Current Standards of Chemotherapy for Pancreatic Cancer

May Tun Saung, MD; and Lei Zheng, MD, PhD

The Sidney Kimmel Comprehensive Cancer Center, Department of Oncology, The Johns Hopkins University School of Medicine, Baltimore, Maryland

ABSTRACT

Purpose: Pancreatic cancer has a dismal prognosis due to the early development of systemic metastatic disease. Chemotherapeutic agents are the only systemic therapy that offers patients meaningful benefit.

Methods: This study reviewed the literature for recently published Phase III clinical trials whose results have guided the current standards of chemotherapy for pancreatic cancer.

Findings: Although combination chemotherapy regimens are shown to be superior to gemcitabine monotherapy for both metastatic pancreatic cancer and adjuvant chemotherapy after surgical resection, it should be recognized that all combination chemotherapy regimens offer only limited benefits. In addition, there is a paucity of clinical trials that directly compare the various combination chemotherapy regimens.

Implications: With the advancement of systemic cancer treatment beyond chemotherapy, it is important to devote more investigation into better understanding the biology of these chemotherapy regimens, such that we combine them with targeted therapeutics and immunotherapeutics in a rational and scientific manner. For the current treatment of pancreatic cancer, the available chemotherapy regimens have shown modest but statistically significant improvements in survival. However, it is important to avoid cross-comparisons of trials and choose regimens based on patient characteristics and the side-effect profiles of the regimen. (*Clin Ther*. 2017;▮:▮▮▮–▮▮▮)

Key words: adjuvant, capecitabine, FOLFIRINOX, gemcitabine, liposomal irinotecan metastatic, nab-paclitaxel, pancreatic cancer.

INTRODUCTION

Although pancreatic cancer is the tenth most common cancer among men and eleventh in women, it is the fourth leading cause of cancer death in the United States.[1] Its incidence is also increasing. Over a span of 5 years, from 2009 to 2013, the average annual percentage change in incidence increased by 1% among men and by 1.1% among women. There has been very limited progress in the treatment of pancreatic cancer over the last few decades, with its 5-year survival rate increasing from 2.5% (95% CI, 2.0–3.0) in 1975–1977 to 8.5% (95% CI, 8.0–9.0) in 2006–2012. It is therefore projected to become the second leading cause of cancer mortality before 2030 due to improving therapies for other cancers compared with those for pancreatic cancer.[2] One of the major reasons for the dismal prognosis of pancreatic cancer is its early development of systemic metastatic disease. Although enormous efforts have been enlisted in developing innovative therapies, chemotherapeutic agents are essentially the only systemic treatment that is proven to be effective and also offers a meaningful, albeit limited, prolongation of patients' lives.

The goal of the present review was to discuss the current standards of chemotherapy for pancreatic adenocarcinoma.

FIRST-LINE SYSTEMIC TREATMENT FOR ADVANCED PANCREATIC CANCER

Most patients diagnosed with pancreatic cancer have advanced disease, and their estimated 5-year survival rate is dismal. For the 29% who are diagnosed with regional disease (ie, regional lymph node involvement),[3] the 5-year survival is 10%.[4] Fifty-two percent have distant metastases at diagnosis,[3] and their 5-year survival plummets to 2%.[4]

Accepted for publication August 24, 2017.
http://dx.doi.org/10.1016/j.clinthera.2017.08.015
0149-2918/$ - see front matter

The single agent gemcitabine had been a standard-of-care first-line treatment for advanced pancreatic cancer for >2 decades[5] until the PRODIGE[6] and MPACT (Metastatic Pancreatic Adenocarcinoma *Clinical Trial)*[7] clinical trials showed that 2 combination chemotherapy regimens, FOLFIRINOX and gemcitabine/nab-paclitaxel, respectively, achieved higher response rates and longer median overall survival than gemcitabine (**Table I**). These 2 combination chemotherapy regimens are the 2 current standard-of-care first-line treatment regimens for advanced pancreatic cancer. They have also become the chemotherapy regimens of choice for neoadjuvant therapy for borderline resectable pancreatic cancer or locally advanced pancreatic cancer.

FOLFIRINOX

FOLFIRINOX, the *5-fluorouracil (5*-FU), leucovorin, irinotecan, and oxaliplatin combination, was chosen based on preclinical[8–12] and clinical[13–15] studies, suggesting synergy between the different therapies and nonoverlapping toxic effects of the drugs. PRODIGE[6] was a Phase II/III, open-label trial that compared FOLFIRINOX with gemcitabine (171 evaluable patients in each arm) for the treatment of patients with advanced pancreatic cancer. FOLFIRINOX increased the median overall survival by 4.3 months (11.1 vs 6.8 months; hazard ratio [HR], 0.57 [95% CI, 0.45–0.73]; $P < 0.001$). This outcome was in contrast to the modest improvement in overall survival of 0.33 month with the gemcitabine/erlotinib combination, the only regimen before FOLFIRINOX that improved survival compared with gemcitabine (median overall survival of 6.24 months with gemcitabine/erlotinib and 5.91 months with gemcitabine).[16,17] Analysis indicated that the survival benefit of FOLFIRINOX was not due to use of subsequent second-line therapy. All subgroups favored FOLFIRINOX for improved survival, except for those with metachronous metastases, ≥3 metastatic sites, or a biliary stent, which favored gemcitabine monotherapy.

FOLFIRINOX is notable for its higher incidence of grade 3 to 4 adverse events, including neutropenia (45.7% vs 21.0%), febrile neutropenia (5.4% vs 1.2%), thrombocytopenia (9.1% vs 3.6%), diarrhea (12.7% vs 1.8%), and peripheral neuropathy (9% vs 0%) compared with gemcitabine. However, despite higher rates of grade 3 to 4 toxicity, the initial analysis[6] found that the quality of life was not statistically different during the first 8 cycles of FOLFIRINOX treatment. At 6 months, 31% of patients in the FOLFIRINOX arm had a decrease in quality of life scores compared with 66% in the gemcitabine arm (HR, 0.47 [95% CI, 0.3–0.7]; $P < 0.001$). Subsequent analysis indicated that there was a statistically significant improvement in quality of life with FOLFIRINOX compared with gemcitabine.[18] This result suggested that disease progression affected the quality of life in patients with advanced pancreatic cancer more than the toxicity of chemotherapy.

Gemcitabine/Nab-Paclitaxel

MPACT was a Phase III, open-label trial in which 431 patients were randomized to receive gemcitabine/nab-paclitaxel, and 430 were randomized to receive gemcitabine alone.[7] The median overall survival was 8.5 months (95% CI, 7.89–9.53) with gemcitabine/nab-paclitaxel compared with 6.7 months (95% CI, 6.01–7.23) with gemcitabine, with an HR for death of 0.72 (95% CI, 0.62–0.83; $P < 0.001$). Analysis also showed that the survival benefit of gemcitabine/nab-paclitaxel was not due to use of subsequent second-line therapy. Patients with more advanced disease benefited from the combination treatment (ie, those with metastatic disease at initial diagnosis, liver metastasis, >3 metastatic sites, carbohydrate antigen 19-9 concentration at or >59 times the upper limit of normal). There was a trend toward improvement in survival with gemcitabine/nab-paclitaxel compared with gemcitabine alone for those patients aged ≥65 years.

Among the common grade 3 or higher adverse events, the gemcitabine/nab-paclitaxel arm experienced more neutropenia (38% vs 27%), febrile neutropenia (3% vs 1%), fatigue (17% vs 7%), peripheral neuropathy (17% vs 1%), and diarrhea (6% vs 1%) than the gemcitabine arm.[7] However, there were no grade 4 neuropathies in either arm. Neuropathy was cumulative and reversible for most patients after temporary discontinuation of treatment, and some patients could restart therapy at a reduced dose of nab-paclitaxel. Thus, neuropathy caused by gemcitabine/nab-paclitaxel seems to be better tolerated than that caused by FOLFIRINOX.