



Pierre-Auguste Renoir. *Oarsman at Chatou*, 1879.

Molecular-targeted agents are being tested alone and in combination in patients with pancreatic cancer.

Molecular-Targeted Agents in Pancreatic Cancer

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Background: *Despite the acceptance of gemcitabine as the standard first-line agent for the treatment of advanced pancreatic cancer as well as the improved response rates seen with gemcitabine combinations, novel therapies are needed for this disease, which has one of the lowest survival rates. The growing understanding of the molecular basis of pancreatic cancer and the recent introduction of targeted therapeutic agents have initiated novel studies that have the potential to improve on existing treatments.*

Methods: *We review the rationale and the clinical studies of therapeutic agents that target some of the molecular abnormalities commonly found in pancreatic cancer.*

Results: *Matrix metalloproteinase inhibitors (MMPi), farnesyltransferase inhibitors (FTIs), and tyrosine-kinase inhibitors and monoclonal antibodies against growth factors or their receptors are novel agents that have undergone phase II or III trials. Phase III studies of MMPi, alone or in combination with gemcitabine, and phase III studies of FTIs have produced disappointing results. Other agents in earlier phases of clinical development remain promising.*

Conclusions: *Despite the negative studies of MMPi and FTIs, the results of phase II trials of other drugs are encouraging. Targeted agents may improve the prognosis of pancreatic cancer.*

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Introduction

Complete surgical resection remains the only potentially curative treatment modality for patients with pancreatic cancer. Unfortunately, only approximately 20% of patients present with truly resectable disease. The vast majority of patients present with unresectable or metastatic disease. Even among patients undergoing a potentially curative resection, many will develop metastatic disease. Therefore, systemic therapeutic agents will have to be considered for most of the approximately 30,000 people who develop pancreatic cancer in the United States every year,¹ many of whom will die within 4 to 6 months of the initial diagnosis.

Given its superiority to fluorouracil (5-FU) in terms of quality of life and survival, gemcitabine has been accepted as the standard first-line agent for the treatment of patients with advanced pancreatic cancer.² The results achieved among patients treated with single-agent gemcitabine have been similar across several phase III trials, in which the median survival ranged from 5.4 to 5.6 months, and the 1-year survival rate ranged from 16% to 19%.^{2,5} Therefore, novel therapeutic strategies are needed in order to improve the prognosis of patients with pancreatic cancer. Among these strategies, drugs that target molecular abnormalities hold the greatest promise for the near future.

Matrix Metalloproteinase Inhibitors

Tissue invasion and the ability to metastasize are among the hallmarks of cancer.⁶ Disruption of cellular junctions and the interactions between cells and the extracellular matrix (ECM) are essential prerequisites for cell detachment from the primary tumor, invasion of the blood stream, and growth at distant sites. Several families of proteases are implicated in these processes. The largest and best characterized is the family of matrix metalloproteinases (MMPs), which are zinc-dependent proteolytic enzymes with different substrate specificities for ECM molecules (eg, collagen, fibronectin, laminin, and elastin). Among the various family members, MMP-2 and MMP-9 are most commonly implicated in tumor angiogenesis. The activity of MMPs may be inhibited by members of the family of proteins known as tissue inhibitors of metalloproteinases (TIMPs). In pancreatic cancer, overexpression of several MMPs has been demonstrated in several studies.⁷ It has been suggested that an imbalance between MMPs and TIMPs plays a role in pancreatic tumor progression⁸ and that MMP-2 activation correlates with more-advanced pathologic stages and with early recurrence after resection.⁹

Synthetic MMP inhibitors (MMPIs) have been developed and are being tested against a variety of tumors.¹⁰ One such MMPI is marimastat, an orally bioavailable drug that is active against several MMPs. In preclinical models, marimastat and other MMPIs delay tumor growth and prolong animal survival, but no cytotoxic effect is observed. Phase I studies found an inflammatory polyarthritis to be the dose-limiting toxicity of marimastat.¹¹⁻¹³ Pharmacokinetic analyses showed that marimastat is rapidly absorbed and eliminated, with time to maximum concentration of 1 to 2 hours and an elimination half-life of 4 to 5 hours.

In a dose-finding study among patients with pancreatic cancer, marimastat doses of 5 mg, 10 mg, and 25 mg twice daily were considered adequate.¹² CA19-9 changes in that study suggested evidence of activity, which was also noted in a phase II trial in which patients who had CA19-9 stabilization or responses (30% of cases) lived longer than

patients with a rising tumor marker.¹³ Based on these findings, randomized trials of marimastat were performed.

Bramhall et al⁴ randomized 414 patients with advanced pancreatic cancer to receive either gemcitabine (30-minute infusions of 1000 mg/m² per week for 7 consecutive weeks followed by a 1-week rest in the first cycle, and 1000 mg/m² per week for 3 consecutive weeks every 28 days thereafter) or marimastat at one of three dose levels: 5 mg b.i.d., 10 mg b.i.d., or 25 mg b.i.d. The primary endpoint of the trial was overall survival. Although the median survival in the 25-mg marimastat group was lower than that in the gemcitabine group (125 days vs 167 days), the log-rank analysis showed no difference between the survival curves of the two groups (hazard ratio = 0.96). Survival of patients treated with the other doses of marimastat (5 mg b.i.d. and 10 mg b.i.d.) was much lower than that of patients given gemcitabine. A subgroup analysis of patients with metastatic disease (approximately 65% of the cases) suggested an interaction between marimastat and disease stage: the median survival of patients with nonmetastatic disease was longer than that of patients with metastatic disease. In the gemcitabine group, there was no difference in median survival between patients with and without metastases. Consistent with the mode of action of these two drugs, the median progression-free survival among patients treated with marimastat, which has no cytotoxic effect, was approximately half that of patients treated with gemcitabine. Likewise, the reported response rates were lower in the marimastat arms of the trial (3% vs 26% for gemcitabine). Musculoskeletal toxicity was reported in 39% to 55% of patients across different dose levels of marimastat, but this toxicity was grade 3 or 4 in only 7% to 12% of cases. Other side effects were infrequent and usually mild to moderate.⁴

A different approach was taken in a second phase III trial,⁵ in which 239 patients were treated with gemcitabine (in the same schedule as in the preceding study) and were concurrently randomized to receive marimastat (10 mg b.i.d.) or placebo. The median and 1-year survival were nearly identical in the two groups. Likewise, the log-rank comparison between the two survival curves yielded no differences in overall or progression-free survival, with hazard ratios of 0.99 and 0.95, respectively. In this trial, there was no interaction between marimastat and disease stage.

The results of these trials indicate that marimastat, alone or in combination with gemcitabine, has no role in the treatment of advanced pancreatic cancer. Furthermore, another MMPI, BAY12-9566, proved inferior to gemcitabine in a randomized trial of 277 patients with advanced pancreatic cancer.¹⁴ Therefore, the currently available studies of MMPIs show that these agents have no role in the treatment of advanced pancreatic cancer. However, due to their cytostatic effect, it is conceivable that the administration of marimastat or other MMPIs to patients with tumors in earlier stages could improve on the exist-

ing therapies.¹⁵ The suggested interaction between marimastat and disease stage in one of the trials⁴ is in line with this hypothesis.

Farnesyltransferase Inhibitors

Ras designates several related 21-kd proteins that are encoded by three distinct genes (H-ras, K-ras, and N-ras).¹⁶ K-ras is the family member most commonly implicated in solid tumors, and somatic mutations of K-ras are found in up to 85% of pancreatic tumors.¹⁷ These mutations may lead to constitutive activation of the protein. Normal Ras is located in the inner surface of the cell membrane, where it plays an essential role in signal transduction. The protein cycles between inactive guanosine 5'-diphosphate-bound and active guanosine 5'-triphosphate (GTP)-bound configurations. Upon ligand binding to extracellular receptors, GTP-bound Ras interacts with Raf kinase and other proteins and leads to downstream activation of several intracellular pathways.

Membrane localization and function of Ras depend on the addition of a 15-carbon farnesyl moiety to the C-terminus of the protein. This reaction is catalyzed by the enzyme farnesyltransferase. Several oral, small-molecule farnesyltransferase inhibitors (FTIs) have been synthesized and are being tested in clinical trials. FTIs are cytotoxic or cytostatic against a variety of solid and hematologic tumor types. However, the precise mechanism of action of these drugs remains questionable¹⁸ since Ras may also be prenylated by other enzymes such as geranylgeranyl transferase.¹⁹ In addition, targeting of other farnesylated proteins such as RhoB may be partly responsible for the antitumor activity of FTIs.

Phase I trials of the FTIs tipifarnib (R115777)²⁰⁻²³ and lonafarnib (SCH66336) have demonstrated the safety of these drugs and their ability to inhibit protein farnesylation in vivo. Furthermore, responses have been seen among patients with acute myeloid leukemia²² and non-small-cell lung cancer (NSCLC)²⁴ treated in these trials.

Two phase II studies of tipifarnib in patients with advanced pancreatic cancer have shown disappointing results.^{25,26} In these trials, tipifarnib was administered orally at the dose and schedule previously determined in one of the phase I studies (300 mg b.i.d. for 21 days of a 28-day cycle).²⁰ Fatigue and nausea/vomiting were the most frequent toxicities; myelosuppression and elevation of transaminases, alkaline phosphatase, and bilirubin were also common. In one of the trials, 20 patients received only 33 cycles of therapy.²⁶ Despite significant in vivo inhibition of farnesyltransferase activity, no objective responses were seen, and the median survival was approximately 4 months. In the other trial, a preliminary analysis of 47 patients showed a median survival of only 2.7 months.²⁵ The median time to treatment failure was approximately 5 weeks in both trials. The authors of these

studies concluded that tipifarnib, given at this dose and schedule, is inactive in advanced pancreatic cancer.

Tipifarnib has also been studied in combination with gemcitabine. On the basis of a phase I trial that demonstrated the safety of the combination,²⁷ a phase III trial was conducted in Europe and the United States.²⁸ In this multicenter trial, 688 patients were randomized to treatment with gemcitabine plus tipifarnib or gemcitabine plus placebo. Overall survival (193 days vs 182 days) and 6-month and 1-year survival rates were not significantly different between the two arms of the study. Myelosuppression, diarrhea, and hypokalemia were slightly more frequent among patients randomized to tipifarnib.

The lack of clinically significant activity for tipifarnib in advanced pancreatic cancer remains unexplained. One pharmacodynamic hypothesis is that farnesyltransferase inhibition is not sufficient to abrogate Ras function. As stated above, Ras may still undergo posttranslational prenylation by other enzymes, such as geranylgeranyl transferase. In preclinical models, tumor cell lines with wild-type Ras or mutated N-ras or H-ras are more sensitive to tipifarnib than those with K-ras mutations, which are more frequent in pancreatic cancer; in addition, one study demonstrated that tipifarnib has a predominantly cytostatic effect on CAPAN-2 pancreatic cancer cell lines.¹⁸ It is also conceivable that tipifarnib produces insufficient inhibition of protein farnesylation at clinically tolerable concentrations.²⁶ Finally, the heterogeneity of pancreatic tumors and their dependence on multiple pathways for survival may explain the apparent failure of FTIs in advanced disease. Interestingly, tipifarnib has clinical activity in advanced breast cancer, a disease in which Ras mutations are rare.²⁹ Furthermore, tipifarnib has produced complete or partial remissions among patients with several types of myeloid malignancies.^{30,31} The activity of tipifarnib in earlier stages of pancreatic cancer warrants investigation. The Radiation Therapy Oncology Group is currently conducting a randomized phase II trial of combined chemoradiation, followed by tipifarnib or observation, in patients with advanced pancreatic cancer.³²

Agents That Target the Epidermal Growth Factor Receptors

Cancer cells often express membrane receptors for a variety of polypeptide growth factors. The epidermal growth factor receptor (EGFR) family includes EGFR (or *erbB-1*), HER-2 (or *erbB-2* or *neu*), HER-3, and HER-4.³³ Many of the features of the malignant phenotype, such as increased proliferation, angiogenesis, and evasion of apoptosis, are associated with the signaling networks that involve EGFR and its family members. Targeting of these receptors with monoclonal antibodies has become possible with the recent introduction of chimeric and humanized antibodies.

Among patients with pancreatic cancer, EGFR may be detected by immunohistochemistry in approximately 90% of clinical specimens.³⁴ Cetuximab (IMC-C225), a chimeric antibody against EGFR, has shown preclinical activity in a variety of tumor models.³⁵ In clinical trials, the main toxicity of cetuximab has been skin rash and occasional allergic reactions. The combination of cetuximab and gemcitabine was at least additive in preclinical models.³⁶ Cetuximab has been evaluated in combination with gemcitabine for the treatment of patients with advanced pancreatic cancer.³⁴ Cetuximab was given in a loading dose of 400 mg/m², followed by weekly doses of 250 mg/m² until progression. After two courses of therapy, 5 (12%) of 41 patients achieved a partial response, and 16 (39%) had stable disease. The 1-year survival rate was 32.5%. Treatment-related toxicities were mild to moderate and included skin rash, fatigue, and fever. These results prompted the investigators to design a phase III trial of gemcitabine with or without cetuximab (J. L. Abbruzzese, MD, personal communication, June 2003).

HER-2, another member of the EGFR family, is expressed in up to 45% of pancreatic tumors.³⁷ Overexpression, defined as 2+ or 3+ scores on immunohistochemistry, was detected in 17% of 123 archival specimens.³⁸ The administration of combined gemcitabine and trastuzumab to 18 evaluable patients with HER-2-overexpressing advanced pancreatic tumors produced four partial responses (22%) and CA19-9 falls greater than 50% in 9 cases.³⁹ No unexpected toxicity was seen in this study.

Members of the EGFR family possess intrinsic tyrosine-kinase activity whereby ligand binding to the extracellular portion of the receptor leads to autophosphorylation in tyrosine residues located on intracellular domains of the receptor. The inhibition of this autophosphorylation and subsequent signaling events is possible with small molecules administered orally.⁴⁰ These drugs are competitive inhibitors of adenosine triphosphate, and they display a relatively selective activity against specific receptors. Among these drugs, inhibitors of the EGFR are in more advanced phases of clinical development. Two such inhibitors are gefitinib (ZD1839) and erlotinib (OSI-774). Both have undergone phase I trials that demonstrated their safety in patients with solid tumors. The predominant side effects seem to be class-specific and include an acneiform skin rash and diarrhea. Continuous daily doses recommended for phase II studies were 250 mg and 500 mg for gefitinib^{41,42} and 150 mg for erlotinib.⁴³ Based on its single-agent activity in the treatment of patients with advanced NSCLC refractory to platinum- and docetaxel-based chemotherapy,⁴⁴ gefitinib (250 mg daily) has been recently approved by the Food and Drug Administration. Clinical trials investigating the activity of EGFR tyrosine-kinase inhibitors in pancreatic cancer are currently ongoing. Erlotinib may be safely combined with gemcitabine,⁴⁵ and the National Cancer Institute of Canada has recently completed a phase III

trial of this combination vs the standard gemcitabine treatment. The results of this trial are eagerly awaited, despite the negative results of two phase III trials of gefitinib in combination with chemotherapy in the first-line treatment of advanced NSCLC.^{46,47}

Vascular Endothelial Growth Factor as a Target

Vascular endothelial growth factor (VEGF) variants are among the most potent angiogenic molecules described thus far.⁴⁸ Angiogenesis has prognostic importance in pancreatic cancer, a disease in which VEGF expression correlates positively with local recurrence, metastatic potential, and overall survival.⁴⁹⁻⁵¹ VEGF and its receptors may be co-expressed in pancreatic tumors.⁵² The VEGF pathway has thus emerged as a therapeutic target in pancreatic cancer.

Among the many potential strategies that aim at blocking the signal transduction of VEGF receptors, the use of antibodies that bind to the ligands (eg, VEGF) is in more advanced phases of clinical development. Bevacizumab is a humanized antibody that can be used safely, either alone⁵³ or in association with several chemotherapy combinations.^{54,55} Bevacizumab has a favorable toxicity profile, with asthenia, fever, and headaches being the most common side effects. However, hypertension and bleeding have been reported. The combination of bevacizumab and chemotherapy has recently been shown to increase the response rate and prolong the progression-free and overall survival of patients with advanced colorectal cancer, when compared to chemotherapy alone.⁵⁶

In a recent phase II trial among patients with advanced pancreatic cancer, bevacizumab was combined with gemcitabine.⁵⁷ The results were promising, given the fact that 7 (27%) of the first 26 patients had a confirmed partial response and the median time to progression was 6 months. The estimated survival rate after 1 year was 53%, which compares favorably with the historical control of approximately 18%.²⁵ The toxicity profile of the combination was acceptable, with 36% of patients developing grade 3 or 4 neutropenia. One patient died due to bleeding caused by tumor erosion into the duodenum.

Other Targeted Agents in Pancreatic Cancer

There is increasing evidence that cyclooxygenase-2 (COX-2) is important in carcinogenesis. This inflammatory enzyme is induced in response to growth factors, tumor promoters, and carcinogens, and it may be involved in tumor proliferation and angiogenesis. COX-2 protein expression has been demonstrated in 67% to 90% of pancreatic tumors.^{58,59} Selective COX-2 inhibitors decrease the proliferation of pancreatic tumor cell lines through a

mechanisms that may be COX-2- independent.^{58,60} Nevertheless, COX-2 inhibitors are being investigated in the treatment of pancreatic cancer. The preliminary report of a phase I trial of the selective COX-2 inhibitor celecoxib combined with gemcitabine suggested that celecoxib may enhance the myelotoxicity of gemcitabine.⁶¹ In a phase II trial of this combination, no unexpected toxicity was noted, and 17% of patients had a partial response.⁶² Lipoxygenases, other key enzymes in arachidonic acid metabolism, are also under investigation as therapeutic targets in pancreatic cancer.⁶³

Several immunotherapeutic approaches to treat pancreatic cancer are being pursued.⁶⁴ Among them, immunization with naturally occurring or synthetic peptides, often conjugated with adjuvants, has been shown to elicit immunologic responses in patients with pancreatic cancer.^{65,66} In these studies, patients who developed immunity to the gastrin immunoconjugate G17DT⁶⁶ and to the synthetic mutant Ras peptide⁶⁵ survived longer than patients who did not develop immunity. Another immunotherapeutic approach consists in the administration of vaccines made with allogeneic pancreatic tumor cells. These cells may be genetically modified to express immunologic adjuvants. In one study, 3 of 14 patients receiving two different pancreatic tumor cell lines that expressed granulocyte-macrophage colony-stimulating factor developed an enhanced delayed-type hypersensitivity to autologous tumor collected at the time of surgery.⁶⁷ Preclinical studies also suggest a role for dendritic-cell-based vaccination of patients with pancreatic cancer.⁶⁸ Several other vaccine approaches are theoretically possible, and their potential as targeted therapies for patients with cancer are under investigation.⁶⁹

Conclusions

Several pharmacodynamic hypotheses have been proposed as possible explanations for the failure of some targeted agents in the treatment of various types of solid tumors. Among these hypotheses, it appears that solid tumor heterogeneity and the dependence of activity on various signaling events other than the one being targeted may partly explain the therapeutic failures seen in some clinical trials reported to date. The disappointing results of the phase III trials of MMPis and FTIs in advanced pancreatic cancer parallel those of gefitinib trials in NSCLC.^{4,5,28,46,47} It remains to be determined whether some targeted agents are more likely to be effective when used in earlier stages of rapidly progressing diseases such as pancreatic cancer and NSCLC.

Despite the negative studies of MMPis and FTIs in advanced disease, phase II studies of EGFR- and VEGF-based approaches, COX-2 inhibitors, and different immunotherapeutic strategies have been encouraging. Results of the ongoing and completed phase III trials of

cetuximab and erlotinib are expected within the next few years. In addition, the oncology community is likely to witness the discovery and development of many other targeted agents that will eventually be used alone or in combination with currently available treatment modalities, and this may ultimately improve the prognosis of patients with pancreatic cancer.

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