In the last decade, continued efforts in pancreas cancer research have led to the development of new, more effective therapies. Additionally, progress in understanding the molecular processes underlying the development and progression of this disease provides hope for the development of more effective treatment strategies. Recent clinical trials have provided reason for hope that novel chemotherapy combinations and molecularly targeted agents will lead to improved clinical outcomes for patients with this disease. This article will summarize the data that has led to the current standards of therapy for patients with resectable and advanced pancreatic cancer and review new treatment strategies for this disease.

Pancreas cancer is the fourth leading cause of cancer death in the United States. The lethality of this malignancy is demonstrated by the fact that the annual incidence (32,000) is approximately equal to the annual deaths (31,000).1 Unfortunately, carcinoma of the pancreas is increasing in incidence, and its exact risk factors remain poorly understood; only 5%–10% of all pancreatic adenocarcinomas have a clear hereditary association, and cigarette smoking is the only consistently identified modifiable risk factor.2–4 Over 95% of pancreatic malignancies originate in the pancreatic ducts and are adenocarcinoma by histology. This paper will address the use of systemic therapy in pancreatic adenocarcinoma, hereafter referred to as pancreas cancer.

There are several factors that contribute to the high mortality rate associated with pancreatic cancer. First of all, with the exception of painless jaundice, there are few signs or symptoms associated with early stage pancreatic cancer. As a result, up to 90% of patients will present with locally advanced or metastatic disease. Second, there is no effective screening test to detect disease in asymptomatic patients. Third, pancreatic cancer is one of the most intrinsically drug-resistant tumors. Finally, there is a high rate of relapse, even in patients with early stage disease who receive adjuvant therapy. Thus, although surgical resection remains the only chance at cure, <10% of patients diagnosed with pancreas cancer can actually have a curative resection.5 Despite surgery with curative intent, actuarial 5-year survival rates for these patients remain at approximately 20%, indicating that even patients with localized small cancers (<2 cm) with no lymph node metastases are likely to die of metastatic disease.5 Therefore, improvements in therapy that serve as adjuncts to surgery and systemic treatments for the more common scenario of advanced disease provide the greatest hope of improving the clinical outcomes in this disease.

As is the case with most tumors, the TNM staging of pancreatic cancer is helpful in determining prognosis. However, for treatment purposes, a simplified classification is used in which tumors are divided into resectable, locally advanced, unresectable, and metastatic. It is important to note that there is some variation in the definition of “resectability” that is primarily because of the experience and skill of the surgeon and the extent to which the surgeon will go with regard to lymph node resection and venous reconstruction.

Adjuvant Therapy of Pancreas Cancer

Patients with resectable disease comprise the smallest subgroup of pancreas cancer patients (~10%). Although all visible disease may be removed by surgery, the cure rate for patients managed with surgery alone is low.5 Therefore, researchers have focused on adjuvant therapy in an effort to increase the rate of long-term survival. Adjuvant therapy is post-operative treatment administered to patients with no detectable evidence of residual disease but who are
likely to harbor microscopic tumor deposits that, left untreated, will lead to tumor recurrence and death. Four randomized trials have been reported that evaluate the impact of postoperative adjuvant therapy in patients with resected pancreatic cancer.

### Randomized Trials

The Gastrointestinal Tumor Study Group (GITSG) trial from 1985 is the only American trial conducted comparing surgery alone to surgery and adjuvant therapy. The GITSG study randomized 43 patients to either surgery alone or surgery followed by combined chemotherapy and radiation (“chemoradiation”) for 4 weeks followed by 24 months of chemotherapy. The chemotherapy administered throughout was 5-fluorouracil (5-FU), an antimetabolite pyrimidine analog. In this study, radiation was administered in a pair of 2-week courses separated by a 2-week break. In addition, 5-FU was given as a bolus (quick injection) on each of the first 3 days of each 2-week course. The median survival for patients treated with adjuvant therapy, 20 months, was significantly longer than for those patients who did not receive any postoperative therapy, 11 months \((P = .035)\) (Table 1). However, several criticisms have long plagued the GITSG trial, including the long duration of accrual (8 years), the small size of the study, and the measurement of survival from the date of surgery as opposed to date of randomization. Subsequent to the GITSG trial, knowledge about the principles of radiation therapy changed the standard to a more continuous radiation schedule (ie, no 2-week break). Additionally, technology now allows for continuous administration (24 hours a day, 7 days a week) of 5-FU, which, when combined with radiotherapy in adjuvant treatment of rectal cancer, has proved superior in terms of survival and local control when compared with bolus 5-FU.\(^7\)

A second early trial conducted in Norway randomly assigned patients to chemotherapy with 5-FU, doxorubicin (an anthracycline), and mitomycin-C (an antitumor antibiotic) after surgery vs surgery alone. No radiation was used in this study. With only 50 patients, it too was a small trial, but it also had a statistically significant median survival improvement for the adjuvant therapy arm (Table 1). However, by 3 years, there was no difference in the number of survivors in each arm, and further investigation of the chemotherapy arm was abandoned because of the low cure rates in both arms of the study. In addition, these results may have been confounded by the fact that this study included patients with tumors of the Ampulla of Vater, which may have a different treatment sensitivity profile and prognosis.

After these 2 trials, the European Organization for the Research and Treatment of Cancer (EORTC) conducted a clinical trial comparing continuous infusion 5-FU and radiation after surgery vs surgery alone. No radiation was used in this study. With only 50 patients, it too was a small trial, but it also had a statistically significant median survival improvement for the adjuvant therapy arm (Table 1). However, by 3 years, there was no difference in the number of survivors in each arm, and further investigation of the chemotherapy arm was abandoned because of the low cure rates in both arms of the study. In addition, these results may have been confounded by the fact that this study included patients with tumors of the Ampulla of Vater, which may have a different treatment sensitivity profile and prognosis.

### Table 1. Results of Randomized Trials in Adjuvant Therapy of Pancreas Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Arms</th>
<th>No. patients</th>
<th>Median survival</th>
<th>5-Year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>GITSG</td>
<td>Surgery</td>
<td>22</td>
<td>11 months</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Surgery + chemoXRT</td>
<td>21</td>
<td>20 months ((P = .035))</td>
<td></td>
</tr>
<tr>
<td>Norwegian trial</td>
<td>Surgery</td>
<td>31</td>
<td>11 months</td>
<td>8%</td>
</tr>
<tr>
<td></td>
<td>Surgery + chemotherapy</td>
<td>30</td>
<td>23 months ((P = .02))</td>
<td>4%</td>
</tr>
<tr>
<td>EORTC overall</td>
<td>Surgery</td>
<td>103</td>
<td>19 months</td>
<td>22%</td>
</tr>
<tr>
<td></td>
<td>Surgery + chemoXRT</td>
<td>104</td>
<td>24.5 months ((P = \text{NS}))</td>
<td>28%</td>
</tr>
<tr>
<td>EORTC pancreas cancer subset</td>
<td>Surgery</td>
<td>54</td>
<td>12.6 months</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Surgery + chemoXRT</td>
<td>60</td>
<td>17.1 months ((P = .099))</td>
<td></td>
</tr>
<tr>
<td>EORTC periampullary cancer subset</td>
<td>Surgery</td>
<td>48</td>
<td>40.1 months</td>
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</tr>
<tr>
<td></td>
<td>Surgery + chemoXRT</td>
<td>44</td>
<td>39.0 months</td>
<td></td>
</tr>
<tr>
<td>ESPAC-1 chemo versus no chemo</td>
<td>No chemotherapy</td>
<td>142</td>
<td>15.5 months</td>
<td>8%</td>
</tr>
<tr>
<td></td>
<td>Chemotherapy</td>
<td>147</td>
<td>20.1 months ((P = .0009))</td>
<td>21%</td>
</tr>
<tr>
<td>ESPAC-1 chemoXRT versus no chemoXRT</td>
<td>No chemotherapy</td>
<td>144</td>
<td>17.9 months</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td>Chemotherapy</td>
<td>145</td>
<td>15.9 months ((P = \text{NS}))</td>
<td>10% ((P = \text{NS}))</td>
</tr>
</tbody>
</table>

NOTE. EORTC data are presented with the total population and the 2 subsets. ESPAC-1 data are presented from the final report rather than the early report. Only patients in the 2 × 2 randomized portion are included in that analysis.

ChemoXRT, chemoradiation.
is possible that combining the 2 disease sites with different prognoses and variable responses to the regimen may have blunted any effect that may have occurred in the pancreas cancer subset. In fact, subset analyses demonstrated that the peripancreatic cancer patients had identical survivals with or without adjuvant therapy. Although subset analysis suggested a trend toward improved survival in pancreas cancer patients given adjuvant therapy, it did not reach statistical significance (17.1 vs 12.6 months, respectively, \( P = .099 \)) (Table 1).

The most recent randomized trial, European Study Group for Pancreatic Cancer (ESPAC-1), was designed to address 2 questions using a 2 × 2 randomization design.\(^{10,11}\) One randomization was between postoperative chemoradiation or no chemoradiation. Chemoradiation consisted of two, 2-week courses of radiation therapy combined with bolus 5-FU and separated by a 2-week break: the exact same technique used in the original GITSG study reported 16 years earlier. The other randomization was between chemotherapy or no chemotherapy, consisting of a 6-month course of bolus 5-FU. If a patient was randomized to both chemoradiation and chemotherapy, the chemoradiation was administered before the 6 months of chemotherapy. In the initial report of the results of this trial, survival benefit was observed in those patients who received adjuvant chemotherapy vs those who did not (median survival, 19.7 vs 14.0 months, respectively, \( P = .0005 \)). On the other hand, there did not appear to be any benefit to adjuvant chemoradiotherapy. An updated analysis of the 289 patients randomized in a 2 × 2 fashion on this study confirmed the survival advantage with adjuvant chemotherapy and revealed an apparent detrimental effect for adjuvant chemoradiotherapy (median survival, 15.9 vs 17.9 months, respectively, \( P = .05 \) compared with patients who did not receive postoperative chemoradiotherapy) (Table 1).\(^{11}\)

Both papers were accompanied by editorials that raised some concerns.\(^{12,13}\) The first concern centered on the use of short courses of radiation separated by a break: a technique that may permit tumor regrowth during the break. A second concern related to the use of bolus injections of 5-FU on some days of radiation rather than infusional 5-FU administered throughout the course of radiation. A third concern regarding this study is that there was no central review or quality control with regard to the planning and administration of radiation. A recent trial of adjuvant therapy in gastric cancer found and corrected major or minor deviations in the radiation ports of approximately 35% of patients.\(^{14}\) Because of these many concerns, there has not been universal abandonment of adjuvant chemoradiotherapy. As a result, reasonable options for adjuvant treatment of patients with resected pancreatic cancer include chemoradiotherapy followed by chemotherapy or chemotherapy alone. However, given that the majority of patients treated with either strategy will eventually relapse and succumb to their disease, it could be argued that the best option for this group of patients is participation in a clinical trial. An American intergroup trial (R9704) comparing chemotherapy with gemcitabine or 5-FU has completed accrual, and results are anticipated soon. In that trial, patients were given chemotherapy for 2 months before and 2 months after an identical chemoradiation regimen utilizing continuous infusion 5-FU during radiation. The next intergroup trial, currently under development, will evaluate the safety of incorporating novel agents targeting angiogenesis (bevacizumab) or the epidermal growth factor receptor (EGFR; cetuximab) as well as the safety of switching to an oral prodrug of 5-FU, capecitabine, during the radiation therapy. In Europe, ESPAC-3 was originally designed to evaluate surgery alone vs surgery followed by adjuvant therapy with either gemcitabine or 5-FU. After the updated data from ESPAC-1 became available, the surgery-alone arm was dropped, leaving the randomization to either gemcitabine or 5-FU. Radiation therapy is not included as a component of this trial.

**Other Approaches to Adjuvant Therapy**

Another approach to adjuvant therapy that has been evaluated is a more aggressive regimen of chemoinmunotherapy with radiation. A single-institutional trial combining cisplatin, 5-FU, and interferon with radiation resulted in 1-, 2-, and 5-year estimated survival rates of 95%, 64%, and 55%, respectively.\(^{13}\) Despite a hospitalization rate of 42%, there were no deaths from therapy. This regimen is currently being evaluated in a multi-institutional phase II trial by the American College of Surgeons Oncology Group (ACOSOG) to determine whether similar results can be obtained in a multi-institutional setting.

Another approach has been the neoadjuvant—preoperative—administration of therapy. Surgery devascularizes the tumor bed, resulting in reduced blood flow and hypoxia to the tissues, which, theoretically, could reduce the efficacy of radiation therapy. Additionally, despite significant improvements in morbidity and mortality from pancreatic cancer surgery, up to 25% of patients do not recover quickly enough to receive postoperative adjuvant therapy. Therefore, some have postulated that administering the chemoradiation before surgery may
enhance its efficacy. In addition to the benefits listed above, neoadjuvant therapy might theoretically shrink the tumor and make complete resection more feasible. Although promising results from several trials have been reported, no randomized trials have been conducted.\textsuperscript{16–19} It is unclear whether the neoadjuvant approaches have increased resectability rates or the rates of resection with negative margins (R0) resections (ie, complete resection of the tumor with negative pathologic margins), but these would be very important end points for randomized trials.

**Conclusions About Adjuvant Therapy**

Postoperative adjuvant therapy improves survival in patients with resected adenocarcinoma of the pancreas. Unfortunately, median survival is less than 2 years, and long-term survival is under 20% in most phase III trials. The roles of chemotherapy, radiation, and newer therapies targeted against growth factor receptors and intracellular signaling pathways need to be clarified through randomized trials.

**Locally Advanced Disease**

Locally advanced disease refers to extension of the tumor to adjacent organs such that complete surgical excision with negative pathologic margins is impossible. Local extension includes nearby organs, such as the liver or duodenum, regional lymph nodes, or, most commonly, vascular structures such as the superior mesenteric artery or celiac trunk that cannot be resected.

Treatment of locally advanced disease in the United States has been defined by 2 early GITSG trials and an Eastern Cooperative Oncology Group (ECOG) trial. In a GITSG study published in 1981, 227 patients were randomized to 1 of 3 arms: high-dose radiation (6000 cGy) alone, standard-dose radiation (4000 cGy) with 5-FU, or high-dose radiation with 5-FU.\textsuperscript{20} The 2 chemoradiation arms produced a significantly longer median survival (9.3 and 9.7 months, respectively) compared with the radiation alone arm (5.3 months, \(P < .05\)). The other 2 trials had conflicting results. The GITSG trial published in 1988 demonstrated in 43 patients a statistically significant improvement in survival in favor of chemoradiation (9.7 months) over chemotherapy alone (7.4 months, \(P < .02\)).\textsuperscript{21} The ECOG trial demonstrated no difference in survival between chemoradiation (9.0 months) and chemotherapy (9.0 months) in 50 patients.\textsuperscript{22} However, both trials were small, and neither can be considered conclusive. At the present time, common practice in the United States is for patients with locally advanced pancreatic cancer to receive continuous infusion 5-FU in combination with radiation therapy.\textsuperscript{23}

Newer approaches to chemoradiation for locally advanced disease have largely focused on gemcitabine (\(2',2'-\text{difluorodeoxycytidine}\), a deoxycytidine nucleoside analog incorporated into DNA resulting in chain termination. Gemcitabine is a very potent radiation sensitizer, and it has been difficult to identify an “optimal” dose and schedule for gemcitabine in combination with radiotherapy. Several trials have incorporated gemcitabine into a standard regimen of radiation (currently over 5000 cGy administered over slightly longer than 5 weeks). The first approach to be tested was a once-a-week administration of gemcitabine, which is the way that it is given when used without radiation.\textsuperscript{24} Response rates in these studies have been low (\(\sim 20\%\)). A second approach has been to use a twice-weekly administration schedule based on preclinical data suggesting that gemcitabine radiosensitization lasts for \(\sim 3\) days.\textsuperscript{25,26} A third approach uses full-dose gemcitabine and low-dose radiation.\textsuperscript{27} This method also includes the use of very narrow beams of radiation, focusing on the tumor itself rather than the surrounding tissues. A phase II trial of full-dose gemcitabine and low-dose radiation including patients with local and locally advanced disease had 2 responders and 25 stable disease patients of the 41 patients enrolled.\textsuperscript{28} Of the 12 patients deemed resectable prior to treatment, 8 were able to undergo an R0 resection (pathologically negative margins of resection) and 2 patients initially thought to be unresectable were able to have complete resections.

Other agents that have demonstrated radiosensitization properties such as paclitaxel, rubitecan, and cisplatin have all been tested in combination with radiation with or without other chemotherapy agents.\textsuperscript{16–18,29,30} Newer studies are being designed to incorporate cetuximab, bevacizumab, and other growth-factor and cell-signal inhibitors that may have radiation sensitization properties.

**Conclusions About Therapy for Locally Advanced Disease**

Due to the conflicting results obtained in 3 randomized trials, it is still not clear whether radiation is an essential element of treatment for patients with locally advanced pancreatic cancer. Because of that uncertainty, the current Intergroup study E4201, a phase III trial comparing gemcitabine alone to gemcitabine and radiation therapy for locally advanced disease patients, is a critical study. It will define the current role of radiation therapy for patients with inoperable disease that is not metastatic.

In any discussion of locally advanced pancreatic cancer, it is important to recognize that the determination of
operable vs inoperable disease may be surgeon dependent. There are, in fact, probably different levels of unresectability. Patients with tumors completely encasing the vasculature may differ from those who have tumors that abut the major vessels. ECOG 1200 is a randomized phase II trial that seeks to identify patients with “borderline” unresectable tumors. These patients are randomized to 1 of 2 chemoradiation regimens and reevaluated for surgery. The primary end point of this study is to determine which, if either, of the regimens is capable of converting patients with surgically unresectable disease to fully resectable disease.

Chemotherapy for Advanced Disease

Metastatic pancreatic cancer tends to be a rapidly progressing disease, often accompanied by a constellation of debilitating symptoms. More than half of all patients with advanced pancreatic cancer suffer from weight loss, visceral abdominal pain, anorexia, nausea, and/or depression. Although no curative treatment exists for this group of patients, newer systemic therapies have emerged over the past decade that provide meaningful alleviation of tumor-related symptoms and prolong survival.

Gemcitabine

Gemcitabine is a nucleoside analogue that is sequentially phosphorylated to gemcitabine triphosphate and incorporated into replicating DNA, resulting in premature chain termination and apoptosis. Although significant tumor shrinkage (ie, ≥50% tumor shrinkage) was achieved in only 5% of patients, a substantial subset of patients had significant and sustained alleviation of tumor-related symptoms. As a result of these observations, a pivotal phase III trial was designed to capture prospectively and quantify this effect in a cohort of patients with metastatic, symptomatic pancreatic cancer. One hundred twenty-six patients who had not received prior chemotherapy for metastatic disease were randomized to weekly gemcitabine (n = 63) or weekly bolus 5-FU (n = 63). Overall survival in patients treated with gemcitabine was significantly improved compared with patients treated with 5-FU (median survival, 5.7 vs 4.4 months respectively; P = .0025). The 1-year survival rates were 18% for patients treated with gemcitabine vs 2% in patients treated with 5-FU. The primary efficacy measure in this study was clinical benefit response, defined as a significant reduction in 1 or more of these measures lasting for at least 4 weeks without deterioration in another parameter, was experienced by 24% of the patients treated with gemcitabine compared with only 5% of the patients treated with 5-FU (P = .0022). Clinical benefit response was seen in some patients who did not achieve a radiologic response, demonstrating that patients could have an improvement in symptoms while on chemotherapy for a highly symptomatic disease without tumor shrinkage. Additional randomized studies have since confirmed the efficacy of single-agent gemcitabine.

More recent clinical trials with single-agent gemcitabine have focused on the optimal administration of this prodrug. As noted previously, one of the main mechanisms of action of gemcitabine is impairment of DNA synthesis. The rate-limiting enzyme in this process, deoxycytidine kinase, appears to be saturable. The ability of deoxycytidine kinase to activate gemcitabine may be overwhelmed by the standard dosing administration of 1000 mg/m2 over 30 minutes. Based on preclinical models, an alternative method for administration of gemcitabine, termed “fixed-dose rate infusion,” administers the drug at a rate of 10 mg/m2/ min (using current dosing, this works out to be 1500 mg/m2 over 150 minutes). A randomized phase II trial in advanced pancreatic cancer demonstrated that those patients administered gemcitabine by fixed dose rate had 3-fold higher levels of gemcitabine triphosphate incorporated into peripheral blood mononuclear cell DNA compared with those given the standard 30-minute infusion and an encouraging 8-month median survival. Fixed-dose rate gemcitabine is now being evaluated in phase III trials against standard single-agent gemcitabine and gemcitabine-based combinations in patients with advanced pancreatic cancer.

5-FU

Prior to the FDA approval of gemcitabine, the antimetabolite 5-FU was considered standard therapy for advanced pancreas cancer. Although response rates up to 26% have been reported for treatment with 5-FU, most of these reports predated the era of CT-imaging and were based primarily on clinical tumor evaluation. More modern phase II trials have reported response rates ≤7% for 5-FU alone or with leucovorin.

Clinical trials comparing 5-FU combination regimens against best supportive care (BSC) demonstrated that the 5-FU regimens conveyed a survival and quality-of-life (QOL) advantage over BSC. Unfortunately, efforts to build on this through the addition of other drugs to 5-FU were unsuccessful. In several phase III trials, combination regimens offered no survival benefit despite
increased toxicity when compared with 5-FU as a single agent.47,48

Recent Phase II and III Clinical Trials in Metastatic Pancreatic Cancer

The FDA approval of gemcitabine for the treatment of patients with advanced pancreatic cancer in 1996 was a major step forward in the treatment of this disease. However, the 1-year survival rate was only 18%, indicating that metastatic pancreatic cancer remains a devastating illness. Several recent clinical trials in patients with metastatic pancreatic cancer have tried to improve on the clinical outcomes of these patients (Table 2). The design of these trials falls into 2 broad categories: comparison of the new agent directly against gemcitabine or combination of the new agent with gemcitabine.

Gemcitabine Combined With Chemotherapy

Antimetabolites. Results from the randomized studies comparing 5-FU to gemcitabine as single agents have been described in prior sections. As far as studies combining gemcitabine with 5-FU, 3 phase II trials evaluated a combination of gemcitabine with bolus 5-FU, with or without the biochemical modifier leucovorin.49–51 Median survival times in these studies varied from 4.3 to 11 months and prompted a phase III ECOG sponsored study comparing gemcitabine alone to gemcitabine and 5-FU. Although the combination regimen demonstrated a trend toward improved survival (Table 2) for the combination arm (median survival: gemcitabine, 5.4 months vs gemcitabine + 5-FU, 6.7 months), that trend did not reach statistical significance ($P = .09$).38 Although these results were not sufficient to establish the combination of gemcitabine + 5-FU as the new standard for front-line chemotherapy, additional phase III trials were undertaken using different and, possibly superior, 5-FU dosing strategies to determine whether survival could be meaningfully increased over single-agent gemcitabine. The results of those trials are pending.

Another antimetabolite tested in pancreas cancer is the multitargeted antifolate, pemetrexed (Alimta). In addition to thymidylate synthase, pemetrexed also inhibits dihydrofolate reductase and glycaminamide ribonucleotide formyltransferase, thereby inhibiting purine as well as pyrimidine nucleoside synthesis. Pemetrexed demonstrated provocative antitumor activity in single-agent studies and in phase II trials in combination with gemcitabine.52,53 As single agents, there have been no reported randomized studies comparing pemetrexed with gemcitabine, but a phase III study comparing the combination of gemcitabine and pemetrexed with gemcitabine alone enrolled over 450 patients in a randomized design (Table 2).54 Patients in the pemetrexed plus gemcitabine arm had a significantly higher response rate (18.3% vs 9.1%, respectively, $P = .006$) and a longer time to tumor progression (5.2 months vs 3.6 months, respectively, $P = .042$). However, the overall survival was unchanged between the 2 treatment arms (6.2 months vs 6.3 months, respectively), and, unfortunately, neutropenia was significantly higher in the gemcitabine plus pemetrexed arm (45.1% vs 12.8%, respectively, $P < .001$). Therefore, this treatment approach has not been adopted as a standard therapy.

Topoisomerase I Inhibitors. The camptothecin-derived topoisomerase I inhibitors exatecan, irinotecan, and rubitecan have all demonstrated response rates and survival times of approximately 10% and 5–6 months, respectively, in phase II clinical trials in patients with
advanced pancreatic cancer. There have been no reported randomized studies comparing irinotecan with gemcitabine as single agents. In a combination study, a phase III clinical trial randomly assigned patients to either a combination of irinotecan and gemcitabine (n = 173) or gemcitabine (n = 169) alone. Tumor response rates were 16.1% for the combination therapy vs 4.4% for gemcitabine alone (P < .001). Unfortunately, there was no significant difference between the 2 treatments in the parameters of median time to tumor progression (3.5 months vs 3.0 months, respectively) or median survival (6.3 months vs 6.6 months, respectively).

A recently reported phase III study compared single-agent exatecan head-to-head against gemcitabine (Table 2). In this comparison, exatecan was inferior to gemcitabine as far as time to tumor progression, 12 month survival, overall survival, and in quality-of-life measures. Another recently reported randomized phase III study involving exatecan compared the combination of exatecan and gemcitabine with gemcitabine alone. The study evaluating the combination regimen showed similar response rates between the 2 regimens, with the exatecan plus gemcitabine arm having a slightly higher response rate (8.2% vs 6.3%, respectively). However, the time to tumor progression, as well as the overall survival, was essentially unchanged. Patients in the gemcitabine plus exatecan treatment arm had greater frequency of grade 3 and 4 toxicities, including neutropenia, thrombocytopenia, and nausea/vomiting, than those who received single-agent gemcitabine.

In vitro models suggest that platinum agents have significant, nonschedule-dependent synergy when combined with gemcitabine. Cisplatin has been shown to have some antitumor activity in pancreas cancer, both as single agent and in combination with gemcitabine, but a randomized study comparing single-agent cisplatin vs gemcitabine has not been reported. A phase III trial comparing gemcitabine alone with gemcitabine and cisplatin (Table 2) demonstrated a longer time to tumor progression for the gemcitabine and cisplatin arm compared with gemcitabine alone (20 weeks vs 8 weeks, respectively, P = .048). Similarly, the response rate was improved for gemcitabine and cisplatin when compared with gemcitabine alone (26.4% vs 9.2%, respectively, P = .02). However, median survival times were not significantly different in the 2 arms.

Another platinum agent, oxaliplatin, has not been compared with gemcitabine as a single agent but has demonstrated encouraging response rates (30.6%) and median (9.2 months) and 1-year survival times (36%) in a phase II trial when administered along with gemcitabine and prompted a phase III study of this combination regimen. The subsequent European GERCOR phase III study compared gemcitabine and oxaliplatin with gemcitabine alone (Table 2). The combination arm demonstrated a significantly improved response rate of 28.7% vs 16.7% (P = .02) for treatment with gemcitabine alone. Progression-free survival was also improved, with the gemcitabine plus oxaliplatin treatment group having a 5.5-month progression-free survival vs 3.7 months for gemcitabine alone (P = .04). The overall survival for gemcitabine plus oxaliplatin was 9 months vs 7 months for gemcitabine alone, a difference that did not reach statistical significance (P = .13). This regimen has not replaced single-agent gemcitabine as standard therapy, but the results have been encouraging enough to warrant continuing investigation in cooperative group studies combining oxaliplatin with fixed-dose rate infusion gemcitabine and comparing it with standard gemcitabine alone or in a fixed-dose rate infusion (E6201).

Taxanes. The available taxanes, paclitaxel (Taxol) and docetaxel (Taxotere), have been tested in phase II as first-line therapy for pancreas cancer as single agents or in combination with gemcitabine with varying success. As single agents, the taxanes have very limited or no significant clinical activity. The objective response rates in 2 studies combining gemcitabine and docetaxel were 12% and 18%, respectively, and the median survivals were 4.7 and 8.9 months, respectively. Unfortunately, hematologic toxicities have been prohibitive in most of these trials, and investigations of these regimens have been limited, with no phase III studies reported with either of the taxanes as single agents or in combination with gemcitabine.

Gemcitabine Combined With Molecularly Targeted Agents

Over the past several years, agents have been developed to exploit specific molecular targets in the tumor cell or in the tumor microenvironment. Incorporating these targeted therapies into standard treatment regimens have yielded clinical benefits in other malignancies, including breast, lung, and colorectal cancer, and have therefore generated interest in the evaluation of these agents against pancreatic cancer. Enthusiasm about targeted therapy in pancreatic cancer is somewhat tempered by the previous failure of matrix metalloproteinases (proteins that regulate tumor invasion, metastasis, and angiogenesis) and farnesyl transferase (inhibitors that prevent K-ras activation and K-ras-mediated cellular proliferation) to improve clinical outcomes in phase III clinical trials.
Antiangiogenic Agents

Tumor angiogenesis is a complex and dynamic process involving factors essential for the development of new tumor blood vessels, tumor growth, and metastasis. Angiogenesis has been shown to be predictive for prognosis or clinical stage in most solid tumors that have been assessed, and the rationale for antiangiogenic approaches as an anticancer strategy has been extensively reviewed.

Bevacizumab (Avastin) is a recombinant humanized monoclonal antibody to vascular endothelial growth factor subtype A (VEGF-A) that has undergone extensive clinical evaluation. Bevacizumab was approved by the FDA in 2004 for the treatment of advanced colorectal cancer and has shown promise in the treatment of renal cell cancer. A phase II study of gemcitabine and bevacizumab recently reported provocative and encouraging results, including a median survival of 8.7 months and a 1-year survival of 29%, which would be modestly greater than the generally accepted median survival and 1-year survival for gemcitabine alone. Nineteen percent of the patients on this treatment demonstrated a response to therapy. A larger phase III study (CALGB 80303) comparing gemcitabine alone vs gemcitabine + bevacizumab is accruing patients to try to confirm these results.

EGF Tyrosine Kinase Receptors

Epidermal growth factor receptor (EGFR; HER-1) is a member of the HER family of tyrosine kinase growth factor receptors and is a potent stimulator of cell growth. The importance of EGFR in tumor progression has been extensively reviewed. The binding of molecules (ligands) to the receptor leads to receptor homodimerization or heterodimerization with another HER family receptor, receptor activation through phosphorylation, and a cascade of intracellular signals, eventually resulting in the promotion of cancer cell growth and proliferation. Two main targeting strategies have been developed to block activation of the EGFR axis: antibodies to EGFR to block ligand binding and receptor activation or small molecule tyrosine kinase inhibitors (TKIs) that inhibit phosphorylation of the intracellular tyrosine kinase domain and block downstream signaling. Pancreatic cancer is one of many tumors that over-expresses EGFR, thereby making it a rational target for antitumor therapy in this disease. Recently, EGFR-targeted agents, specifically gefitinib (Iressa), erlotinib (Tarceva), and cetuximab (Erbitux), have been FDA approved for the treatment of advanced lung cancers (gefitinib and erlotinib) and advanced colorectal cancers (cetuximab).

A phase II trial was performed of gemcitabine and cetuximab as first-line chemotherapy in patients with
advanced stage pancreatic cancer. Most of the patients screened for this study (89%) had tumors that over-expressed EGFR. The results of this trial were encouraging, with an objective response rate of 12%, a median time to progression of 16 weeks, and a 1-year survival rate of 32%. The Southwest Oncology Group (SWOG) has taken this regimen into phase III trial (S0205) against single-agent gemcitabine in patients with advanced pancreatic cancer.

The small molecule TKI anti-EGFR agents gefitinib (Iressa) and erlotinib (Tarceva) are being evaluated in current clinical trials. In preliminary data available from a study of 569 patients randomized to receive gemcitabine and erlotinib vs gemcitabine and placebo, a small but statistically significant increase in survival was observed in those patients treated with the gemcitabine and erlotinib combination. The death hazard ratio, adjusted for performance status and extent of disease, for the gemcitabine and erlotinib group relative to gemcitabine and placebo group was 0.79 (95% CI: 0.66–0.95, P = .011). The median survival was 6.37 months in the gemcitabine and erlotinib arm and 5.91 months in the gemcitabine and placebo arm. Although the death hazard ratio was reduced by 21% in erlotinib-treated patients, median survival in both arms was modest, and patients treated with erlotinib experienced higher rates of moderate diarrhea and rash than the placebo-treated patients. As a result, the clinical implications of this trial are unclear.

Figure 2. Simplified illustration of a tumor cell depicting the EGFR axis and showing ligand interaction and receptor dimerization leading to tyrosine kinase phosphorylation and activation of intracellular signaling pathways that are important for tumor progression. The sites of action for anti-EGFR monoclonal antibodies and tyrosine kinase inhibitors are depicted.

Conclusion

Although significant advances have occurred in our knowledge of the factors that lead to the development and progression of pancreatic cancer, this knowledge has not yet translated into clinical breakthroughs in this disease. However, the emergence of molecularly targeted agents has led to a dramatic increase in research activity and the number of new clinical trials in patients with all stages of pancreatic cancer. In addition to trying to improve survival, in patients with advanced stage disease, many other clinically important questions remain to be answered, including the role of radiation therapy in the adjuvant and locally advanced stage settings and the optimal drug(s) for use in all stages of disease.

The chemotherapy agent gemcitabine remains a cornerstone of treatment for pancreas cancer. The role of 5-FU and the other cytotoxic therapies need to be defined, and several ongoing randomized trials should provide further insight into the best way to utilize gemcitabine as well as the true efficacy of the other cytotoxic agents as single agents or in combination regimens. The newer treatment paradigms of angiogenesis inhibition and signal transduction inhibition through targeting of the EGFR axis has resulted in clinical benefits for patients with other malignancies, and, as such, they provide optimism about future treatments for pancreatic cancer. The clinical trials of some of the targeted agents have shown results that indicate that these agents may provide an incremental improvement in patient out-
comes. Rationally designed and well-executed clinical trials will be instrumental in improving the outcomes for patients with this devastating disease.

References


