Cancer Chemother Pharmacol (2004) 54 (Suppl 1): S69–S77
DOI 10.1007/s00280-004-0890-2

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Molecular targeting therapy for pancreatic cancer

Published online: 13 August 2004

Abstract Pancreatic carcinogenesis is driven by multiple genetic and epigenetic changes. The epidermal growth factor receptor (EGFR) and its downstream signaling pathways, Ras-Raf-MEK-ERK axis, play important roles in pancreatic cancer development. The phosphoinositol 3 kinase (PI3 K)/Akt and the nuclear factor κB (NF-κB) pathways control both proliferation and resistance to apoptosis of pancreatic cancer. The role of cyclooxygenase (COX) and lipoxygenase (LOX) in the development of pancreatic cancer has been made known recently. The elucidation of these molecular events has led to several distinct therapeutic advances, including therapies that target EGFR, the Ras-Raf-MEK-ERK axis, the COX-2 and LOX pathways, and others. Many novel agents have been developed and are undergoing clinical investigation, such as monoclonal antibodies against EGFR, tyrosine kinase inhibitors (TKIs), farnesyl transferase inhibitors (FTIs), Bay43-9006, CI-1040, CCI-779, celecoxib, and LY293111. This review highlights recent advances in the development of these agents.

Keywords Pancreatic cancer · Molecular targeting therapy · EGFR inhibitors · Ras inhibitors · COX-2 inhibitors

This work was presented at the 19th Bristol-Myers Squibb Nagoya International Cancer Treatment Symposium, "State of the Arts for Digestive Organs", 14–15 November 2003, Nagoya, Japan.

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Molecular targets in pancreatic cancer

The development, continued growth, and metastasis of pancreatic cancer are driven by multiple genetic and epigenetic changes, including inactivation of tumor suppressor genes and activation of protooncogenes. Some of the important genetic and epigenetic changes that have been targeted for drug development are summarized in Table 1. A key molecular event is the overexpression of the epidermal growth factor receptor (EGFR) and activation of its downstream signaling molecules. EGFR is a receptor tyrosine kinase that undergoes dimerization and activation of its intrinsic kinase upon binding of its ligands. The activated EGFR subsequently recruits and activates its downstream signaling molecules. Ras is a key signaling molecule downstream of EGFR. Ras is activated through a guanine exchange factor, Sos, which is activated through interaction with EGFR and adapters such as Grb 2 and Shc. Subsequently, Ras activates Raf, and a dual specific kinase MEK1, and finally extracellular signal-regulated kinase (ERK), which ultimately translocates to the nucleus and regulates transcription factors. This Ras-Raf-MEK-ERK signaling pathway or axis is conserved among different species, indicating its fundamental role in the normal physiology of cells [5, 65].

Dysregulation of the signal transduction pathways may lead to uncontrolled cell growth and hence tumor development. The role for EGFR and its downstream signaling molecules in tumorigenesis is evidenced by their ability to transform normal cells to a neoplastic phenotype when expressed in mutated, unregulated forms, or when expressed to an abnormally high level. Moreover, activation mutation or overexpression of EGFR and its downstream signaling molecules occurs frequently in a variety of human cancers, including pancreatic cancer. The most recent study indicated that EGFR was detectable in more than 95% of patients with pancreatic cancer [1]. In most cases, EGFR is concomitantly expressed with its ligands, EGF or tumor growth

Table 1 Molecular targets and novel agents in pancreatic cancer

Targets	Frequency (%)[a]	Novel agents
Receptor tyrosine kinases		
EGFR	90	mAbs: cetuximab, ABX-EGF, EMD 72000 TKIs: gefitinib (ZD1839, Iressa), erlotinib (OSI-774, Tarceva), EKB-569
HER2/Neu	10	Herceptin, CI-1033
Ras-Raf-MEK-ERK signaling pathways		
Ras	90	FTIs: R115777, SCH66336, BMS-214662
Raf		Bay 43-9006
MEK		CI-1040
PI3 K/Akt pathways		
Akt		17-AAG (nonspecific)
mTOR		CCI-779, RAD001
NF-κB	67	Curcumin (nonspecific), bortezomib (PS-341, VELCADE) (nonspecific)
Other molecular targets		
COX-2	75	Celecoxib, rofecoxib
LOX		LY293111
IL-8	70	ABX-IL8

[a]Mutation/expression rate in pancreatic cancer

factor α, and the increased expression of ligand and receptor forms an autocrine loop that constantly stimulates cell proliferation [35, 43]. Finally, in pancreatic cancer, expression of EGFR and its ligands is associated with a poor prognosis [22, 72].

After being synthesized in the cytoplasm, the Ras proteins undergo a series of post-translational modifications culminating in membrane association. The first of these processing steps is farnesylation near the carboxy-terminal cysteine residue by farnesyl protein transferase. *Ras* carries a mutation at codon 12 (*K-ras*) in more than 90% of pancreatic cancer specimens [4]. The K-ras mutation results in constitutive activation of an intracellular signaling pathway, leading to cellular proliferation and thus conferring transforming properties onto cells containing point mutations in this gene. *Ras* mutation is considered an early genetic event in the development of pancreatic cancer, but *ras* mutation is not associated with tumor stage or prognosis, indicating that the *K-ras* oncogene may be related to the initiation of carcinogenesis, but is not linked to malignant potential or promotion of human pancreatic cancer [42].

One of the key downstream targets of the Ras family is phosphoinositol 3 kinase (PI3 K), a heterodimer consisting of a p85 regulatory subunit and a p110 catalytic subunit [14]. Activation of PI3 K can occur by binding of the p85 subunit to activated receptor tyrosine kinases or by binding of the p110 subunit to constitutively active Ras. Preclinical studies have shown that inhibitors of PI3 K, such as wortmannin and LY294002, induce dose-dependent apoptosis of pancreatic cancer cells that display constitutive Akt activity in vitro, and inhibit tumor growth of pancreatic cancer xenografts [10]. Activation of PI3 K is implicated in pancreatic cancer resistance to apoptosis induced by chemotherapeutic or molecular targeting agents, as several studies have demonstrated that treatment with the PI3 K inhibitors substantially enhances apoptosis induced by gemcitabine in a concentration-dependent manner [11, 12, 45, 46]. Furthermore, Western blotting has shown that the reduction of phosphorylated Akt levels correlates with the enhancement of gemcitabine-induced apoptosis, suggesting that the PI3 K/Akt pathway plays a significant role in mediating drug resistance in human pancreatic cancer cells. Inhibition of the PI3 K/Akt signaling pathway also sensitizes pancreatic tumor cells to nonsteroidal antiinflammatory drugs (NSAIDs) such as sulindac [76]. Since the PI3 K/Akt signaling pathway plays an important role in tumor growth and resistance to apoptosis, it is a reasonable target for novel drug development.

The tumor suppressor gene PTEN is known to play a major role in embryonic development, cell migration and apoptosis [71]. PTEN acts as a lipid phosphatase that regulates major signal transduction pathways and effectively terminates PI3 K-mediated signaling [48]. PTEN mutation, which occurs frequently in many solid tumors, is associated with constitutive activation of the PI3 K/Akt pathway, resulting in tumors that are generally resistant to apoptosis. In pancreatic cancer, PTEN is not mutated but functionally abrogated through loss of expression. It was found that over 60% of pancreatic cancer cell lines and tumor tissues had decreased or loss of expression of PTEN (S. Reddy, personal communication). PTEN status in tumor cells has been implicated as an important predictor of sensitivity to sirolimus (formerly known as rapamycin) analogs [55] that inhibit the mammalian target of rapamycin (mTOR), a downstream effector of Akt.

Nuclear factor κB (NF-κB) is a transcription factor that predominantly exists as p65 (RelA)/p50 heterodimer [27]. In most cells, NF-κB is sequestered in the cytoplasm in an inactive form through a noncovalent association with the inhibitor IκBα. This association masks the nuclear localization signal of NF-κB and thus prevents NF-κB nuclear translocation. Wang and

colleagues reported that RelA, the p65 subunit of NF-κB, was constitutively activated in approximately 67% of pancreatic adenocarcinomas, but not in healthy pancreatic tissues, and IκBα was overexpressed in human pancreatic tumor tissues and cell lines [67]. These data are consistent with the possibility that RelA is constitutively activated by the upstream signaling pathway, such as Ras, in pancreatic tumor cells. NF-κB may play an important role in tumor resistance to apoptosis induced by cytotoxic agents [6, 23]. Arlt and coworkers reported that pancreatic cancer cells resistant to gemcitabine exhibit a high basal NF-κB activity. Furthermore, gemcitabine showed a dose-dependent induction of NF-κB. Suppression of NF-κB by pharmacological or genetic approaches diminished the resistance against gemcitabine. NF-κB is, therefore, a potential target of novel drug development [6, 19, 25, 53].

Cyclooxygenases are enzymes that catalyze the conversion of arachidonic acid to various prostaglandins and thromboxanes and have a key role in inflammation and regulation of physiological functions. Two isoforms of the enzyme have been identified: cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). COX-1 supplies tissues with the prostaglandins required to maintain physiological organ function, such as cytoprotection of the gastric mucosa and regulation of renal blood flow. In contrast, COX-2 behaves as an immediate early gene and is subject to rapid regulation at the transcriptional level in response to inflammation, growth factors, cytokines and tumor promoters. Studies within the past decades have provided evidence that COX-2, but not COX-1, is induced in several types of human cancers, including pancreatic cancer. It has been reported that COX-2 expression can be detected in approximately 75% of pancreatic adenocarcinomas, with 50% of samples characterized as having high expression relative to adjacent normal tissue [26, 40, 64]. Numerous studies have shown that the NSAIDs and COX-2-specific inhibitors, celecoxib and rofecoxib, inhibit cell growth in both COX-2-positive and COX-2-negative pancreatic tumor cell lines in vitro and in vivo [19, 40, 63, 74, 75]. However, suppression of cell growth was significantly greater in the COX-2-expressing cell lines compared with COX-2-negative cell lines. The antiproliferative effect of COX-2 inhibitors is the consequence of their effect on cell-cycle arrest. Studies have indicated that treatment with COX-2 inhibitors results in the accumulation of proteins that are involved in arresting the cell cycle at G_1, including p27, p21/WAF1 and others [63, 75]. The anti-angiogenic property of COX-2 inhibitors may also contribute to their antitumor activity [34, 37]. Leahy and colleagues reported that celecoxib inhibited proliferation and promoted apoptosis of endothelial cells in celecoxib-treated xenograft tumors [34]. A recent study has demonstrated that celecoxib and NSAIDs directly induce apoptosis of endothelial cells in a pancreatic cancer xenograft model, but not through decreased production of angiogenic factors (Raut C. et al., submitted for publication). Thus, the antitumor activity of celecoxib may be attributable, at least in part, to a direct effect on endothelial cells. These data suggest that COX-2 may play an important role in pancreatic tumorigenesis and therefore may be a promising chemotherapeutic target for the treatment of pancreatic cancer.

Lipoxygenase (LOX) pathways metabolize arachidonic acid to produce several potent biological mediators, including leukotriene B_4 (LTB_4), the peptidoleukotrienes and hydroperoxyeicosatetraenoic acids (HETE) [21]. LOX, like COX, may play an important role in pancreatic carcinogenesis [20]. First, expression of LOX is upregulated in pancreatic cancer [18, 29]. Second, LOXs and their products enhance proliferation of pancreatic cancer cells [2, 19, 29, 62]. It was reported that expression of 5-LOX and the LTB_4 receptor in human pancreatic cancer tissues is markedly elevated and functions as an autocrine loop that stimulates proliferation of pancreatic cancer [29]. Third, inhibitors of LOX, such as LY293111, block growth of pancreatic cancer in vitro and in vivo [62].

Another important genetic event that is a potential therapeutic target is the overexpression of interleukin 8 (IL-8). IL-8 is a pleiotropic cytokine that plays an important role in inflammation, proliferation and angiogenesis, which are all significantly relevant to tumor growth and metastasis. IL-8 is overexpressed in about 70% of human pancreatic cancer cell lines [33]. Studies of pancreatic cancer cell lines that have different expression levels of IL-8 have indicated that increased IL-8 expression correlates with fast tumor growth, increased angiogenesis and more frequent metastasis [33, 57]. Moreover, abrogation of IL-8 expression using the antisense approach effectively suppresses tumor growth rate, angiogenesis and metastasis. Furthermore, preclinical studies have demonstrated that EGFR inhibitors suppress tumor growth in xenograft models in part through antiangiogenesis, including inhibition of IL-8 expression. A fully human anti-IL-8 antibody, ABX-IL8, is available and has shown antiangiogenic activity and activity against melanoma and bladder cancer, but there has been no further development for pancreatic cancer [31, 39].

Detailed understanding of these molecular events in pancreatic carcinogenesis has provided a foundation for the development of novel therapies targeting these molecular events. The rest of this review focuses on discussion of novel therapies that are in clinical development (Table 1). There are many other genetic changes, especially in tumor suppressor genes such as p53, p16, SMAD, etc. These genetic changes are important in pancreatic cancer development, but they are not easily "drugable" and are not discussed here.

EGFR as a therapeutic target

Since EGFR plays a central role in controlling the activity of the Ras-Raf-MEK-ERK signaling pathway, great effort has been spent on developing strategies targeting EGFR. Monoclonal antibodies (mAbs) against the extracellular domain have proven a successful

approach to inhibit EGFR. The advent of hybridoma technology in the mid-1970s enabled fast mass production of mAbs. Using such a technique, Mendelsohn and his colleagues generated M225, a mAb that blocks activation of EGFR through specific binding to the extracellular domain of EGFR and competes with the natural ligands [51]. In vitro and in vivo studies have demonstrated that blockade of EGFR results in the arrest of cell-cycle progression and tumor growth inhibition [69]. Cetuximab (IMC-C225) is a chimeric mAb generated from fusion of the variable region of the murine M225 and the human IgG1 constant region. The resultant antibody retains high affinity for and specificity to EGFR and reduces immunogenicity. Preclinical studies have demonstrated that IMC-C225 alone effectively inhibits the proliferation of a variety of EGFR expressing cells in vitro and tumor growth in xenograft models [28].

Subsequent molecular and genetic engineering studies have further improved murine mAbs by introducing human immunoglobulin genes into mice by transgenic technology (XenoMouse) [17, 38, 49]. ABX-EGF is a human antibody against EGFR that is generated using the XenoMouse technique and is in the early phase of clinical development [73]. Another humanized anti-EGFR antibody, EMD 72000, entered clinical development recently [32]. The advantage of using an antibody as a drug is its high affinity and predictable specificity. EGFR undergoes internalization and subsequent degradation upon ligand binding. MAbs bind to EGFR in a way that mimics ligands, causing EGFR degradation, and therefore further enhances their inhibitory effects. Although several mAbs against EGFR are available, only cetuximab has been studied extensively in pancreatic cancer models. Cetuximab, as expected, can effectively block EGFR autophosphorylation in vitro and in vivo. An additive inhibitory effect was observed when cetuximab was combined with either gemcitabine or fluorouracil [13, 47].

Histological study of tumor specimens obtained from mice that received treatment with either cetuximab or cetuximab in combination with gemcitabine revealed that cetuximab induces apoptosis and suppresses proliferation of tumor cells [12]. More interesting was the finding that EGFR-targeted therapies induce apoptosis of endothelial cells, which are not thought to be direct targets of EGFR inhibition. In addition, decreased microvascular densities, as well as production of VEGF and IL-8, were observed in the tumor in response to cetuximab. These data suggested that, besides antiproliferative activity, antiangiogenic activity contributes significantly to the antitumor effects of EGFR inhibitors. A phase II trial of cetuximab in combination with gemcitabine for advanced pancreatic cancer was reported recently [1]. In that trial, 41 patients whose tumors expressed EGFR were treated with cetuximab at 400 mg/m^2 for the first dose and then 250 mg/m^2 weekly plus gemcitabine at standard dose and schedule. A partial response rate of 12.2% and disease control (sum of partial response and stable disease) of 75.6% were observed. The median survival duration was 7.1 months and the 1-year survival rate was 31.7%. This encouraging activity prompted the proposal of a phase III trial comparing gemcitabine to gemcitabine plus cetuximab by the US Southwest Oncology Group.

Despite the fact that protein tyrosine domains share significant amino acid sequence homology and a highly conserved core structure, the ATP-binding site has been proven to be an exciting target for drug design. Many small molecules of tyrosine kinase inhibitors (TKIs) have been synthesized and are in different phases of clinical development, including gefitinib (ZD1839, Iressa), erlotinib (OSI-774, Tarceva) and EKB-569. The potential advantages of TKIs include the potentially easy production of large quantities and the fact that one molecule can potentially inhibit a family of tyrosine kinases that share a similar structure. At present, TKIs have been studied in combination with gemcitabine for advanced pancreatic cancer. The results of a phase I trial of EKB-569 in combination with gemcitabine for advanced pancreatic cancer were presented at the 2003 American Society of Clinical Oncology (ASCO) annual meeting [41]. The dose-limiting toxicities were grade 3 diarrhea and elevation of transaminases. The maximum tolerated dose (MTD) for the combination was EKB-569 25 mg plus gemcitabine 750 mg/m^2. Twenty patients were treated at the MTD, allowing adequate assessment of the antitumor activity of this combination. The National Cancer Institute of Canada is conducting a randomized placebo-controlled phase III study of erlotinib plus gemcitabine versus gemcitabine in patients with advanced pancreatic cancer. The accrual has been completed and the results are eagerly awaited.

Ras-Raf-MEK signaling pathways as therapeutic targets

Ras proteins undergo serial steps of modification. The key step is farnesylation by the enzyme farnesyl-protein transferase (FPTase), which adds the 15-carbon farnesyl isoprenoid to a cysteine residue four amino acids from the COOH-terminus of Ras. Oncogenic forms of Ras, as well as wildtype Ras, require this COOH-terminal prenylation for their biological and/or transforming functions. These findings provided the impetus to develop farnesyl transferase inhibitors (FTIs) as a means of targeting Ras for the treatment of cancer [54]. FTIs inhibit the growth of both normal cells and cancer cells containing either wildtype or mutant forms of *ras*, although cells transformed with oncogenic *H-ras* tend to be much more responsive than cells harboring wildtype *ras* or *K-ras*, or *N-ras* [24]. Several FTIs are in clinical development, including R115777 (Zarnestra) [16, 36, 66], SCH66336 (Lonafarnib, Sarasar) [61] and BMS-214662.

R115777, an oral agent, is a selective nonpeptidomimetic inhibitor of FPTase. Preclinical studies demonstrated that R115777 competitively inhibits farnesylation of lamin B and K-RasB peptides at nanomolar concentrations while inhibiting proliferation

of pancreatic cancer cell lines and xenografts. However, the results of phase II and III clinical studies have been disappointing. A phase II trial of R115777 as initial therapy for patients with advanced pancreatic cancer in which 20 patients were enrolled yielded no objective responses. Median survival time was 19.7 weeks and the estimated 6-month survival rate was 25%. In this study, inhibition of FPTase activity in peripheral blood mononuclear cells was measured; a partial inhibition of FPTase activity was observed despite lack of clinical activity [16]. In a double-blind phase III trial, Van Cutsem and colleagues [66] tested R115777 in combination with gemcitabine against gemcitabine plus placebo. The median overall survival times were 193 and 182 days for patients in the R115777 and placebo arms, respectively. There were no differences in the rate of progression-free survival, 6-month survival, or 1-year survival.

The disappointing clinical results raise the question of whether Ras is a valid target for pancreatic cancer. Ras is a key member of the signaling pathways that regulate critical cellular functions, and *ras* mutation has the ability to transform normal cells into neoplastic phenotype and occurs frequently in human cancers. Therefore, Ras appears to be an important target for drug development. However, in pancreatic cancer, *ras* mutation occurs early, indicating its role in the early development of pancreatic cancer. In contrast, its role in established pancreatic cancer is not clear. Moreover, more than 90% of pancreatic cancers bearing *K-ras* have been demonstrated to be less sensitive to FTIs. In addition, Ras isoforms and oncogenic Ras can be geranylgeranylated (by geranylgeranyl transferase I), an alternative lipidation that can substitute for farnesylation. Finally, advanced pancreatic cancer, like many solid tumors, gains multiple survival advantages that may compensate for ras inhibition.

Raf is a signaling protein downstream of Ras. Ras activates the Raf-MEK-ERK pathway by first localizing Raf to the plasma membrane, where Raf initiates a mitogenic kinase cascade that leads to cell proliferation. Studies with dominant-negative mutants and antisense molecules suggest that inhibition of Raf kinase is an important target for cancer therapy. Bay 43-9006 is a small-molecule inhibitor that was designed specifically to target Raf kinase. Preclinical studies indicate that Bay 43-9006 is a potent inhibitor of Raf kinase in vitro and in vivo, with significant dose-dependent antitumor activity. Pancreatic cancer should be a good tumor type for the clinical investigation of Bay 43-9006, since the Ras-Raf-MEK-ERK pathway is constitutively activated. A phase I study of Bay 43-9006 in combination with gemcitabine has determined that the recommended phase II dose is BAY 43-9006 400 mg twice daily and gemcitabine 1000 mg/m^2 weekly $\times$7, followed by 1 week rest, then weekly $\times$3 every 4 weeks [58]. The efficacy of this combination in pancreatic cancer is being evaluated at the recommended phase II dose. An ongoing phase II study of Bay 43-9006 for patients with solid tumors, including colorectal cancer, renal cell carcinoma, malignant melanoma, pancreatic cancer and other tumor types, will also provide an initial assessment of the antitumor efficacy of Bay 43-9006 as a single agent.

CI-1040 is an oral, highly selective, small-molecule inhibitor of the dual specificity kinase MEK1/2. Preclinical antitumor activity has been demonstrated in a pancreatic cancer xenograft. A phase II study of CI-1040 was conducted for patients with advanced small-cell lung cancer, breast cancer, colon cancer, and pancreatic cancer [68]. The study employed a two-stage design: in each tumor type, either one objective response (CR/PR) or four clinical benefit responses (CBR = CR/PR/SD) in stage 1 ($n = 13$) would trigger stage 2 ($n = 30$) enrollment, resulting in a total of 43 patients for each of the four tumor types. Unfortunately, the study did not advance to stage 2 due to limited antitumor activity.

Antiapoptotic signaling pathways as targets

Two potential antiapoptotic signal transduction pathways have been linked to chemoresistance of pancreatic carcinoma cell lines: the PI3 K/Akt pathway and the NF-κB pathway. Besides the growth-promoting potential of the PI3 K/Akt pathway, its antiapoptotic properties are closely linked to the resistance of cancer cells to a broad spectrum of apoptotic stimuli. Therefore, the PI3 K/Akt pathway is an important target for drug development, but no specific agents have entered clinical development yet. Recent studies have indicated that Akt is a client protein of heat shock protein 90 (Hsp90), which can be inhibited by the benzoquinone ansamycin antibiotics (BA), herbimycin, geldanamycin and 17-allylamino-17-demethoxygeldanamycin (17-AAG). It was reported that occupancy of the Hsp90 pocket by ansamycins results in a reduction in Akt half-life and protein expression secondary to Akt ubiquitination and proteasomal degradation [9]. 17-AAG has undergone phase I clinical investigations [8]. It would be interesting to test 17-AAG as monotherapy or in combination for pancreatic cancer.

mTOR, a downstream molecule of Akt, is located predominantly in the nuclear fraction of both neoplastic and normal cells [77]. mTOR activation triggers resting cells to increase the translation of a subset of mRNAs whose proteins are required for cell-cycle progression from G_1 to S phase. CCI-779, an ester of the macrocyclic immunosuppressive agent sirolimus, reacts with the ubiquitous intracellular FK506-binding protein 12 (FKBP12) [7, 26]. The CCI-779/FKBP12 complex is a potent inhibitor of the highly conserved kinase mTOR. Inhibition of mTOR leads to suppression of several downstream signaling effectors, including the ribosomal subunit p70^{S6} kinase and the eukaryotic initiation factor 4 binding protein 1 (4E-BP1) [11]. The extent of phosphorylation of these two downstream proteins (p70^{S6} kinase and 4E-BP1) may therefore serve as indicators of CCI-779 biologic activity in vivo. Clinical trials have

shown that CCI-779 is well tolerated at a variety of doses and schedules. Furthermore, antitumor activity has been observed in breast cancer and renal cell carcinoma [15, 30]. Pancreatic cancer is hypothesized to be sensitive to CCI-779 since PTEN expression is either undetectable or significantly decreased. A phase II trial of CCI-779 for advanced pancreatic cancer is being planned.

NF-κB is an important target for therapeutic intervention because of its role in promoting cancer cell growth and developing resistance to apoptosis. However, no NF-κB-specific agents are available for clinical development. The activity of NF-κB is regulated by IκBα, which is degraded by the ubiquitin-proteasome pathway. Bortezomib (PS-341, VELCADE) is a dipeptide boronate antagonist of the proteasome and blocks IκBα degradation and subsequent NF-κB activation. In vitro and in vivo studies have demonstrated that bortezomib exhibits a wide range of activity, from extremely sensitive to resistant, against pancreatic cancers. However, these effects do not correlate with differential inhibition of NF-κB activation, indicating that inhibition of NF-κB per se is not always sufficient to induce apoptosis [44]. Ryan and coworkers [50] combined bortezomib (administered twice weekly for 2 weeks) with gemcitabine (given on days 1 and 8) in a phase I clinical study of advanced solid tumors. The combination of gemcitabine at a dose of 1000 mg/m^2 and bortezomib at a dose of 1.0 mg/m^2 showed good tolerability. However, the efficacy of bortezomib for the treatment of pancreatic cancer remains to be elucidated.

Curcumin (diferuloylmethane), a polyphenol derived from the plant *Curcuma longa*, has demonstrated activity against a wide range of tumor cells in vitro and in vivo through inhibition of NF-κB and a variety of other molecules involved in cell growth [3]. Despite its diverse effect against many molecules and promising antitumor activity in animal studies, the clinical development of curcumin has lagged behind. A phase I study of curcumin revealed that curcumin extract was well tolerated and dose-limiting toxicity was not reached, but bioavailability was low [56].

COX and LOX as targets

Both COX and LOX are implicated in pancreatic carcinogenesis, although the role of LOX has been less defined than the role of COX. The NSAIDs have long demonstrated antitumor activity. The development of COX-2-specific inhibitors (for example, celecoxib and rofecoxib), drugs that maintain their antiinflammatory properties while preserving the biosynthesis of protective prostaglandins, further raised interest in targeting COX-2 in cancer therapy. A phase I trial of gemcitabine in combination with celecoxib was conducted to study potential drug interactions [70]. The results showed that there was no alteration of gemcitabine conversion to its active metabolite with the addition of celecoxib. The study determined that the doses recommended for further study were gemcitabine 650 mg/m^2 over a 65-min infusion for three consecutive weeks with 1 week rest and celecoxib 400 mg twice daily. The preliminary results of a phase II trial of gemcitabine plus celecoxib were presented at the ASCO 2003 meeting [59]. The study enrolled 20 patients with advanced pancreatic cancer; three patients had partial responses and four had stable disease.

LY293111 is a biphenyl substituted diaryl ether carboxylic acid originally discovered as an LTB_4 receptor antagonist. Phase I studies of LY293111 as a single agent or in combination with gemcitabine showed that LY293111 was well tolerated, with diarrhea as the most frequently reported adverse event [52, 60]. There was no interaction between LY293111 and gemcitabine, and gemcitabine could be administered at full dose when combined with LY293111. A randomized, double-blind phase II trial of gemcitabine plus LY293111 versus placebo for patients with advanced pancreatic cancer has completed accrual and the results are eagerly awaited.

Conclusion

The advance of molecular biology has led to the elucidation of molecular events important for pancreatic carcinogenesis and provided a foundation for the development of novel therapies. Several classes of agents, such as, TKIs, FTIs, and COX-2 and LOX inhibitors, have shown promising activity in the preclinical setting, but the clinical data so far are less impressive. Cetuximab, a monoclonal antibody against EGFR, in combination with gemcitabine has shown promising antitumor activity for advanced pancreatic cancer, and a further phase III randomized trial of this combination versus gemcitabine is being planned. Meanwhile a phase III trial of gemcitabine plus erlotinib versus placebo has completed accrual. At the present time, gemcitabine remains the standard chemotherapy for advanced pancreatic cancer.

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