Original Article

Treatment of Metastatic Pancreatic Cancer

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Key Words

Pancreatic cancer, systemic therapy, gemcitabine, targeted agents

Abstract

Pancreatic adenocarcinoma represents the fourth-leading cause of cancer-related mortality in the United States. The vast majority of patients are diagnosed at advanced stages of the disease when surgery is no longer an option. For these patients, systemic therapy remains the mainstay of care. Although single-agent gemcitabine has remained the standard of care since its approval in 1997, improvements in patient outcomes may potentially be realized by (1) applying pharmacokinetic principles to optimize drug delivery, such as the administration of gemcitabine at a "fixed-dose rate" infusion; (2) combining gemcitabine with other cytotoxic agents for which evidence of synergy exists, such as platinum compounds; and (3) integrating novel targeted agents such as bevacizumab, erlotinib, and cetuximab into treatment paradigms, based on an increasing understanding of the molecular pathways that govern pancreatic tumor growth and maintenance. This article provides the evidence to support each of these approaches and highlights future directions in the management of metastatic pancreatic cancer. (*JNCCN* 2005;3:627–636)

Pancreatic cancer currently represents the fourth leading cause of cancer-related mortality in the United States, with an estimated 31,800 deaths attributable to this disease in 2005.[1] The five-year survival rate for all stages combined is approximately 3% to 4%, the lowest of any cancer site.[1] Because of the propensity for pancreatic cancer to metastasize early, the lack of effective screening tools, and the frequently nonspecific presenting symptoms, most patients are diagnosed at advanced stages of disease, when curative surgical resection no longer represents a viable option. For these patients, systemic therapy remains the mainstay of care.

Many pancreatic cancer trials include both patients with locally advanced unresectable disease and those with clear evidence of metastases, all subsumed under the general heading of advanced disease. However, these subgroups have different prognoses and different natural histories, and thus it is important to examine the percentage of each subgroup included in any given study because this distribution may certainly influence treatment outcomes. The question of whether patients with locally advanced disease should be treated identically to those with clear evidence of metastases requires further investigation. For example, radiation may play a role in palliation of cancer-related pain and obstructive symptoms. Radiation may also be useful for providing local disease control. However, its morbidity and debatable impact on overall survival as well as the necessity of delaying administration of full (and theoretically, optimal) doses of systemic therapy, all raise concerns of whether this is a necessary component of treatment.[2–4] This article focuses exclusively on systemic therapeutic options for patients with inoperable advanced pancreatic cancer, including the status of ongoing research efforts and future directions in this field.

Have We Moved Beyond Single-Agent Gemcitabine?

At present, gemcitabine (Gemzar; Eli Lilly and Company, Indianapolis, IN), a deoxycytidine analogue, represents the only Food and Drug Administration (FDA)-approved drug for the treatment of advanced pancreatic cancer. Approval of this drug was based on a phase III clinical study in which 126 previously untreated patients with advanced pancreatic cancer were randomized to receive either weekly infusions of gemcitabine or bolus 5-fluorouracil (5-FU).[5] The primary study endpoint was clinical benefit response, a parameter consisting of the

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composite of decreased pain intensity or analgesic consumption, improved performance status, or increased weight. This trial showed that gemcitabine was significantly superior to 5-FU with regard to clinical benefit response (24% vs. 5% of patients, respectively, $P = .0022$) and median survival (5.7 vs. 4.4 months, $P = .0025$). One-year survival rate was also superior for patients receiving gemcitabine (18% vs. 2%). Subsequently, outcomes for gemcitabine treatment were analyzed in a registry of more than 3,000 patients on a compassionate-need basis.[6] For all 2,380 patients for whom survival data were available, median survival was 4.8 months with a 1-year survival rate of 15%.

Gemcitabine monotherapy, given as a 30-minute infusion on a 3-week-on, 1-week-off schedule, has since been adopted as the reference standard in most subsequent studies of advanced pancreatic cancer. Attention naturally has turned toward improving the outcomes achieved with this single agent. One strategy has been to use pharmacokinetic principles to optimize drug delivery, such as administration of gemcitabine as a fixed-dose rate (FDR) infusion. Grunewald et al.[7] and Abbruzzese et al.[8] showed in early phase I studies that the accumulation of gemcitabine triphosphate (the active metabolite form of the drug) by mononuclear and leukemic cells is optimized using a fixed dose rate approximating 10 mg/m^2/min. Subsequently, a phase II study was conducted by Tempero et al.[9] in which 92 patients with locally advanced and metastatic pancreatic adenocarcinoma were randomized to 1 of 2 different dosing regimens: (1) weekly doses of high-dose gemcitabine (2,200 mg/m^2) administered as a standard 30-minute infusion or (2) weekly doses of gemcitabine at 1,500 mg/m^2, given as a FDR infusion of 10mg/m^2/min. Overall, FDR resulted in a twofold increase in median peak intracellular gemcitabine triphosphate concentration compared with standard infusion. A median survival of 8 months was observed with the FDR regimen compared with 5 months in the standard-infusion arm ($P = 0.013$). One- and 2-year survivorship on the FDR arm was also superior compared with the standard infusion arm (Table 1).

Although promising, these results require further validation before this concept reaches widespread acceptance, particularly in light of the fact that the strategy is also associated with a significantly higher degree of hematologic toxicity (for example, a 48.8% rate of grade 3 to 4 neutropenia for the FDR arm compared with 26.5% for the standard infusion arm). Furthermore, the lack of statistically significant differences between the 2 arms in terms of response rate, time to treatment failure, or time to tumor progression calls into question whether the reported survival differences are attributable to the superior antitumor activity of FDR gemcitabine. Several cooperative groups, including the Eastern Cooperative Oncology Group (ECOG) and the Cancer and Leukemia Group B (CALGB), have included FDR infusion of gemcitabine as one arm in their randomized trials to evaluate whether this strategy confers a distinct advantage in clinical outcomes compared with standard-infusion gemcitabine regimens, as is discussed in further detail later in the article.

Table 1 Efficacy Results of Randomized Phase II Trial of Standard Infusion Versus Fixed-Dose Rate Infusion Gemcitabine

	Gemcitabine standard infusion (2,200 mg/m^2 over 30 min)	Gemcitabine fixed-dose rate infusion (1,500 mg/m^2 over 150 min)	*P* value
Patients, *n*	49	43	
Median TTF, mo	1.8	2.1	0.09
Median survival, mo	5.0	8.0	0.013
One-year survival rate	9%	28.8%	0.014
Two-year survival rate	2.2%	18.3%	0.007
Patients receiving 2nd-line therapy, %	25%	50%	

Source: Used with permission from Tempero et al. Randomized phase II comparison of dose-intense gemcitabine: thirty-minute infusion and fixed dose rate infusion in patients with pancreatic adenocarcinoma. J Clin Oncol 2003; 21:3402–3408.

Gemcitabine Combined With Other Cytotoxic Agents

In addition to optimization of pharmacokinetics, another conceivable strategy to improve the results achieved by gemcitabine monotherapy involves combining this drug with other cytotoxic agents for which evidence of additive or synergistic effects exist. A

plethora of phase II trials have been conducted over the past decade, some with very promising results. However, only recently have data emerged from larger randomized phase III studies that address the efficacy of gemcitabine-containing combination regimens compared with gemcitabine as a single agent (Table 2).

Gemcitabine Plus Fluoropyrimidine

The ECOG performed the first phase III study of a gemcitabine-containing combination, in which 327 patients with locally advanced or metastatic pancreatic cancer were randomized to receive either single-agent gemcitabine or gemcitabine plus 5-FU.[10] Rationale for this trial was based on evidence of additive effects with gemcitabine and 5-FU in preclinical studies as well as the fact that the latter drug had represented the standard of care for patients with advanced pancreatic cancer (despite its inefficacy) before the approval of gemcitabine. No difference in median survival was detected between the 2 study arms (5.4 months for gemcitabine alone, 6.7 months for gemcitabine plus 5-FU; $P = .09$), although a statistically significant advantage

Table 2 Selected Phase III Trials of Gemcitabine Monotherapy Versus Gemcitabine in Combination with an FDA-Approved Cytotoxic Agent

	n	% With Metastatic (Stage IVb) Disease	RR[1]	Median PFS/TTP[1]	Median Survival	Study
Gemcitabine (1,000 mg/m^2 × 3 of 4 weeks)	162	90.1%	5.6%	PFS 2.2 mo*	5.4 mo	Berlin et al.[10]
Gemcitabine (1,000 mg/m^2) + 5-FU (600 mg/m^2), both × 3 of 4 weeks	160	89.4%	6.9%	3.4 mo*	6.7 mo	
Gemcitabine (1,000 mg/m^2 × 7 of 8 weeks, then 3 of 4 weeks)	160	79%	7.9%	PFS 4.0 mo	7.3 mo	Herrmann et al.[11]
Gemcitabine (1,000 mg/m^2 × 2 of 3 weeks) + capecitabine (650 mg/m^2 bid × 14 days every 3 weeks)	159	80%	10.1%	4.8 mo	8.4 mo	
Gemcitabine (1,000 mg/m^2 × 3 of 4 weeks)	100	79.2%	8.0%	TTP 2.5 mo*	6.0 mo	Heinemann et al.[20]
Gemcitabine (1,000 mg/m^2) + cisplatin (50 mg/m^2), both every other week	98	80.2%	10.2%	4.6 mo*	7.6 mo	
Gemcitabine (1,000 mg/m^2 × 7 of 8 weeks, then 3 of 4 weeks)	156	70%	17.3%*	PFS 3.7 mo*	7.1 mo	Louvet et al.[21]
Gemcitabine (1,000 mg/m^2 at FDR infusion on day 1) + oxaliplatin (100 mg/m^2 on day 2), both every other week	157	68%	26.8%*	5.8 mo*	9.0 mo	
Gemcitabine (1,000 mg/m^2 × 7 of 8 weeks, then 3 of 4 weeks)	180	80.6%	4.4%*	TTP 3.0 mo	6.6 mo	Rocha Lima et al.[22]
Gemcitabine (as above) + irinotecan (100 mg/m^2 × 2 of 3 weeks)	180	82.2%	16.1%*	3.5 mo	6.3 mo	
Gemcitabine (1,000 mg/m^2 × 3 of 4 weeks)	282	91.9%	7.1%*	PFS 3.3 mo	6.3 mo	O'Reilly et al.[23]
Gemcitabine (1,250 mg/m^2 × 2 of 3 weeks) + pemetrexed (500 mg/m^2 on day 8 every 3 weeks)	283	90.1%	14.8%*	3.9 mo	6.2 mo	

Abbreviations: *n*, number; RR, response rate; PFS, progression free survival; TTP, time to progression.

*Statistically significant differences.

in progression-free survival was noted in the combination arm (3.4 vs. 2.2 months; $P = .022$). The authors concluded that this particular combination was not a suitable replacement for gemcitabine monotherapy in patients with advanced pancreatic cancer. However, of note, after the investigators performed a proportional hazards model that adjusted for imbalances in performance status (more patients in the gemcitabine/5-FU arm had an ECOG performance status of 1), differences in overall survival between the treatment arms reached statistical significance, with a P value just below the 0.05 level.

A more recent phase III trial by Herrmann et al.[11] randomized 319 patients with locally advanced and metastatic pancreatic cancer to receive either gemcitabine alone or in combination with the oral prodrug of 5-FU, capecitabine, prompted by encouraging results using this combination in earlier phase I/II studies.[12,13] No statistically significant improvements were seen for the combination treatment arm in terms of response rate (10.1% vs. 7.9%), progression-free survival (4.8 vs. 4.0 months; $P = .207$), or overall survival (8.4 vs. 7.3 months; $P = .314$). Furthermore, patients receiving the 2-drug combination experienced higher rates of grade 3 or 4 nausea, vomiting, and diarrhea. Subset analysis suggested a survival advantage for combination therapy only in patients with good performance status (Karnofsky Performance Scale [KPS] of 90 or 100). Another randomized phase III trial evaluating this gemcitabine/capecitabine combination using a slightly different dosing schedule was recently completed in the United Kingdom with results expected to be presented in 2005.

Gemcitabine Plus Cisplatin

The addition of a platinum agent to gemcitabine has been a subject of considerable interest based on several lines of evidence. The combination represents a biologically sensible approach, given the synergistic effects shown by combining these agents together in vitro. Gemcitabine inhibits DNA repair after cisplatin-induced DNA damage, while cisplatin can affect metabolism of gemcitabine through ribonucleotide reductase inhibition.[14,15] After encouraging results from multiple phase II studies,[16–18] several groups sought to compare this combination with gemcitabine monotherapy in larger randomized phase III trials. The Gruppo Oncologico dell'Italia Meridionale showed that gemcitabine plus cisplatin resulted in superior clinical outcomes compared with gemcitabine alone in their randomized study of 107 patients with locally advanced and metastatic pancreatic cancer.[19] Specifically, the combination arm experienced a longer median time to disease progression (20 vs. 8 weeks; $P = .048$) and higher response rate (26.4% vs. 9.2%; $P = .02$). Although a trend toward improved median survival rate was seen for the gemcitabine/cisplatin arm as well, this difference did not achieve statistical significance (30 vs. 20 weeks; $P = .43$).

More recently, Heinemann et al.[20] conducted a multicenter randomized phase III trial of 198 patients in which participants received either gemcitabine alone or in combination with cisplatin. The investigators reported statistically significant improvements for the combination arm in terms of time to disease progression (4.6 vs. 2.5 months; $P = .016$ by log-rank) and rate of disease control (partial response plus stable disease) (70.2% vs. 49%; $P < .001$). Again, as in the Italian study, a trend toward improved overall survival was also seen, but this did not reach statistical significance (7.6 vs. 6.0 months; $P = .12$ by log-rank). The lack of a statistically significant improvement in survival may have resulted from the conservative sample size chosen (the study investigators initially sought to show an improvement in median survival from 5 to 8 months with the gemcitabine/cisplatin combination), in addition to an unexpectedly high survival rate in the control arm. Toxicities did not differ significantly between the 2 arms except for a higher incidence of grade 3 to 4 nausea and vomiting in the combination arm (22.2% vs. 5.8%; $P = .002$).

Gemcitabine Plus Oxaliplatin

In the GERCOR/GISCAD Intergroup study, Louvet et al.[21] reported results from 313 patients with advanced pancreatic cancer who were randomized to receive either single-agent gemcitabine or the combination of gemcitabine and oxaliplatin. Of note, aside from the addition of oxaliplatin, patients assigned to the GEMOX arm also received gemcitabine at the FDR infusion of 10 mg/m^2/min, whereas patients on the gemcitabine monotherapy arm received their therapy as a standard 30-minute infusion. Statistically significant differences were seen in favor of the combination arm in terms of progression-free survival (5.8 vs. 3.7 months; $P = .038$) and objective response (26.8% vs. 17.3%; $P = .04$). Whether these differences were the result of the addition of the oxaliplatin, the different infusional strategies of gemcitabine between the 2 arms, or both factors, could not be determined.

However, as was the case in the Heinemann study, these improvements did not translate into a statistically significant improvement in overall survival (9.0 vs. 7.1 months; $P = .13$). Of note, although approximately half of the patients on each arm received second-line therapy, a much higher percentage of patients on the gemcitabine-alone arm received second-line platinum-based therapy, a fact which might help explain the lack of clear survival differences seen in this study. Not unexpectedly, a higher overall incidence of grade 3 to 4 toxicities were experienced among patients receiving GEMOX (52.2% vs. 39.7%; $P = .03$), including thrombocytopenia, vomiting, and peripheral neuropathy.

Gemcitabine Plus Irinotecan

Rocha Lima et al.[22] performed a randomized multicenter phase III study comparing gemcitabine plus irinotecan versus gemcitabine alone. A total of 360 patients with either locally advanced or metastatic pancreatic cancer were enrolled in this trial. Aside from a statistically significant difference seen in objective response rate (16.1% for gemcitabine/irinotecan compared with 4.4% for gemcitabine alone), no improvements in any other outcome variables were witnessed in the combination arm, including time to disease progression, quality of life, or overall survival (6.3 months for gemcitabine/irinotecan vs. 6.6 months for gemcitabine alone; log-rank, $P = .789$). The major difference in toxicity profiles between the 2 arms was the higher incidence of grade 3/4 diarrhea in the combination arm (18.5% compared with 1.8%). Two other phase III studies evaluating the efficacy of another topoisomerase I inhibitor, exatecan mesylate (DX-8951F), also failed to demonstrate any benefit of this drug for patients with advanced pancreatic cancer,[23,24] suggesting a limited role for this class of agents in combination with gemcitabine.

Gemcitabine Plus Pemetrexed

Richards et al.[25] conducted a randomized phase III trial of 565 patients with advanced pancreatic cancer to evaluate whether the addition of pemetrexed, a multitargeted antifolate agent, to gemcitabine would confer any benefit compared with gemcitabine alone. Although combination therapy did produce statistically significant improvements in time to disease progression (5.2 vs. 3.6 months; $P = .042$) and objective response rate (14.8% vs. 7.1%; $P = .004$), no differences between the 2 arms were seen in terms of overall or 1-year survival (6.2 months and 21.4% vs. 6.3 months and 20.1%, gemcitabine/pemetrexed vs. gemcitabine; P = NS). Furthermore, higher rates of grade 3 to 4 neutropenia, febrile neutropenia, anemia, thrombocytopenia, and fatigue were seen in the combination arm, although no differences in global quality of life scores were reported.

Ongoing Cooperative Group Studies

Investigators from CALGB recently performed a randomized phase II study (CALGB 89904) comparing 3 gemcitabine-containing combination regimens (gemcitabine/cisplatin, gemcitabine/docetaxel, gemcitabine/irinotecan) with single-agent gemcitabine administered by FDR.[26] Each of the 4 regimens appears to have an acceptable toxicity profile. Specifically, the highest incidence of grade 3 or 4 hematologic toxicity was seen with the gemcitabine/cisplatin combination, although this did not translate into an increased incidence of febrile neutropenic episodes compared with the other arms. Not surprisingly, patients receiving gemcitabine/cisplatin also had the highest rates of grade 3 or 4 nausea and vomiting, while those receiving gemcitabine/irinotecan had the highest rate of grade 3 or 4 diarrhea. Maturation of data is required to determine whether any of these arms appears superior to the others from an efficacy standpoint. A multicenter randomized phase II trial is also being conducted in Germany comparing 2 gemcitabine-containing doublets (gemcitabine/capecitabine and gemcitabine/oxaliplatin) with a non-gemcitabine-containing regimen (capecitabine/oxaliplatin).[27] Early analysis suggests that all of these options may deserve further study. Finally, an ECOG study comparing standard infusion gemcitabine to FDR infusion gemcitabine, with GEMOX as a third arm, has completed accrual and will be very helpful in crafting future strategies.

Cytotoxic Agents Beyond Gemcitabine

Although gemcitabine has been the primary basis on which clinical trials have been designed, a number of other cytotoxic agents either alone or in combination have also been studied in advanced pancreatic cancer, including taxanes, platinum compounds, topoisomerase inhibitors, and fluoropyrimidines.[28–34] These agents may be important as alternatives to gemcitabine-based regimens in the first-line setting, for use in gemcitabine-intolerant patients, or possibly as salvage treatment for gemcitabine-refractory disease, for which few options

Table 3 Non-gemcitabine–containing cytotoxic regimens for the first-line treatment of advanced pancreatic cancer

	n	RR	Median TTP (mo)	Median OS (mo)
Docetaxel[28]	43	15%	2.1	7.0
Capecitabine[29]	42	9.5%	N/A	6.0
5-FU/leucovorin/ mitomycin C/ dipyridamole[30]	50	22%	N/A	4.6
Epirubicin/5-FU/ leucovorin[31]	28	21%	2.9*	6.0
Docetaxel/irinotecan[32]	27	11%	4.3†	N/A
Oxaliplatin/5-FU[33]	31‡	10%	4.2	9.0
Folfirinox[34]	47	26%	8.2	10.2

Abbreviations: *n*, number of patients; RR, response rate; TTP, time to tumor progression; OS, overall survival.

*This study reported time to treatment failure.

†This study reported progression free survival.

‡One arm of a randomized phase II study.

have been reported in the medical literature given the small proportion of patients who go on to receive second-line therapy. Table 3 provides published results of various non-gemcitabine-containing regimens, although one should keep in mind that the number of patients evaluated in each of these studies is relatively small.

Novel Targeted Therapies in Advanced Pancreatic Cancer

An expanding knowledge of the molecular pathways that govern pancreatic tumor growth and maintenance has led to the development of targeted compounds specifically designed to disrupt the growth and spread of pancreatic cancer cells at various signaling points. These compounds take many forms: small molecule inhibitors, monoclonal antibodies and immunoconjugates, vaccine-based strategies, and gene therapy. Each is being vigorously pursued as a potential standalone option or as an adjunct to chemotherapy in the treatment of advanced pancreatic cancer.

Several agents, including matrix metalloproteinase inhibitors and farnesyl transferase inhibitors, have already been evaluated in large randomized phase III trials of advanced pancreatic cancer and produced disappointing results, with no clear benefit when added to or compared with gemcitabine.[35–38] However, more recently, the development of new targeted therapies that have gained approval for the treatment of solid tumors has led to renewed excitement that these and similar molecules may play a role in our therapeutic armamentarium against pancreatic cancer. The 3 that have been evaluated most rigorously to date are cetuximab, erlotinib, and bevacizumab.

Cetuximab

Cetuximab (Erbitux; Imclone Systems, New York, NY) is a chimeric monoclonal antibody that competes with natural ligands (EGF, TGF-α) for binding to the EGF receptor. By preventing ligand-receptor binding, cetuximab inhibits activation of the tyrosine kinase enzymatic activity of EGFR, thus abrogating signal transduction pathways mediated by this receptor that are critical to cell growth, cell cycle progression, and angiogenesis.[39] Signaling through this pathway appears to be important in pancreatic tumorigenesis, with expression of EGFR or its ligands associated with a more aggressive clinical course.[40–42]

Xiong et al.[43] conducted a phase II clinical trial testing the combination of gemcitabine (1,000 mg/m^2 weekly times 7 of 8 weeks, then 3 of 4 weeks) and cetuximab (400 mg/m^2 loading dose, then 250 mg/m^2 weekly) in 41 patients with advanced pancreatic cancer, 89% of whose tumors expressed epidermal growth factor receptor. Five of 41 patients (12.2%) showed evidence of a partial response after 2 courses of therapy, and disease stabilization or minor responses in an additional 16 patients (39%). Median time to progression was 3.8 months, with a median survival duration of 7.1 months and, impressively, a 1-year survival rate of 31.7%. Acneiform rash, fatigue, and fevers were the most common adverse effects seen.

Table 4 Ongoing randomized multicenter trials evaluating targeted agents in advanced pancreatic cancer

Study Sponsor	Treatment Arms	Phase
CALGB	Gemcitabine +/− bevacizumab	III
SWOG	Gemcitabine +/− cetuximab	III
ECOG	Docetaxel/irinotecan +/− cetuximab	II
University of Chicago	Gemcitabine/bevacizumab + (cetuximab vs. erlotinib)	II

At present, 2 cooperative group studies have been designed to further study the potential benefit cetuximab may confer when given in combination with standard chemotherapy. The Southwest Oncology Group is conducting a phase III randomized study comparing gemcitabine plus cetuximab versus gemcitabine alone as first-line therapy for patients with advanced disease (Table 4). The ECOG is also performing a randomized phase II trial evaluating the combination of docetaxel and irinotecan with or without cetuximab in the first-line setting.

Erlotinib

Erlotinib (Tarceva; Genentech, South San Francisco, CA) is an orally bioavailable small molecule that also targets the EGF receptor. It acts via binding to the ATP site of the tyrosine kinase region of the EGF receptor,[44] thus inhibiting EGFR's enzymatic activity. This agent received FDA approval in 2004 for the treatment of non-small cell lung cancer.

After an initial cohort to assess the safety of daily doses of erlotinib when combined with gemcitabine,[45] the combination of erlotinib 100 mg/day with gemcitabine 1,000 mg/m^2 weekly 3 of 4 weeks was established as the appropriate dose to test in a large phase III trial for patients with previously untreated advanced pancreatic cancer.[46] In this 569-patient trial, conducted by OSI Pharmaceuticals in collaboration with the National Cancer Institute of Canada Clinical Trials Group, patients were randomized to receive either gemcitabine alone or in combination with erlotinib.[47] This study, with preliminary results reported in 2005, represents a landmark of sorts in that it is the first randomized trial to show a statistically significant survival advantage using a gemcitabine-containing combination, with a hazard ratio for overall survival of 0.81 (P = .025) and for progression-free survival of 0.76 (P = 0.003). The actual magnitude in differences between the 2 groups was quite modest, with median and 1-year survival rates in the gemcitabine/erlotinib arm of 6.37 months and 24%, respectively, compared with 5.91 months and 17% in the gemcitabine/placebo arm. Additionally, no difference in response rate was seen (8.6% for gemcitabine/erlotinib vs. 8.0% for gemcitabine/placebo). Rash, diarrhea, infection, and stomatitis were seen more frequently in patients receiving erlotinib, although the incidence of grade 3 or 4 toxicities was not significantly different between the 2 arms. On the basis of this trial, erlotinib is currently under review by the FDA as to whether pancreatic cancer should be included as one of its indications.

Bevacizumab

Pancreatic tumors often contain foci of enhanced endothelial cell proliferation, and multiple lines of preclinical and clinical evidence lines of data support the concept that angiogenesis may be a critical aspect of pancreatic tumor development and growth.[48–54] Bevacizumab (Avastin; Genentech, South San Francisco, CA), a recombinant humanized monoclonal antibody directed against VEGF, was approved in 2004 on the basis of significantly improving response rates and overall survival when added to standard chemotherapy for the treatment of metastatic colorectal cancer.

Kindler et al.[55] examined the combination of gemcitabine (1,000 mg/m^2 on days 1, 8, and 15 every 28 days) and bevacizumab (10 mg/kg on days 1 and 15 every 28 days) in a phase II study of 52 patients with chemotherapy-naive advanced pancreatic cancer. These investigators reported a response rate of 19%, a median time to disease progression of 5.8 months, a median survival of 8.7 months, and a promising 1-year survival rate of 29%. Significant toxicities included a 14% rate of thromboembolic events and an 8% rate of perforations of the gastrointestinal tract. A larger multicenter study is now underway through CALGB, with advanced pancreatic cancer patients randomized to receive either gemcitabine alone or gemcitabine in combination with bevacizumab (Table 4). This trial is planned to include a total of 590 patients, with a number of correlative studies, including pharmacoeconomic and pharmacogenomic analyses.

Conclusions

Although single-agent gemcitabine currently remains the standard of care for the treatment of advanced pancreatic cancer, data are emerging to support newer strategies for this patient population. The concept of administering gemcitabine at a fixed-dose rate as well as combining gemcitabine with other cytotoxic agents (most notably platinum compounds) have each shown modest advantages, although a statistically significant survival benefit for any of these approaches has yet to be shown in any randomized phase III trial. Evaluation of non-gemcitabine-containing chemotherapy regimens in phase II and III trials is also ongoing, several of which may represent viable alternatives.

Perhaps the most exciting area of investigation is how to optimally integrate novel targeted agents into treatment paradigms, particularly with the first randomized phase III study to show a survival advantage for patients with advanced pancreatic cancer by adding a biologic agent, erlotinib, to gemcitabine. Although inhibitors of the EGFR signaling pathway and anti-angiogenic compounds are the furthest along in clinical development, a multitude of other agents are also undergoing active preclinical and clinical testing as well. As noted previously, more than 90% of pancreatic adenocarcinomas have activation of the *K-ras* oncogene,[56] and therefore targeting this protein and its effector molecules represents a logical approach. A number of agents, for example, have been developed against signal transducers of the mitogen-activated protein (MAP) kinase pathway,[57] downstream targets of Ras. Our expanding knowledge of the molecular pathogenesis of pancreatic cancer will undoubtedly lead to the development of many other agents that should be ready for clinical testing in the near future, including inhibitors of TGF-beta and Hedgehog signaling.[58,59]

In the future, an individualized approach to therapy, based on a greater understanding of genetic characteristics of both host and tumor, may allow one to select the most appropriate therapeutic regimen for any given patient. Accomplishing this task in individuals with pancreatic cancer may present a somewhat greater challenge than in patients with other tumor types, given the difficulty in obtaining adequate tumor samples for molecular analysis. Nonetheless, such a strategy would be immensely useful, both to avoid unnecessary overtreatment in this ill patient population and to help guide the most effective regimen to choose from among a growing portfolio of options.

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