostic factors (tumor size, positive lymph nodes, margin status, tumor grade, and age) the hazard ratio (HR) was significant (HR 1.89; 95% CI, 1.31 to 2.74).

Therapies combining nab-paclitaxel with gemcitabine are under investigation in pancreas cancer given the high expression of SPARC in pancreas cancer. Several studies are underway and preliminary result showed impressive responsive rate and encouraging survival outcome. In a phase I/II trial, 63 previously untreated metastatic patients were treated with nab-paclitaxel and gemcitabine and among the 49 evaluable patients, 1 achieved CR (2%), 12 PRs (24%) and 20 SD (41%) (clinical benefit rate 67%). The response rate and PFS correlated with SPARC expression by immunohistochemistry (89). A single institution retrospective review of this combination in neoadjuvant setting for borderline and unresectable patients confirmed the high response rate (69% PR and 23% SD). About 23% of patients in the study went on to surgical resection with curative intent (90). This regimen is being evaluated in a phase III randomized trial among patients with untreated metastatic pancreas cancer.

Conclusion

Despite advancement in anti-cancer therapeutics, treatment options remain limited and prognosis poor for patients with pancreas cancer. The molecularly targeted agents hold significant promise in pancreas cancer for several reasons, including the better-tolerated toxicity profiles and they target known molecular aberrancies. However, strategies to target angiogenesis and EGFR pathways had, in general, not being successful and the underlying reasons remain unclear. Other exciting molecular targets that can be interrupted by clinical grade drugs include the IGF, Hh and PI3k/Akt/mTOR pathways. As these agents complete early phase evaluation, their role in the treatment of pancreas cancer will be evaluated either alone or in combination therapies. Importantly, in-depth correlative studies using patient blood and tumor samples should be incorporated to better select the patient population most likely to benefit from these agents and also, to understand the mechanism of efficacy (or futility).

An important recent development is the demonstration of the superiority of intense cytotoxic regimen (FOLFIRINOX) over gemcitabine alone in previously untreated pancreas cancer patients. Though the regimen can hardly be accepted as the standard for advanced disease due to its significant side effect profile, the trial points to the continual importance of cytotoxic agents in treating the disease. As such, one eagerly awaits the result from the phase III trial of nab-paclitaxel plus gemcitabine versus gemcitabine alone in metastatic pancreas cancer patients given the encouraging result so far.

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