Treatment of Metastatic Pancreatic Adenocarcinoma: A Review

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Gemcitabine monotherapy has been the standard of care for patients with metastatic pancreatic cancer for several decades. Despite recent advances in various chemotherapeutic regimens and in the development of targeted therapies, metastatic pancreatic cancer remains highly resistant to chemotherapy.

Introduction

Metastatic pancreatic cancer is one of the most aggressive and highly lethal malignancies, with an estimated 5-year survival of less than 5%. In 2013, approximately 45,000 new cases and 38,000 deaths were attributable to pancreatic cancer in the United States alone. The overall median survival is less than 1 year from diagnosis, highlighting the need for the development of newer therapeutic options.[1]

Despite recent advances in chemotherapeutics and in our understanding of the molecular biology of pancreatic cancer, there has been limited progress in therapeutic options for metastatic disease. Over the past 4 decades, studies of several combination therapies have demonstrated minimal or no survival benefit compared with gemcitabine alone. Gemcitabine monotherapy had been the standard of care for patients with metastatic pancreatic cancer for several years, until combination therapy with gemcitabine plus erlotinib was shown to increase median survival by 2 weeks.[2,3] However, the modest survival benefit was tempered by a significant side effect profile and the high cost of treatment. Later, the multidrug combination of leucovorin, fluorouracil, irinotecan, and oxaliplatin (FOLFIRINOX) was noted to provide an increased median survival of 4.3 months; however, given its side effect profile, it is available only to a select group of patients with advanced pancreatic cancer.[4] Recently, the gemcitabine plus nab-paclitaxel combination was shown to increase median survival by 1.8 months, with increased overall survival at 1 and 2 years; adverse effects were reasonable and included cytopenias and peripheral neuropathy.[5]

The current National Comprehensive Cancer Network recommendations suggest acceptable chemotherapy combinations for patients with good performance status (ie, Eastern Cooperative Oncology Group performance status [ECOG PS] of 0 or 1), good pain management, patent biliary stent, and adequate nutritional intake; these combinations include FOLFIRINOX, gemcitabine plus nab-paclitaxel, and gemcitabine plus erlotinib. The only recommended option for patients with poor performance status is gemcitabine monotherapy.[6] The guidelines for choosing an appropriate treatment regimen for patients with metastatic pancreatic cancer thus remain ambiguous, and in the absence of a randomized trial comparing the combination regimens head to head, the dilemma remains regarding appropriate first-line therapy for these patients. Hence, in this review we discuss in detail the efficacy and toxicities of four treatment choices: gemcitabine alone, gemcitabine plus erlotinib, FOLFIRINOX, and gemcitabine plus nab-paclitaxel.

Gemcitabine Monotherapy

Gemcitabine is a pyrimidine analog that is phosphorylated to diphosphate and triphosphate forms to inhibit both ribonucleotide reductase and DNA polymerase. It was initially approved by the US Food and Drug Administration (FDA) in 1997 for the first-line treatment of pancreatic cancer on the basis of work by Burris et al. In a randomized trial of 126 patients with advanced pancreatic cancer, 63 patients were treated with gemcitabine at 1,000 mg/m² weekly for 7 weeks followed by 1 week of rest then weekly for 3 of every 4 weeks thereafter, and 62 patients were treated with fluorouracil, 600 mg/m² once weekly. The gemcitabine group showed improved median overall survival (5.6 vs 4.4 months) and 1-year survival (18% vs 2%) and a better overall response rate (24% vs 5%) compared with the fluorouracil group.[2] Gemcitabine monotherapy is generally well tolerated; the most frequent adverse effect is grade 3/4 neutropenia.
Further studies conducted to evaluate any improvement in survival with the fixed-dose-rate infusion regimen did not show any significant difference in survival benefit. The US Intergroup study of 832 patients with advanced pancreatic cancer compared standard-dose gemcitabine (1,000 mg/m² over 30 minutes weekly for 7 of 8 weeks, then for 3 of every 4 weeks) vs fixed-dose-rate gemcitabine (1,500 mg/m² over 150 minutes weekly for 3 of every 4 weeks) vs combined fixed-dose-rate gemcitabine plus oxaliplatin. Compared with standard-dose gemcitabine alone, there was no significant difference in response rates with the fixed-dose-rate regimen (10% vs 5%, respectively), and there was only a small trend toward improvement in median survival (6.2 vs 4.9 months; hazard ratio = 0.83; \( P = .05 \)).[7] In the absence of strong evidence for significant improvement in survival with the fixed-dose regimen, standard-dose gemcitabine has been most commonly used in clinical practice.

Since the initial approval of gemcitabine for management of advanced pancreatic cancer, studies of several combination regimens with many other active cytotoxic agents, including fluorouracil, capecitabine, cisplatin, docetaxel, oxaliplatin, irinotecan, cetuximab, and pemetrexed, have shown no significant survival benefit.[7-14]

**Gemcitabine Plus Erlotinib**

Almost a decade after the initial approval of gemcitabine by the FDA, a Canadian phase III trial compared gemcitabine (1,000 mg/m² weekly) with and without erlotinib (100 mg daily) in 569 patients with locally advanced or metastatic pancreatic cancer. This study showed positive results; combination therapy was associated with significantly better overall survival compared with gemcitabine alone (hazard ratio = 0.81; \( P = .038 \); median survival, 6.2 vs 5.9 months; 1-year survival, 23% vs 17%, respectively).[3] There was a slight increase in the incidence of grade 3/4 rash and diarrhea (6% vs 1%) in the erlotinib group, but there was no overall difference in quality of life scores between the two groups. Nevertheless, the cost per life year gained was significantly higher than is usually accepted; hence, the modest 2-week improvement in survival remains a source of debate.[15,16]

Recently, Miyabayashi et al found that erlotinib may attenuate mitogen-activated protein kinase signaling induced by gemcitabine.[17] Their results suggest that gemcitabine induces epidermal growth factor receptor (EGFR) ligand expression and that erlotinib inhibits subsequent heterodimerization of EGFR with ERBB2. In a murine model of pancreatic ductal adenocarcinoma, the investigators showed that gemcitabine plus erlotinib was superior to gemcitabine alone, with improved survival and blocked progression of disease.

**FOLFIRINOX**

The efficacy and safety of the combination chemotherapy regimen FOLFIRINOX were compared with that of gemcitabine alone in a phase III trial (ACCORD 11).[4] A total of 342 chemotherapy-naive patients with metastatic pancreatic cancer, an ECOG PS of 0 or 1, and a serum bilirubin level < 1.5 times the upper limit of normal were randomly assigned to gemcitabine alone (1,000 mg/m² weekly for 7 weeks, followed by 1 week of rest, then weekly for 3 of every 4 weeks) or FOLFIRINOX (leucovorin at 400 mg/m², fluorouracil at 400 mg/m², irinotecan at 180 mg/m², and oxaliplatin at 85 mg/m² given as a bolus, followed by 2,400 mg/m² given as a 46-hour continuous infusion, every 2 weeks). The median overall survival, progression-free survival (PFS), and objective response rate were significantly higher with FOLFIRINOX compared with gemcitabine alone (median overall survival, 11.1 vs 6.8 months; PFS, 6.4 vs 3.3 months; objective response rate, 32% vs 9%). However, treatment-related toxicity was also significantly higher with FOLFIRINOX, including grade 3/4 neutropenia (46% vs 21%), febrile neutropenia (5.4% vs 1.2%), thrombocytopenia (9.1% vs 3.6%), sensory neuropathy (9% vs 0%), vomiting (15% vs 8%), fatigue (23% vs 18%), and diarrhea (13% vs 2%). Still, despite the greater toxicities, FOLFIRINOX significantly improved survival compared with gemcitabine alone, with a median increase in survival of 4.3 months.

**Gemcitabine Plus Nab-Paclitaxel**

Overexpression of secreted protein acidic and rich in cysteine (SPARC, an albumin-binding protein, also known as osteonectin and basement membrane 40) in stromal fibroblasts within the pancreatic microenvironment is considered an important cause of chemotherapy resistance and is associated with a poor prognosis.[18,19] SPARC has been suggested to have divergent and even contradictory
roles in various other cancers; it has been implicated in tumor progression, suppression, and metastasis, depending on cancer type. In a detailed review, Tai and Tang proposed that post-translational modifications, including variable proteolysis of the larger SPARC protein, may explain the specific but varying roles suggested by studies that have used different methodologies in assessing or inferring protein function.[20] Targeting SPARC in tumors that overexpress the protein (including pancreatic, breast, and lung cancers, and melanoma) has been shown to have antitumor effects.

Because paclitaxel is a hydrophobic, lipophilic molecule, it is available for parenteral administration in a variety of formulations, including polyoxyethylated castor oil (Cremophor EL, or CreEL), nanoparticle albumin-bound, cationic liposomal, and polymeric micelle formulations.[21-24] The albumin-bound formulation (also known as nab-paclitaxel, or ABI 007) is a solvent-free, colloidal suspension, 130-nm particle form of paclitaxel homogenized with human serum albumin. It has several favorable pharmacokinetic properties, such as larger volume of distribution, higher fraction of unbound drug, and more rapid clearance than other formulations of paclitaxel.[25] In vitro experiments have shown that nab-paclitaxel is four times more efficient than CreEL paclitaxel in crossing layers of endothelial cells.[26]

Nab-paclitaxel binds to albumin receptor binding site gp60 on endothelial cells and activates caveolin-1 and caveolae formation, leading to extracellular transport of drug into the interstitial space, where it binds to SPARC.[26] This gp60/caveolin-1/caveolae/SPARC pathway is a unique mechanism of delivery, enabling higher drug concentrations in close proximity to tumor cells. The favorable pharmacokinetic properties of nab-paclitaxel and receptor-mediated delivery of a higher concentration of drug with rapid clearance contribute to fewer adverse effects than are seen with the CreEL formulation at a similar dose of paclitaxel.[22]

Nab-paclitaxel was initially approved by the FDA in January 2005 for use in metastatic breast cancer after progressive disease following chemotherapy or relapse within 6 months of adjuvant chemotherapy,[27] and in October 2012 it was approved for use in metastatic non–small-cell lung cancer.[28] Preclinical studies have shown that nab-paclitaxel binds to SPARC, causing stromal depletion and an increase in vascularity around the tumor, thereby resulting in higher gemcitabine concentrations within the tumor. The bioavailability and intratumoral concentrations of paclitaxel as nab-paclitaxel have also been shown in preclinical studies to be higher than those achieved with the CreEL formulation. The combination of nab-paclitaxel and gemcitabine resulted in a 2.8-fold increase in gemcitabine concentration compared with gemcitabine alone, and regression occurred in 64% of tumors vs 36% and 18% with nab-paclitaxel and gemcitabine monotherapy, respectively, in primary patient-derived xenograft models.[29] In the phase I/II study conducted in patients with previously untreated metastatic pancreatic cancer, 44 patients who received the maximally tolerated dose (gemcitabine at 1,000 mg/m² followed by nab-paclitaxel at 125 mg/m² on days 1, 8, and 15 of every 28-day cycle) had a response rate of 48% and a median survival of 12.2 months. At this dose, grade 3/4 toxicities included fatigue in 27% of participants, neuropathy in 20%, and neutropenia in 49%. The superiority of the combination regimen was later confirmed in the multinational phase III Metastatic Pancreatic Adenocarcinoma Clinical Trial (MPACT) that included 861 patients with previously untreated metastatic pancreatic adenocarcinoma.[5] Combination therapy was associated with a significantly higher objective response rate (23% vs 7%) and significantly longer median overall survival (8.5 vs 6.7 months) and PFS (5.5 vs 3.7 months) compared with gemcitabine monotherapy. Grade 3/4 adverse events that occurred more often with combination therapy than with gemcitabine alone included neutropenia (38% vs 27%), febrile neutropenia (3% vs 1%), fatigue (17% vs 7%), diarrhea (6% vs 1%), and neuropathy (17% vs 1%). In September 2013, nab-paclitaxel in combination with gemcitabine was approved by the FDA for the first-line treatment of patients with metastatic adenocarcinoma of the pancreas.

The synergistic effect of nab-paclitaxel and gemcitabine is attributable to several factors, including its favorable pharmacokinetic properties that enable delivery of a higher dose of paclitaxel, which not only is directly cytotoxic but also raises intratumoral gemcitabine accumulation through the depletion of the stromal matrix and increases in tumor microvasculature. In addition to SPARC-mediated stromal depletion, inactivation of cytidine deaminase (an important enzyme in gemcitabine inactivation) by nab-paclitaxel also potentiates the efficacy of gemcitabine.[30] Table 1 compares the survival metrics and toxicity profiles of the three major positive trials in advanced pancreatic cancer. Table 2 represents a cost and quality-of-life analysis based on data from Canada’s public health-care system, which suggests that FOLFIRINOX is more cost-effective than gemcitabine or gemcitabine plus nab-paclitaxel in patients with metastatic pancreatic cancer.[31] The cross-trial comparisons in Table 1 lack the validity of a randomized trial, although it
is notable that gemcitabine monotherapy is very similar in its response rates (8%, 9.4%, and 7%), median overall survival durations (5.9, 6.8, and 6.7 months), and median PFS durations (3.6, 3.3, and 3.7 months) across the various studies. The median overall survival duration with FOLFIRINOX in the ACCORD 11 trial was 11.1 months, while it was 8.5 months for gemcitabine plus nab-paclitaxel in the MPACT trial and 6.24 months for gemcitabine plus erlotinib. Although this appears to suggest the superiority of FOLFIRINOX over gemcitabine plus nab-paclitaxel in overall survival, the differences in the trials make it impossible to make this claim. Therefore, both FOLFIRINOX and gemcitabine plus nab-paclitaxel are reasonable choices for first-line therapy in patients with good performance status (ECOG PS 0 or 1). The combination of gemcitabine and nab-paclitaxel is an option for those with modest performance status who cannot tolerate a FOLFIRINOX regimen.

Conclusions

In the past few years, two new and more effective chemotherapy regimens (FOLFIRINOX and gemcitabine plus nab-paclitaxel) have demonstrated improved survival over single-agent gemcitabine in patients with metastatic pancreatic adenocarcinoma. However, median survival rates are still < 1 year; thus, more effective therapies are needed. In addition, all advances so far have been with the use of chemotherapy. Molecularly targeted therapies and immune mediators are being tested in pancreatic cancer and may be able to further alter the natural history of this disease.

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