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REVIEW

Anti-Angiogenesis Therapy in Pancreatic Carcinoma

Muhammad Wasif Saif

Yale University School of Medicine. New Haven, CT, USA

Summary

Pancreatic adenocarcinoma is a leading cause of cancer death in the United States and represents a challenging chemotherapeutic problem. The treatment of advanced pancreatic cancer with gemcitabine has only modest activity with a small survival benefit, and toxicity continues to be a major obstacle. New therapeutic strategies that notably lack cross resistance with established treatment regimens are much needed in pancreatic cancer. One such approach is the pharmacological control of angiogenesis that represents a novel approach to the management of pancreas cancer, since the pathological development of vascular supply is a critical step for tumor growth and may affect its prognosis. Since pancreatic carcinoma show strong tumor neoangio-genesis, overexpression of vascular endothelial growth factor (VEGF), a key mediator of angiogenesis, in pancreatic cancer and consequently are highly vascularized, the role of anti-angiogenic therapies is under exploration at present. Hence, this review covers the summary of the development of anti-angiogenesis as anti-antitumor therapy in pancreatic carcinoma, including matrix-metalloproteinase inhibitors (MMPIs), such as marimastat and BAY 12-9566, anti-VEGF agent, bevacizumab (Avastin, Genentech, South San Francisco, CA, USA), celecoxib (a cyclooxygenase-2 inhibitor), thalidomide and others. Role of markers of angiogenesis in predicting response to therapy is also discussed.

Introduction

Exocrine pancreatic carcinoma is now the fifth leading cause of cancer in the United States, Japan and Europe, with an overall 5-year survival rate of less than 5% [1]. One of the major causes of death is peritoneal dissemination and liver metastasis [2]. Akin to other solid tumors, pancreatic carcinoma also depends on the development of an adequate blood supply through angiogenesis for growth at both primary and secondary sites. The pivotal role of angiogenesis in primary tumor growth and metastasis has been recognized many years before. It is also thought that new blood vessels in tumor are highly permeable and provide a route for cancer cells to enter the circulation [3].

Inhibition of neo-angiogenesis is a new and attractive target for tumor therapy, since it theoretically offers the hope of long-term control of tumor progression. Antiangiogenic therapy offers a number of potential benefits including lack of resistance to some agents, synergistic interaction to other modalities, lack of significant toxicity compared with conventional agents, and a potent antitumor effect [4, 5, 6]. However, the anti-neoplastic actions and side effects of angiogenesis inhibitors and cytotoxic agents were clearly different [4]. Administration of angiogenesis inhibitors might keep the tumor and its metastases dormant (rather than killing it), and co-administration of cytotoxic drugs might kill it [5, 6]. Many studies have been conducted to evaluate the therapeutic effects

of angiogenic inhibitors with in combination with cytotoxic agents. Therefore, angio-cytotoxic therapy has been gradually accepted worldwide in recent years.

Recently, a number of new drugs have been developed for treating patients with pancreatic carcinoma. Early studies with gemcitabine suggested a modest antitumor activity with significant improvement in disease-related symptoms [7]. Therefore, gemcitabine has been generally considered to be the first-line therapy for pancreatic cancer, and is now widely used. The anti-neoplastic actions of angiogenic inhibitors and cytotoxic agents are clearly different. Treatment with antiangio-genic agents could interact in a positive way with a variety of anti-cancer therapies, and the anti-metastatic and anti-tumor effects of combination therapy were stronger than those of angiogenic inhibitors alone and cytotoxic agents alone. In the early era of anti-angiogenic therapy, one focus of research in pancreatic cancer was the use of matrix-metalloproteinase inhibitors (MMPIs), such as marimastat and BAY 12-9566, as an adjunct to conventional chemotherapy. Most recently, agents targeting against vascular endothelial growth factor (VEGF) have been the focus of research.

The author reviews data on these agents:

I - matrix metalloproteinase inhibitors;

II - VEGF-signaling pathway in pancreatic cancer;

III - cyclooxygenase-2 and celecoxib in pancreatic cancer;

IV - others, including thalidomide, mam-malian target of rapamycin (mTOR) inhibitors and epidermal growth factor receptor (EGFR) inhibitors.

I - Matrix Metalloproteinase Inhibitors

Matrix metalloproteinases (MMPs) are a family of proteolytic enzymes that are responsible for the breakdown of connective tissue proteins. These enzymes play an important role in normal processes of growth, differentiation and repair. The activity of MMPs is tightly regulated at several levels including gene expression and inhibition by tissue inhibitors known as tissue inhibitors of metalloproteinases (MMPIs). There is now considerable evidence however, that aberrant MMP expression contributes to the invasive growth and spread of a variety of solid malignancies, including gastrointestinal tumors [8]. MMP-2 (gelatinase A), MMP-9 (gelatinase B) [9], MMP-7 (matrilysin) [10] and MMP-14 (MT1-MMP) [11] are over-expressed in human gastric cancer. It is therefore feasible that specific MMP inhibitors might restore the normal balance of proteolytic activity and thereby prevent further tumor growth and metastasis.

Marimastat (BB-2516) is a broad spectrum, low molecular weight MMP inhibitor with inhibitory concentrations 50% (IC_{50}s) against purified enzymes in the low nanomolar range [12]. The closely related inhibitor batimastat (BB-94) has been shown to inhibit tumor growth and spread in a range of cancer models [13, 14] and marimastat has been shown to inhibit tumor growth in a xenograft model of human gastric cancer [15]. MMP inhibitors have not been shown to cause tumor regression in cancer model studies and it was therefore proposed that these agents be tested in the clinic as oncostatic treatments.

Based on these preclinical data, a randomized study in pancreatic cancer compared marimastat in combination with gemcitabine to gemcitabine alone [16]. Two hundred and thirty-nine patients with unresectable pancreatic cancer were randomized to receive gemcitabine (1,000 mg/m^2) in combination with either marimastat 10 mg *bid* or placebo. There was no significant difference in survival between gemcitabine and marimastat and gemcitabine and placebo (P=0.95, log-rank test). Median survival times were 165.5 and 164 days and 1-year survival was 18% and 17%, respectively. There were no significant differences in overall response rates (11% and 16%, respectively), progression-free survival (P=0.68, log-rank test) or time to treatment failure (P=0.70, log-rank test) between the treatment arms. Grade 3 or 4 musculoskeletal toxicities were reported in only 4% of the marimastat treated

patients, although 59% of marimastat treated patients reported some musculoskeletal events. The results of this study provided no evidence to support a combination of marimastat with gemcitabine in patients with advanced pancreatic cancer [16]. The major criticism on this study was about the dose of marimastat selected, that might have been sub-optimal (10 mg *bid*).

Another study randomized 414 patients with unresectable pancreatic cancer to receive marimastat 5, 10, or 25 mg *bid* or gemcitabine 1,000 mg/m^2 [17]. This study also did not show any significant difference in survival between 5, 10, or 25 mg of marimastat and gemcitabine (P=0.19). Median survival times were 111, 105, 125, and 167 days, respectively, and 1-year survival rates were 14%, 14%, 20%, and 19%, respectively. There was a significant difference in survival rates between patients treated with gemcitabine and marimastat 5 and 10 mg (P<0.003). The results of this study provided evidence of a dose response for marimastat in patients with advanced pancreatic cancer. The 1-year survival rate for patients receiving marimastat 25 mg was similar to that of patients receiving gemcitabine [17].

The prior study [16] was designed and commenced prior to analysis of the results of the comparative study between gemcitabine and marimastat [17]. In this study there was a dose dependent effect of marimastat with the dose of 25 mg *bid* comparing favorably with gemcitabine in pancreatic cancer [17]. In the prior study marimastat dosing was 10 mg *bid* [16] and could be considered sub-optimal, however even in sub-group analysis there was very little indication of synergy between marimastat and gemcitabine. In conclusion the combination of gemcitabine and a MMPI can be safely delivered to patients with pancreatic cancer but there appears little evidence to support further study of this combination.

BAY 12-9566

BAY 12-9566 is a specific inhibitor of MMP-2, MMP-3, MMP-9, and MMP-13 with Ki of 11, 134, 301, and 1,470 nmol/L, respectively [18]. It also has antiangiogenic properties on the basis of its ability to inhibit degradation and invasion of the extracellular matrix by endothelial cells, a process necessary for tumor neovascularization [18]. Phase I studies of BAY 12-9566 have demonstrated that doses up to 1,600 mg/day given continuously were well tolerated and gave serum concentrations greater than 2 to 4 logs higher than the Ki for MMP-2, MMP-3, and MMP-9. Absorption was saturable at the higher doses [19, 20, 21]. Patients on phase I studies have shown stable diseases, and in few sustaining greater than 1 year [19, 20, 21].

Therefore, a randomized Phase III study using a dose of 800 mg *bid* was chosen from three phase I studies [19, 20, 21], randomized chemo-naïve patients with advanced pancreatic adenocarcinoma to receive BAY 12-9566 800 mg orally *bid* continuously or gemcitabine 1,000 mg/m^2 administered intravenously on days 1, 8, 15, 22, 29, 36, and 43 for the first 8 weeks, and then days 1, 8, and 15 of each subsequent 28-day cycle [22]. Two-hundred and 77 patients were enrolled onto the study: 138 in the BAY 12-9566 arm and 139 in the gemcitabine arm. The median survival for the BAY 12-9566 arm and the gemcitabine arm was 3.74 months and 6.59 months, respectively (P<0.001; stratified log-rank test). The median progression-free survival for the BAY 12-9566 and gemcitabine arms was 1.68 and 3.5 months, respectively (P<0.001). Quality of life analysis also favored gemcitabine. The results of the study concluded that gemcitabine is significantly superior to BAY 12-9566 in advanced pancreatic cancer [22].

"When randomized trials failed to show significant efficacy of MMPIs in this tumor entity, anti-angiogenic approaches shifted toward inhibition of the VEGF-signaling pathway".

II - VEGF-Signaling Pathway in Pancreatic Cancer

The VEGF-system is an attractive therapeutic target in another gastrointestinal malignancy, pancreatic cancer [23, 24, 25, 26].

- Both VEGF and VEGF-receptors are overexpressed in pancreatic cancer;
- VEGF promotes pancreatic cancer growth via a paracrine and autocrine mechanism;
- high VEGF - expression correlates with poor prognosis in patients and animal models.

Seo Y *et al.* [24] investigated VEGF expression and microvessel density (MVD) in ductal pancreatic adenocarcinoma and examined the correlations among VEGF expression, clinicopathologic factors, and clinical outcome, especially the liver metastasis. One-hundred and 42 paraffin embedded tumor specimens of surgically resected pancreas carcinoma were immunohistochemically stained for VEGF and MVD. One-hundred and 32 out of 142 (93%) ductal pancreatic adenocarcinomas were positive for VEGF protein by immunohistochemistry. A significant correlation was observed between VEGF positivity and MVD ($P<0.0001$). Multivariate logistic regression analysis indicated a significant association between high VEGF expression and liver metastasis ($P=0.010$) but no other factors, such as age, tumor size, histologic type, lymph node metastasis, venous invasion, neural invasion, peritoneal metastasis, or local recurrence. Patients with tumors that showed moderate or high VEGF expression had significantly shorter survival than patients with low VEGF expression or none at all in their tumors ($P<0.05$). These results indicated that VEGF expression is closely correlated with MVD and seems to be an important predictor for both liver metastasis and poor prognosis in ductal pancreatic adenocarcinoma [24].

Another study by Niedergethmann M *et al.* [25] analyzed the correlation between VEGF expression and MVD with early recurrence and poor prognosis after curative resection, since only curative resection for pancreatic adenocarcinoma is related to a favorable prognosis, but the overall survival after surgery still remains poor, and early recurrence is frequently observed. Seventy patients with ductal adenocarcinoma of the pancreas were studied after curative resection with a follow-up of at least 2 years. The VEGF immunoreactivity was 88.6%, and positive mRNA signals were obtained in the cytoplasm of carcinoma and endothelial cells in 81.4%. Furthermore, we observed tumor-associated macrophages close to infiltrating carcinoma cells. All endothelial cells showed positive immunoreactivity to the anti-CD34 antibody, and a median distribution of 85 vessels/200 field was observed. A significant correlation ($P<0.05$) was found between the MVD and the International Union Against Cancer (UICC) stage. Statistical analysis showed a significant correlation between VEGF expression and the height of MVD ($P<0.05$). Kaplan-Meier analyses revealed that VEGF expression and MVD had a statistically significant correlation with survival after curative resection ($P<0.05$). Furthermore, multivariate analysis indicated that VEGF expression is an independent prognostic marker for cancer recurrence within 8 months after curative surgery ($P=0.003$). In summary, the VEGF expression and the height of MVD in pancreatic adenocarcinoma are closely correlated, and both - rather than UICC stage and TNM classification (tumor size and nodal involvement) - are markers of prognostic relevance after curative resection. Furthermore, VEGF is a predictor of early recurrence after curative resection. The current study indicates that VEGF may promote the distribution of metastases, leading to early cancer recurrence and poor outcome [25].

Bevacizumab

Bevacizumab (Avastin, Genentech, South San Francisco, CA, USA) is a recombinant humanized anti-VEGF monoclonal antibody. In a phase III randomized trial in patients with advanced colorectal cancer, the addition of bevacizumab to standard chemotherapy resulted in a significant improvement in response, survival, and progression-free survival [27]. Inhibitors of VEGF suppress the growth of pancreatic cancer in preclinical models. In addition to inhibiting neovascularization and lymphangiogenesis,

bevacizumab has shown to decrease the interstitial pressure in the tumor, increase the delivery of chemotherapy, and by direct effects on tumor (by decreasing chemotaxis) mediated by the neuropilin-1 receptor [28, 29, 30].

Bevacizumab with Gemcitabine

Based on these findings a phase II trial in 52 patients was initiated combining the chemotherapy standard gemcitabine with bevacizumab as first-line treatment in metastatic (stage IV) pancreatic cancer [31]. In view of bleeding concerns patients that showed obvious involvement of major intra-abdominal blood vessels were excluded from the trial. Patients with previously untreated advanced pancreatic cancer received gemcitabine 1,000 mg/m^2 intravenously over 30 minutes on days 1, 8, and 15 every 28 days. Bevacizumab, 10 mg/kg, was administered after gemcitabine on days 1 and 15. Tumor measurements were assessed every two cycles. Plasma VEGF levels were obtained pretreatment.

Fifty-two patients with metastatic disease (83% had liver metastases) were enrolled on to this study. Eleven patients (21%) had confirmed partial responses, and 24 (46%) had stable disease. The 6-month survival rate was 77%. Median survival was 8.8 months; median progression-free survival was 5.4 months. Pretreatment plasma VEGF levels did not correlate with outcome. Grade 3 and 4 toxicities included hypertension in 19% of the patients, thrombosis in 13%, visceral perforation in 8%, and bleeding in 2%. Pretreatment plasma VEGF levels did not correlate with outcome.

The results of this study were comparable to prior studies of gemcitabine doublets with cytotoxics, such as gemcitabine plus cisplatin or oxaliplatin [32, 33], and a potentially lethal 8% perforation rate justifies a more differentiated assessment of toxicity. In the pivotal phase III trial of bevacizumab in colorectal cancer, Hurwitz *et al*. observed a 1.5% rate of perforation in the treatment group and none in the placebo control [27]. The 8% rate of visceral perforation in this study is significantly higher than that in the colorectal study. Among these patients, one patient developed a perforation after a colon stent placement and another after severe vomiting from a duodenal obstruction. It is suggestive that it would be appropriate to hold additional bevacizumab in these situations.

In addition, other toxicities of bevacizumab includes thromboembolism and gastro-intestinal bleeding. Patients who had venous thromboses that required anticoagulation were excluded from Kindler's study. Grade 3 or 4 thrombosis occurred in 13% of patients. It is quite possible that a selection bias by excluding these patients, was introduced in the study as cancer patients who have experienced thromboembolism may have a worse prognosis [34].

Gastrointestinal bleeding is another potentially lethal complication of pancreatic cancer especially when the pancreatic tumor invades the duodenum, as well as a toxicity of bevacizumab. Fatal bleeding occurred in a patient, whose tumor eroded into his duodenum while on bevacizumab, making it impossible to ascertain whether bevacizumab exacerbated the ultimately fatal bleeding in this patient. However, it is recommended to not to administer bevacizumab in a patient, who has tumor invasion of an adjacent organ, especially duodenum.

Because there have been no dose-finding trials of bevacizumab in pancreatic cancer, the optimal dose of this agent for this disease remains unclear. A 10 mg/kg dose was used in this trial [31]. In contrary, a randomized phase II trial in colorectal cancer suggested that a dose of 5 mg/kg every 14 days was more effective than 10 mg/kg [35] and a randomized phase III trial in similar patient population confirmed the efficacy of the 5 mg/kg dose [27]. Another phase III study in colorectal cancer that used a 10 mg/kg dose in combination with oxaliplatin-based regimen revealed significant activity and tolerable toxicity [36]. In a randomized phase II trial in non-small-cell lung cancer, a dose of 15 mg/kg every 21 days was found to be more active than the 7.5 mg dose, associated with

fewer episodes of significant bleeding at the higher dose [37]. The efficacy and safety of the 15 mg/kg bevacizumab dose in lung cancer has been confirmed in a randomized phase III trial [38]. However, it is reasonable to speculate whether fewer toxicities or alternate efficacy might have been observed had Kindler *et al*. [31] arbitrarily chosen a lower dose than the 10 mg/kg used in this trial, this cannot be definitively ascertained without additional study. A randomized phase III trial of gemcitabine plus bevacizumab versus gemcitabine plus placebo is ongoing in the Cancer and Leukemia Group B (CALGB).

Bevacizumab with Radiation

Crane C *et al*. [39] has investigated bevacizumab in a phase I study as component of a multi-modality approach in combination with capecitabine and radiation for locally advanced pancreatic cancer. Forty-five patients were included in the dose-finding trial for bevacizumab concomitant to 50.4 Gy radiation and capecitabine (final dose: 825 mg/m^2 *bid* continuously Monday-Friday). The addition of bevacizumab did not significantly increase the acute toxicity of the chemoradiation regimen. At the 5 mg/kg level for bevacizumab 6 of 12 patients showed a partial response, overall RR for the whole study population was 19%. Radiation Therapy Oncology Group (RTOG) is currently running a phase II study to further evaluate this tri-modality therapy in patients with locally advanced pancreatic cancer. This study excludes patients with duodenal involvement.

III - Cyclooxygenase-2 and Celecoxib in Pancreatic Cancer

Overexpression of cyclooxygenase-2 (COX-2) is detected in 75% of resected pancreatic cancer and correlates with aggressive tumor biology [40]. COX-2 promotes tumor growth by up-regulating angiogenesis and invasiveness, and inhibiting apoptosis [41]. Celecoxib, a COX-2 specific inhibitor, has demonstrated anti-tumor activity against a variety of human cancers in animal models, including pancreatic cancer xenografts [42].
A phase II study evaluated the role of adding celecoxib to gemcitabine in patients with advanced pancreatic cancer [43]. Twenty-eight patients with pancreatic cancer received gemcitabine (650 mg/m^2 over a 65 min infusion at days 1, 8, and 15 every 4 weeks) and celecoxib (400 mg *per os bid*) continuously. Based on the data presented at the annual meeting of the American Society of Clinical Oncology (ASCO), the Kaplan-Meier median survival duration for 20 patients was 6.2 months, and 3-months survival rate was 72%. Grade 3 or 4 thrombocytopenia and neutropenia developed in two patients each. Clinically relevant treatment related grade 3 or 4 non-hematological toxicities include nausea or vomiting, supraventricular arrhythmia, dyspnea, pleural effusion, and hyponatremia. Grade 3 or 4 gastrointestinal bleeding occurred in one patient. In a pre-clinical study using athymic mice injected with BxPC-3 cells, we also evaluated the efficacy of adding celecoxib to capecitabine and radiotherapy. In irradiated xenografts, capecitabine and external radiation therapy showed synergistic antitumor efficacy ($P=0.008$), which was further improved with the addition of celecoxib ($P<0.001$) [44]. Further evaluation of this agent in pancreatic cancer is halted by the cardiac toxicity affiliated with the agent [45].

IV - Other Anti-Angiogenic Agents

Thalidomide

Thalidomide was first introduced in the 1950s as a sedative but was quickly removed from the market after it was linked to cases of severe birth defects. However, it has since made a remarkable comeback for the U.S. Food and Drug Administration (approved use in the treatment of erythema nodosum leprosum). Further, it has shown its effectiveness in many malignancies, in particular multiple myeloma, renal cell

carcinoma, prostate cancer and hepatocellular cancer [46]. Although the exact mechanism of anti-angiogenesis caused by thalidomide is not know, it was found in a study by Vacca *et al*. that thalidomide markedly down-regulates the genes in a dose-dependent fashion in active multiple myeloma endothelial cells and Kaposi sarcoma cell line [47]. Secretion of vascular VEGF, basic fibroblast growth factor (bFGF) and hepatocyte growth factor also diminishes according to the dose in culture conditioned media of active these cell lines.

Based on its anti-angiogenic activity, a Phase I/II study evaluated the safety and efficacy of the addition of thalidomide to celecoxib and gemcitabine [48]. Twelve patients with advanced pancreatic cancer received gemcitabine (1,000 mg/m^2) on days 1 and 8 every 21 days, celecoxib 400 mg *per os bid* and thalidomide 200 mg *per os* one at night time and titrating to 300 mg *per os* one at night time if tolerated after one week. Celecoxib and thalidomide were started 2 weeks prior to the first dose of gemcitabine and continued throughout the treatment. Among 12 patients, 5 achieved a partial biochemical response and no radiographic responses were noted. Mean survival of patients from time of diagnosis was 10 months. Toxicities included 3 patients with a skin rash and 1 patient with pulmonary embolism.

Moreover, thalidomide, which is an inhibitor of tumor necrosis factor alpha (TNF-alpha) synthesis [49]. Because proinflammatory cytokines, especially TNF-alpha, play a prominent role in the pathogenesis of cancer cachexia., thalidomide represent a novel and rational approach to the treatment of cancer cachexia. To assess the safety and efficacy of thalidomide in attenuating weight loss in patients with cachexia secondary to advanced pancreatic cancer, 50 patients with advanced pancreatic cancer who had lost at least 10% of their body weight were randomised to receive thalidomide 200 mg once a day *per os* or placebo for 24 weeks in a single centre, double blind, randomized controlled trial [50]. Thirty-three patients (16 control, 17 thalidomide) were evaluated at 4 weeks, and 20 patients (8 control, 12 thalidomide) at 8 weeks. At 4 weeks, patients who received thalidomide had gained on average 0.37 kg in weight and 1.0 cm^3 in arm muscle mass (AMA) compared with a loss of 2.21 kg (absolute difference: -2.6 kg; 95% confidence interval (CI): -4.3 to -0.8 kg; P=0.005) and 4.46 cm^3 (absolute difference: -5.6 cm^3; 95% CI: -8.9 to -2.2 cm^3; P=0.002) in the placebo group. At 8 weeks, patients in the thalidomide group had lost 0.06 kg in weight and 0.5 cm^3 in AMA compared with a loss of 3.62 kg (absolute difference: -3.57 kg; 95% CI: -6.8 to -0.3 kg; P=0.034) and 8.4 cm^3 (absolute difference: -7.9 cm^3; 95% CI: -14.0 to -1.8 cm^3; P=0.014) in the placebo group. Improvement in physical functioning correlated positively with weight gain (r=0.56, P=0.001). This study revealed that thalidomide was effective at attenuating loss of weight and lean body mass in patients with cachexia due to advanced pancreatic cancer.

Mammalian Target of Rapamycin (mTOR) Inhibitors

The mTOR is a serine/threonine kinase that has been increasingly recognized as key to the regulation of cell growth and proliferation. mTOR either directly or indirectly regulates translation initiation, actin organization, tRNA synthesis, ribosome biogenesis, and many other key cell maintenance functions, including protein degradation and transcription functions. Inhibition of mTOR blocks traverse of the cell cycle from the G_1 to S phase [51]. Preclinical data show inhibition of tumor growth in a number of cell lines and xenograft models. Clinical trials are ongoing, including pancreatic cancer.

Epidermal Growth Factor Receptor (EGFR) Inhibitors

EGFR is a cell surface molecule that mediates signal transduction from the cell surface to cytoplasm. Elevated expression of EGFR or its ligand correlates with worse prognosis in a variety of human cancers, including pancreatic cancer [52]. Therefore, blockade of

EGFR activity would provide a novel strategy for the treatment of cancer. Two classes of EGFR inhibitors, monoclonal antibodies and tyrosine kinase inhibitors, have been described. In addition to EGFR inhibition, EGFR inhibitors also inhibit VEGF. A phase II study treated 41 EGFR-positive patients with pancreatic cancer with gemcitabine plus cetuximab [53]. Five patients (12.2%) achieved a partial response, and 26 (63.4%) had stable disease. The median time to disease progression was 3.8 months, and the median overall survival duration was 7.1 months. The most frequently reported grade 3 or 4 adverse events were neutropenia (39.0%), asthenia (22.0%), abdominal pain (22.0%), and thrombocytopenia (17.1%). Currently, a Phase III study (Southwest Oncology Group: SWOG) is evaluating the role of cetuximab in combination with gemcitabine in patients with advanced pancreatic cancer.

A recent phase III trial of the combination of gemcitabine with erlotinib was associated with a significant prolongation of survival, which led to its approval by FDA [54]

The results of two randomized trials looking at the combination of bevacizumab and cetuximab are anxiously awaited. Potential combinations with other biologic agents are being investigated. Also the combination of different target agents, such as combining the EGFR blockers - such as erlotinib and the cyclooxygenase-2 inhibitor (celecoxib) - needs to be investigated in clinical trials. Similarly, the combination of cetuximab with bevacizumab warrants investigation, especially in patients where chemotherapy is either not an option or not desired.

Conclusion

Pancreatic cancer is a major cause of morbidity and mortality worldwide. When curative surgical resection is not an option, pancreatic carcinoma tends to respond very poorly to chemotherapy and carry a dismal prognosis. There is, therefore, an urgent need for novel treatment strategies for this deadly disease. Great strides have been made in colon cancer treatment with the recent introduction of several novel agents, including capecitabine, irinotecan, oxaliplatin, and most recently anti-angiogenesis therapy in the form of bevacizumab in combination regimens. VEGF plays a key role in the growth and metastasis of many tumors including pancreatic cancer. A Phase II study has evaluated the combination of bevacizumab and gemcitabine in patients with advanced pancreatic cancer and the Cancer and Leukemia Group B is currently accruing to a 590-patient, double-blind, placebo-controlled, randomized phase IV trial (CALGB 80303) that compares gemcitabine plus bevacizumab to gemcitabine plus placebo using the doses and schedule used in this phase II study. Further research into their optimal use either alone or in combination regimens should be a priority.

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Abbreviations AMA: arm muscle mass; ASCO: American Society of Clinical Oncology; bFGF: basic fibroblast growth factor; CALGB: Cancer and Leukemia Group B; COX-2: cyclooxygenase-2; EGFR: epidermal growth factor receptor; MMPI: inhibitor of metalloproteinases; mTOR: mammalian target of rapamycin; MVD: microvessel density; RTOG: Radiation Therapy Oncology Group; SWOG: Southwest Oncology Group; UICC: International Union Against Cancer

Correspondence
Muhammad Wasif Saif
Section of Medical Oncology
Yale University School of Medicine
333 Cedar Street; FMP: 116
New Haven, CT 06520
USA
Phone: +1-203.737.1569

Fax: +1-203.785.3788
E-mail: wasif.saif@yale.edu

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