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Complete pathological response following gemcitabine and nab-paclitaxel chemotherapy for borderline resectable pancreatic adenocarcinoma: A case report and review of the literature

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Abstract

Cases of pathological complete response after neoadjuvant chemoradiation for pancreatic adenocarcinoma have been scarcely reported in the literature. Different regimens have been used as chemoradiation prior to pancreaticoduodenectomy for borderline and localized pancreatic cancer. We report the case of a 57 year old man with borderline resectable pancreatic carcinoma who achieved pathological complete response post neoadjuvant chemoradiation with a less intensified regimen of Gemcitabine, and nanoparticle albumin-bound (nab) paclitaxel, chemotherapy. Our patient tolerated the regimen with no complications. 22 months have passed after his initial diagnosis and the patient is currently doing well with no evidence of disease recurrence.

Introduction

Pancreatic ductal adenocarcinoma (PDA) is the fourth leading cause of cancer-related death, among both men and women, in the Western World. 5-year overall survival rate ranges between 2-6% and has shown minimal advancement in survival over the past 30 years despite all advances in diagnosis and treatment [1]. Most patients present with advanced disease, with 30 to 40% of patients having locally advanced cancer attributed to abutment of the celiac axis, aortic invasion or important superior mesenteric artery encasement at time of presentation [2]. Adequate surgical resection remains the only treatment option associated with long term survival [3]. However, less than 20% of patients with PDA have a resectable tumor at diagnosis [4]. Even after potentially curative surgical resection, the 5-year survival rate is approximately 20% with a median survival of around 12 to 20 months [5,6]. Neoadjuvant chemotherapy and chemoradiation, especially in borderline resectable cases, is used in order to reduce tumor volume, to treat micrometastasis and to increase margin negative resection rates [7,8]. Evans et al. conducted a trial of neoadjuvant intravenous infusion of gemcitabine and cisplatin plus external beam radiation therapy (EBRT), where results showed partial pathologic response in fifty-eight percent of patients and pathologic complete response (pCR) in two patients [7].

On the other hand, pCR has been associated with a lower incidence of local recurrence and better survival in patients with adenocarcinoma of esophageal and rectal, who received neoadjuvant therapies [9,11-13]. Conversely, for patients with PDA who had neoadjuvant chemoradiation therapy, the frequency and prognostic value of pCR are not clear. Few are the studies that have investigated the clinicopathological significance of pCR in PDA patients that received neoadjuvant therapy [8,14-17]. In this report, we relay the case of pCR in a patient with PDA after three months of neoadjuvant chemoradiation therapy.

Case report

A 57 year old man presented to our hospital in March 2015 with a two month history of jaundice, pruritis, dark urine, light colored stool and weight loss. As past medical history, he had a percutaneous coronary intervention with stent placement in 2002 and was being treated for hypertension. He was a previous smoker, drank alcohol only occasionally and had no family history of malignancy. His physical exam was remarkable for icteric skin and sclera. Laboratory findings showed an increased Direct bilirubin 9.2 mg/dl (Normal Value: 0-0.2 mg/dl) and a CA 19-9 of 7300 U/ml. The patient then underwent an Endoscopic Ultrasound (EUS) which showed a 3.3 x 2.6 cm mass that appeared to be abutting the Portal Vein (PV) and a Fine Needle Aspiration (FNA) was performed which confirmed pancreatic adenocarcinoma. An Endoscopic Retrograde Cholangiopancreatography (ERCP) showed a distal Common Bile Duct stricture where a metal stent was placed successfully to relief obstruction. Computed Tomography (CT)

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scan then showed a 3.2 × 2.8 cm pancreatic head mass adjacent to the ampulla, with no evidence of vascular infiltration to either the SMA or SMV, along with the presence of few enlarged lymph nodes in the peripancreatic fat at the level of the head of the pancreas, the largest measuring 0.5 cm in short axis. And the patient was then referred to Surgical Oncology for assessment. The tumor was considered borderline resectable for abutting of the PV (4).

Therefore, the patient was referred to the oncology team for consideration of neoadjuvant treatment. A chemotherapy protocol consisting of combination of Gemcitabine (at the dose of 1200 mg/m^2) and nanoparticle albumin-bound (nab) paclitaxel (at the dose of 125 mg/m^2) on days 1, 8, 15, and 22 was started as neoadjuvant chemotherapy. Patient received two cycles of chemotherapy from March 17th till May 7th. After two months of neoadjuvant chemotherapy the patient was experiencing weight gain and monitoring of the CA 19-9 values showed a linear drop until it reached 599 U/ml. CT scan done after two months of treatment showed an interval decrease in size of the mass from 3.2x.2.8 cm to 2.8x2.2 cm with less surrounding fat stranding; in addition to an interval decrease in the size of the previously mentioned peripancreatic lymph nodes. The CT scan also showed hypoattenuating avidly enhancing non nodular hepatic lesions that on Magnetic Resonance Imaging (MRI) were proven to be benign hemangiomas.

Patient was then planned to receive concurrent chemoradiation. Between the 8th of June and the 10th of July, the patient received a total of 55.4 Gy divided in 28 fractions. Concurrently 8 cycles of reduced dose gemcitabine was given as radio sensitizer weekly from the 2nd of June till July the 21st. Patient tolerated chemoradiation very well with minimal side effects, the main one being diarrhea that was managed symptomatically. Patient was clinically doing well and his CA 19-9 continued to decrease reaching 125 U/ml at the completion of his chemoradiation treatment.

A Whipple's pancreaticoduodenectomy was done without complications one month after chemoradiation. All surgical specimens including ten lymph nodes (pericholeducal, periperipancreatic, pancreatico-duodenal, juxto-ileal vein, etc) were negative for any sign of disease. Pathological complete response (pCR) post neoadjuvant chemoradiation was diagnosed as microscopic examination showed foci of intraparenchymal and peripancreatic fibrosis containing degenerated non-viable tumor glands intermixed with normal exocrine and endocrine components.

Two months after surgery, the patient received completion adjuvant gemcitabine chemotherapy at the dose of 1000 mg/m2 given on days 1, 8, and 15 of each cycle for a total of 3 cycles. Patient finished treatment on December 30th of 2015 and is currently doing well with no evidence of disease recurrence 22 months after his initial diagnosis.

Discussion

Our case represents the second published case report that showed complete pathological response post neoadjuvant chemoradiation with gemcitabine and nab-paclitaxel. Olowokure et al presented a case of locally advanced pancreatic carcinoma that showed complete pathological response with gemcitabine/nab paclitaxel and Gem-based chemoradiation [18]. Their treatment started with 2 cycles of gemcitabine/nab-paclitaxel given weekly for 3 weeks every 28 days which was followed by Gem-based chemoradiation for 6 weeks [18]. As CT scan results showed stable disease and no evidence of tumor shrinkage, they decided to administer 8 additional cycles of the same regimen of gemcitabine/nab-paclitaxel [18]. The reduced number of treatment cycles in our case (2 cycles only of gem/nab-paclitaxel and 8 weeks of Gem-based chemoradiation 55.4 Gy) is unprecedented in a case of pCR present in the literature except for a case that showed pCR after $5_{1/2}$ weeks of 300mg/m^2 of gemcitabine with concurrent 28 fractions of external beam radiation of a total of 50.4 Gy only [19]. Multiple case reports and trial cases were documented in the literature to have reached pCR with diverse chemotherapy regimens with or without concurrent radiation most of them having either gemcitabine or 5-FU based regimens [8,14- 17,19-22].

Pathological response has shown better prognosis in a study done by Chun et al that showed that patients achieving major pathologic response denoted by (95-100% fibrosis) in histopathologic specimen had significantly improved survival rates in contrast to minor (less than 50% fibrosis) and partial (50-95% fibrosis) response [8]. The focus of published studies and cases to report pCR is fueled by the hope of reaching a favorable regimen to treat borderline/ locally advanced pancreatic cancer in attempt to increase survival. Conversion from unresectable/ borderline resectable to resectable tumors has shown in more than one large study to have an overall survival equivalent to those diagnosed as resectable initially on presentation [23].

Our choice of adding nab-paclitaxel to gemcitabine is favored by both NCCN 2015 guidelines for neoadjuvant treatment of borderline resectable PDA and those of the preclinical studies favoring the action of nab-paclitaxel in stromal rich tumors [24]. Nab-paclitaxel has been shown to have a role in inhibiting cytidine deaminase in mice, an important gemcitabine catabolic enzyme [18]. In addition, studies have presented data that albumin bound particles of paclitaxel have better delivery to tumor site through over expressing secreted acidic and rich in cysteine proteins (SPARC) [22]. This makes the combination of chemotherapeutic drugs used in our regimen even more compelling, especially in view of the favorable data in metastatic pancreatic cancer [25].

Neoadjuvant therapy for pancreatic cancer is becoming a new tide as chemotherapy and radiation have less toxicities on patients before they undergo surgery; in addition to their beneficial role in eradicating micrometastasis [26]. It also seems to be an important selection tool to try to avoid unnecessary large surgeries for patients who would eventually manifest themselves as poor resection candidates due to aggressive and/or primary progressive or metastatic disease. However, randomized clinical trials that evaluate the role of neoadjuvant chemoradiation in pancreatic cancer are lacking in comparison to the extensive studies done on adjuvant therapy [26]. Additionally, the data on the role of neoadjuvant treatment role in borderline resectable pancreatic cancer is even scarcer with only one ongoing prospective randomized trial studying the role of neoadjuvant chemoradiation with gemcitabine reaching phase II/III [26]. Furthermore there is only one phase II trial that is ongoing studying the combination Neoadjuvant chemotherapy (Gemcitabine and Nab-Paclitaxel vs. mFOLFIRINOX) and Stereotactic Body Radiation Therapy for Borderline Resectable Pancreatic Cancer [27]. However the same combination has reached phase III trials for resectable pancreatic cancer as neoadjuvant therapy [26].

According to a study done by Barugola et al, elevated level of CA 19-9 on presentation, long duration of preoperative symptoms (>40 days), and pathological grading (G3-G4) are associated with high risk of early relapse and then could be implemented as criteria to define who may benefit from neoadjuvant chemotherapy in patients with resectable pancreatic cancer [28]. Our patient had an initial CA 19-9 of 7300 U/ml which was the highest among reported cases of pCR

case reports and had symptoms for two months prior to presenting for workup; despite that our patient achieved pCR after undergoing preoperative chemotherapy and chemoradiation.

In conclusion, we presented a case of borderline resectable pancreatic adenocarcinoma achieving pCR after a combination of gemcitabine/nab-paclitaxel chemotherapy followed by gemcitabine based chemoradiation, which is the second reported case of pathological complete response for this regimen in the literature. Our patient even received a less intensified regimen than the one used by Olowokure et al for treatment. Lastly, more prospective clinical trials using this combination regimen are needed in borderline resectable pancreatic tumors in attempt to better define the role of this approach in the treatment of his highly lethal disease.

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