Case Report

Gemcitabine plus Nab-Paclitaxel with chemoradiation in locally advanced pancreatic cancer (LAPC)

Olugbenga Olowokure, Maria Patricia Torregroza-Sanchez, Ivan Dario Bedoya-Apraez

University of Cincinnati, Department of Internal Medicine, Division of Hematology Oncology, Cincinnati OH, 45267, USA

Corresponding to: Olugbenga Olowokure, MD. Assistant Professor of Medicine, University of Cincinnati, Department of Internal Medicine, Division of Hematology Oncology, 231 Albert Sabin Way, Medical Sciences Building, RM 7462, Cincinnati OH, 45267, USA. Email: olowokoo@ucmail.uc.edu.

Abstract: Gemcitabine (GEM) is a cytotoxic agent that is potent against pancreatic adenocarcinoma. Nab-paclitaxel (nab-P), an albumin-bound formulation of paclitaxel, appears to decrease levels of cytidine deaminase, which is the primary gemcitabine catabolic enzyme, this likely increases sensitivity to GEM when these agents are combined. Here we present a case of a 52 year old female with locally advanced pancreatic cancer with elevated CA19-9 at diagnosis who received GEM + nab-P followed by GEM based chemoradiation who underwent surgical resection despite persistent stable disease on radiographic studies and was found to have complete pathologic response.

Key Words: Locally advanced pancreatic cancer (LAPC); gemcitabine (GEM); nab-paclitaxel (nab-P)

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A 52 year-old Caucasian female was seen in clinic for evaluation of a pancreatic mass. She had earlier presented to her primary care physician with a one month history of epigastric pain, abdominal fullness and decreased appetite with no other constitutional or GI symptoms. Initial physical examination revealed normal vital signs without jaundice, lymphadenopathy, abdominal tenderness, masses or hepato-splenomegaly. Initial laboratory values included white blood cells 5,900/μL, hemoglobin 12.5 g/dL, platelets 194,000/μL, and normal liver function tests. CA19-9 was 164 U/mL. Abdominal CT demonstrated a 3.6 cm × 2.6 cm pancreatic mass encasing the superior mesenteric artery (SMA) and likely the common hepatic artery with occlusion of the portal vein. Multiple non-enlarged lymph nodes were noted in the mesentery just inferior to the pancreatic mass with ill-defined stranding. Endoscopic ultrasound with transgastric fine needle aspiration of the pancreatic mass was positive for adenocarcinoma. Further work-up revealed T4N×M0, Stage III, unresectable locally advanced pancreatic cancer (LAPC).

Combined chemotherapy with gemcitabine (GEM) 1,000 mg/m^2 and nab-paclitaxel (nab-P) 100 mg/m^2 was administered weekly for 3 weeks every 28 days for 2 cycles. CA 19-9 peaked at 259 U/mL approximately 1 month after initiation of treatment, before gradually decreasing to 126 U/mL at the end of the second cycle. Follow up CT scan showed stable disease. The patient subsequently received GEM-based chemoradiation (54 Gy total) with GEM dosed at 600 mg/m^2 weekly for 6 weeks. Repeat CT after chemoradiation did not show significant change in tumor size, but CA 19-9 decreased to 48 U/mL. Following radiation, 8 additional cycles of GEM at 1,000 mg/m^2 and nab-P at 100 mg/m^2 weekly for 3 weeks every 28 days were administered, and CA19-9 normalized by cycle 2 day 15 post-chemoradiation. The patient tolerated chemotherapy well, with only four doses of GEM/nab-P being delayed. Other than intermittent fatigue, thrombocytopenia, neutropenia and anemia necessitating occasional blood transfusions and growth factor, she had minimal complaints while on therapy. CT scan obtained after the eighth cycle remained stable with persistently normal CA19-9.

At this point it was unclear if the radiographic imaging findings represented viable disease or necrotic tumor. The patient was taken to the operating room to determine resectability. She underwent exploratory laparotomy with splenectomy, subtotal distal pancreatectomy and abdominal lymphadenectomy multiple biopsy samples were obtained from the SMA, superior mesenteric vein, and retroperitoneum, all of which were negative for carcinoma. Histologic examination of the pancreatic specimen revealed

complete pathologic response with fibrotic thickened pancreas without evidence of residual adenocarcinoma. No invasion of the vascular structures or retroperitoneum was evident, and there was no evidence of lymph node metastasis. Postoperative course was complicated by development of chylous ascites requiring paracentesis, which improved following the institution of a low fat diet. Abdominal CT scans performed 3 and 10 months after resection were remarkable only for some ascites with no evidence of local or metastatic tumor recurrence. CA 19-9 was still within the normal limits as of the last office visit 10 months after resection.

Discussion

Pancreatic cancer is the fourth leading cause of cancer related death among both genders in the United States. Despite advances in diagnostic and treatment strategies, there has been little improvement in overall survival in the last 30 years. 43,920 new cases are projected to occur in the United States in 2012, accounting for 6% of all incident cancer cases and 13% of all cancer-related deaths (1). The only treatment modality proven to have curative potential is surgical resection; however only 10-20% of cases are potentially resectable at presentation (2).

Neoadjuvant chemotherapy has been proposed to downstage unresectable LAPC and enable surgical intervention, reduce the incidence of late relapse and decrease the rate of positive margins. A meta-analysis published in 2011 suggested that approximately 40% of patients with unresectable disease receiving neoadjuvant therapy underwent surgical resection. In that series, however, criteria for resectable disease were broad and in many cases were not defined (3).

Current National Comprehensive Cancer Network (NCCN) guidelines suggest GEM-based combination chemotherapy plus or minus chemoradiation as an option in LAPC patients with good performance status. Other options include clinical trials, FOLFIRINOX, single agent GEM, GEM plus erlotinib, or fluoropyrimidine-based chemotherapy (4). GEM is a cytotoxic agent that is potent against pancreatic adenocarcinoma cells *in vitro* with known short half-life. Nab-P, an albumin bound formulation of paclitaxel particles, appears to have advantages over the soluble formulation, with less toxicity and increased local concentration targeting stromal-rich tumors. In a mouse model, it has been shown to decrease levels of cytidine deaminase, the primary gemcitabine catabolic enzyme, through the generation of reactive oxygen species, thereby increasing sensitivity to GEM (5). This suggests potential benefit from the combination of both agents.

A phase I/II trial exploring GEM plus nab-P in metastatic pancreatic adenocarcinoma showed substantial antitumor activity with tolerable side effects. At a maximum tolerated dose of 1,000 mg/m^2 of GEM and 125 mg/m^2 of nab-P administered once a week for 3 weeks every 28 days, there was a 48% response rate and a 48% 1-year survival (6). At this time, no phase III studies evaluating this combination in pancreatic cancer have been published.

A single center retrospective review evaluated 13 patients with LAPC undergoing neoadjuvant chemotherapy with GEM/nab-P plus or minus chemoradiation. The regimen was given as cycles of GEM 1,000 mg/m^2 and nab-P 100 mg/m^2 weekly, 3 weeks on and one week off, with appropriate modifications. 77% of patients received chemoradiation and 38% underwent resection. Overall survival was 85% at six months and 77% at twelve months. Progression-free survival at six months was 100% and 88% in the resected and non-resected groups, respectively (7).

The timing for surgical exploration after neo-adjuvant therapy remains debatable. Some centers reserve surgical exploration only for patients with evidence of tumor downsizing. Other centers consider exploration for patients with radiographic stable disease and normalization of CA19-9 (8).

The decision whether to offer patients the possibility of surgery and cure and avoid prolonged courses of neoadjuvant treatments requires a multidisciplinary approach and the development of clearer guidelines. Other investigators observations and well-designed phase II trials using this combination with or without chemoradiation will go a long way in defining its efficacy in LAPC and its possible role as neoadjuvant or definitive therapy in locally advanced disease.

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