Pancreatic Cancer is refractory to most chemotherapy. For many years, the only active agent for this disease was gemcitabine, which has very modest activity. Two new regimens, gemcitabine plus erlotinib and gemcitabine plus capecitabine, have recently demonstrated statistically significant survival improvements compared with single-agent gemcitabine. Several key negative studies have also been reported recently. This review discusses recent trials that have changed the standard of care for patients with advanced pancreatic cancer.

Introduction

Pancreatic cancer is a nearly universally fatal malignancy with incidence and mortality rates that are almost identical. In 2006 an estimated 33,730 new cases of pancreatic cancer occurred, with 32,300 deaths due to the disease in the United States [1]. Only 1% to 4% of all pancreatic cancer patients survive for 5 years; long-term survival is limited to patients who have resectable tumors. Because symptoms generally arise late, over 80% of patients present with locally advanced or metastatic disease. Their survival is measured in months [2].

For many years, the only drug approved to treat pancreatic cancer was single-agent gemcitabine, which improves quality of life but has relatively modest antitumor activity [3]. Many drug combinations have been tested in this disease. Despite numerous reports of promising activity in phase II studies, until recently no drug has been reported to improve survival in phase III trials [4]. This bleak landscape changed in 2005, when two phase III trials that evaluated the combinations of gemcitabine plus erlotinib and gemcitabine plus capecitabine reported statistically significant improvements in survival over single-agent gemcitabine for patients with advanced disease [5••,6••]. Key negative studies that tested gemcitabine/oxaliplatin, fixed-dose-rate gemcitabine, and gemcitabine/bevacizumab were also reported recently [7••,8]. This review discusses the recent trials that have changed the standard of care for patients with advanced pancreatic cancer.

Single-agent Gemcitabine: The Standard of Care for a Decade

Single-agent gemcitabine, the standard of care in chemotherapy for advanced pancreatic cancer since 1996, produces real but very modest improvements in survival and quality of life. In the pivotal randomized trial reported by Burris et al. [3], 126 patients with advanced pancreatic cancer were randomly assigned to gemcitabine (1000 mg/m² intravenously [IV] over 30 minutes weekly × 4, then weekly for 3 weeks every 4 weeks) or 5-fluorouracil ([5-FU] 600 mg/m² IV bolus weekly). Gemcitabine treatment resulted in an improvement in 1-year (18% vs 2%) and median overall survival (5.7 months vs 4.4 months, \( P = 0.0025 \)). More importantly, patients who received gemcitabine experienced superior clinical benefit (24% vs 5%, \( P = 0.0022 \)), consisting of improvements in pain and performance status and stabilization of weight. In subsequent phase III trials, single-agent gemcitabine has consistently demonstrated a median survival of 5 to 6 months and a 1-year survival rate of about 20% [4].

The Long Search for a Better Regimen

Many cytotoxic and targeted agents have been pitted against or combined with gemcitabine in randomized phase III trials in attempts to improve upon the very modest results achieved with single-agent gemcitabine. Unfortunately, until recently, no drug was shown to be superior to gemcitabine alone. Single agents that have failed to demonstrate an improvement in survival when compared with gemcitabine include the matrix metalloproteinase inhibitors BAY 12-9566 and marimastat and the topoisomerase I inhibitor exatecan [9–11]. Many more drugs have failed to improve survival when they have been added to gemcitabine, including bolus and infusional 5-FU, capecitabine, pemetrexed, irinotecan, exatecan, cisplatin, and oxaliplatin [4,12–19].

In 2005, two randomized phase III trials, which compared single-agent gemcitabine to gemcitabine plus erlotinib and gemcitabine plus capecitabine, respectively, demonstrated a statistically significant advantage in
overall survival for the gemcitabine-containing combinations [5••,6••]. Given so many years of negative results from so many phase III trials, the news that the addition of any agent to gemcitabine could yield a statistically significant improvement in survival in advanced pancreatic cancer was very exciting. The results of these two trials are summarized in Table 1.

With these new data, several questions arise. First, are these improvements in survival clinically meaningful enough to regard either or both as a new standard of care? Is the addition of the new drug worth the added expense and toxicity? Is it still ethical to prescribe single-agent gemcitabine?

The National Cancer Institute of Canada Clinical Trials Group Study: The Gemcitabine/Erlotinib Combination

Up to 90% of pancreatic cancers overexpress the epidermal growth factor receptor (EGFR). In pancreatic cancer patients, coexpression of EGFR and its ligands has been associated with the presence of liver metastases and decreased survival [20]. The EGFR tyrosine kinase inhibitor erlotinib inhibits proliferation of pancreatic cancer cell lines and improves survival in murine pancreatic cancer models [21].

A phase IIb trial of erlotinib in combination with gemcitabine in advanced pancreatic cancer patients demonstrated the safety and tolerability of this combination at both the 100- and 150-mg doses of erlotinib [22]. Partial responses were observed in 7% of the 14 pancreatic cancer patients enrolled, and 64% had stable disease.

The National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) performed a double-blind, placebo-controlled randomized phase III trial that compared gemcitabine plus erlotinib to gemcitabine plus placebo in 569 previously untreated patients with locally advanced or metastatic pancreatic cancer [5••]. Five-hundred twenty-one patients received the 100-mg daily oral dose of erlotinib or placebo, and an additional 48 patients were treated at the 150-mg dose.

The two arms were well balanced for prognostic factors, except that there were more women (52% vs 43%) on the erlotinib arm. The objective response rates of 8.6% for erlotinib plus gemcitabine and 8% for the placebo arm were not significantly different. Median survival was 6.37 months for the experimental arm versus 5.91 months for the control arm, which corresponds to a hazard ratio (HR) of 0.81 (P=0.025). The 1-year survival rates were 24% versus 17%, respectively. Median progression-free survival durations were 3.75 and 3.55 months for the erlotinib and placebo arms, respectively (HR of 0.76, P=0.003).

As expected, rash, diarrhea, infection, stomatitis, and pneumonitis were greater on the erlotinib-containing arm. Quality of life, evaluated by the European Organization for Research and Treatment of Cancer (EORTC) QLQ-c30, demonstrated no differences in any domains, including global quality of life, except for a significant difference in favor of the placebo arm for diarrhea (P<0.001).

Fifty-three percent of patients were EGFR positive by immunohistochemistry. There was no difference in survival by EGFR status. EGFR mutation status has not yet been reported in this study; however, other investigators have observed that these mutations occur very rarely in pancreatic adenocarcinomas [23,24].

Interestingly, those patients on either arm who developed a grade 2 or greater rash had statistically significantly longer survival (P<0.0001) than those who experienced a grade 0 or 1 rash. The 79 patients who did not develop any rash had a median survival of 5.29 months and a 1-year survival rate of 16%, compared with a median survival of 10.51 months and a 1-year survival rate of 43% for the 103 patients who developed a grade 2 or greater rash.

This NCIC-CTG study is important because it was the first randomized trial to demonstrate that any drug added to gemcitabine could prolong survival in pancreatic cancer patients. These data led to the US Food and Drug Administration (FDA) approval of erlotinib for pancreatic cancer in 2006. Although statistically significant, the survival benefit is still modest, and the overall impact on clinical practice remains uncertain. One of the key questions concerns the cost-effectiveness of this regimen. The retail cost of 6 months of erlotinib is $16,613. Given an increase in median survival of 0.4 months over single-agent gemcitabine, the retail cost of the addition of erlotinib per year of life gained is $498,379. Thus, adding erlotinib to gemcitabine does not approach cost-effectiveness at even the highest year-per-life gained parameters [25•].

The National Cancer Research Network Upper Gastrointestinal Cancer Clinical Study Group Trial

The National Cancer Research Network (NCRN) Upper Gastrointestinal Cancer Clinical Study Group reported the preliminary results of a randomized phase III trial that compared gemcitabine plus capecitabine (GEM-CAP) to gemcitabine monotherapy [6••]. Five hundred thirty-three previously untreated advanced pancreatic cancer patients received either gemcitabine (1000 mg/m² IV over 30 minutes weekly for 3 weeks every 4 weeks) plus capecitabine (1660 mg/m² daily for 21 days every 28 days) or gemcitabine alone (1000 mg/m² IV over 30 minutes weekly x 4, then weekly for 3 weeks every 4 weeks).

Randomization was stratified by disease extent (locally advanced vs metastatic) and performance status (0, 1 vs 2). The two arms were well-balanced for prognostic factors. The objective response rate of 14.2% for GEM-CAP was statistically superior to the 7.1% observed for single-agent gemcitabine (P=0.008). Median survival was 7.4 months...