

Clinically Meaningful Responses to Sequential Gemcitabine-Based Chemotherapy Regimens in a Patient with Metastatic Pancreatic Cancer

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Key Words

Pancreatic cancer, response to chemotherapy · Best responders to gemcitabine, pancreatic cancer · Second- and third-line gemcitabine-based chemotherapy, pancreatic carcinoma · Pharmacogenomics of gemcitabine, pancreatic adenocarcinoma · Naturopathic regimens, pancreatic cancer

Abstract

Pancreatic cancer exhibits profound chemoresistance resulting either from pre-existing (intrinsic) mechanisms, or from anticancer drug treatment itself (acquired chemoresistance). We present the case of a patient with pancreatic adenocarcinoma metastatic to the liver who experienced clinical, radiographic and tumor marker response to three lines of gemcitabine-based chemotherapy. The regimens included: 8 cycles of gemcitabine and oxaliplatin (GEMOX), 8 cycles of gemcitabine, docetaxel and capecitabine (GTX) and more than 3 cycles of gemcitabine and nab-paclitaxel, with an exceptional response 2 years from the initiation of chemotherapy for metastatic pancreatic cancer.

Introduction

Pancreatic cancer is the fourth leading cause of cancer death in the Western world and shows the worst mortality among common malignancies with a 5-year survival rate of lower than 5% [1]. Pancreatic ductal adenocarcinomas represent approximately 90% of the cancers of the pancreas. The current standard of care includes surgical resection when appropriate and gemcitabine-based chemotherapy. Recent data suggests the use of

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FOLFIRINOX as initial treatment of patients with metastatic disease who have a good performance status improves survival [2].

Single-agent gemcitabine is often administered to patients with advanced, metastatic pancreatic cancer. Studies with gemcitabine have demonstrated a significant clinical response (decreased pain, increased functional status) even in the absence of a measurable tumor response [3].

Unfortunately, there is currently no standard second-line chemotherapy for metastatic pancreatic cancer. One of the current major challenges is the lack of validated markers for prediction of response to chemotherapy in the metastatic pancreatic cancer setting.

Case Report

A 49-year-old Hispanic male, with a 25-pack year smoking history, moderate alcohol consumption and a family history reportedly noncontributory for gastrointestinal malignancies or liver disease, was found to have a biopsy-proven poorly differentiated ductal adenocarcinoma of the pancreas. The patient had a past medical history of gastritis; pancreatitis; new onset insulin-dependent diabetes mellitus; depression, and anxiety.

A diagnostic CT of the abdomen performed at an outside institution immediately prior to presentation to our center, revealed an infiltrative mass of the head of the pancreas measuring 4.6×3.5 cm in transverse and anteroposterior diameters and approximately 3.4 cm in longitudinal diameter, which was obstructing the common bile duct and pancreatic duct, infiltrating the peripancreatic and perivascular spaces and occluding the superior and mesenteric vein. There were several liver lesions detected in the right lobe of the liver.

The pathology report described a poorly differentiated pancreatic adenocarcinoma that had metastasized to the liver. The patient's CA19-9 was 5,590 U/ml at presentation, and CEA 2.8 U/ml (both doubled in value over a period of approximately 2 weeks prior to presentation to our center; [table 1](#)). Symptoms at presentation consisted of fatigue and intermittent abdominal pain, controlled by pain medications (opioids). The patient also reported an approximately 7–9 kg weight loss over a period of 3–4 months (weight at presentation 59.4 kg). The patient also had obstructive jaundice and had a biliary stent placed. The ECOG performance status (PS) at the initial visit was 1.

A CT-guided biopsy of the anterolateral right lobe liver lesion confirmed metastatic pancreas cancer. The immunostains performed on paraffin sections were supportive of the above diagnosis: the tumor was positive for CK7, CK20 and CA19-9 and negative for TTF1.

It was decided to pursue with chemotherapy consisting of a doublet – gemcitabine and oxaliplatin (GemOx). The patient received gemcitabine at 850 mg/m²/dose on day 1 and day 8 and oxaliplatin at 100 mg/m²/dose on day 2, every 21 days. The patient also received L-Glutamine powder 15 g twice/day dissolved in protein shakes. Other supplements were taken along with chemotherapy (self-administered): herbal mixtures Anamu (Cuba) and Brim (Ecuador).

The first three cycles of chemotherapy were reasonably well tolerated without any significant side effects. The patient's appetite and nutritional intake improved and weight gain was noted. Mild hyperkalemia was observed, presumed to be due to increased potassium intake (nutritional shakes). There were no new abdominal symptoms. The patient had an ECOG PS of 1.

A PET/CT evaluation performed after 3 cycles of chemotherapy revealed decreased FDG uptake within the lesion in the head of the pancreas (SUV of 2.8 compared to 6.5 on previous examination) and left adrenal gland (SUV –2.7 decreased from 3.8), compatible with

response to therapy. There was complete resolution of the focus of mildly intense FDG uptake in the anterior right lobe of the liver. New minimal FDG uptake was observed in the left lower lobe of the lung, presumed to be of inflammatory etiology. The CT scan of the abdomen showed overall decrease in size and volume of the pancreatic head lesion and of the tiny left adrenal nodule, as well as resolution of anterior right hepatic lesion consistent with response to therapy.

The patient completed 8 cycles of chemotherapy with complete radiographic and excellent tumor marker response (CA19-9 level decreased from 5,590 U/ml to 130 U/ml) and minimal symptoms. Two treatment delays/dose reductions due to neutropenia developed during the 6-month treatment period.

At the 1-month evaluation, the CA19-9 level continued to decrease from 130 U/ml to 55 U/ml, markedly decreased from 5,590 U/ml prior to initiation of therapy. The CT scan of the chest, abdomen and pelvis, revealed no definite pancreatic masses or liver metastases. The evaluation performed two months later, after a treatment break, showed essentially stable findings, with the CA19-9 slowly trending upwards to a value of 125 U/ml.

At another 2-month interval, the PET/CT scan showed mild interval disease progression in the pancreatic head surrounding the common bile duct stent and interval progression of multifocal hepatic metastatic disease in both liver lobes, which was also evidenced on CT scan. Increased FDG uptake was noted. The radiographic changes were paralleled by the elevation of CA19-9 level from 125 to 7,730 U/ml. At this point in time the patient was in overall good health, with good appetite and an ECOG PS of 0.

Second-line therapy with GTX regimen was initiated consisting of the following dosages/schedule: gemcitabine 600 mg/m² day 1 and day 8, docetaxel 30 mg/m² day 4 and day 11, and capecitabine at 1,000 mg p.o. twice daily on day 1 through day 14.

An evaluation performed after 3 cycles of the second-line chemotherapy program revealed the patient to be doing reasonably well with mild numbness and tingling noted in the hands and feet. He had lost approximately 1.8 kg in weight but otherwise remained in reasonably good health. The ECOG PS was 1. The CA19-9 level had decreased to 493 U/ml (from 7,730 U/ml prior to the initiation of GTX regimen). The restaging CT scan of the chest, abdomen, and pelvis performed at this visit showed interval response to therapy of multifocal hepatic metastatic disease.

At a subsequent evaluation performed after 5 cycles of this therapy there was continued evidence of a response, with the CT scan revealing a decreased size of the pancreatic head mass. However, there was a mild increase in size of two previously noted liver lesions and one small lesion was unchanged in size from the previous examination. The CA19-9 continued to decline and reached the level of 155 U/ml after 5 cycles of therapy, consistent with an ongoing treatment response. The ECOG PS remained 1. Treatment with GTX regimen continued and the patient completed 8 cycles with good overall tolerance. At this point imaging studies revealed stable disease with a slight increase in the CA19-9 level (from 155 U/ml to 264 U/ml). The patient opted for chemotherapy break at this point in time.

Three months later the patient presented for a follow-up evaluation with reportedly increased epigastric and right upper quadrant pain, increased flatulence and a 4-kg weight loss during the previous two months. No mucocutaneous icterus was noted and ECOG PS was 1. A restaging CT scan of the chest, abdomen and pelvis showed significant interval progression within the liver with a large heterogeneous 9-cm central mass centered at the hepatic hilum with near occlusion of the right portal vein and mild to moderate bilateral intrahepatic biliary ductal dilatation. There were also a minimum of 10 scattered lesions throughout the liver. The CA19-9 level had increased from 264 to 90,200 U/ml.

The treatment management plan consisted of initiation of third-line chemotherapy with gemcitabine and nab-paclitaxel (Abraxane). The regimen dosages/schedule were as follows: gemcitabine 700 mg/m² and nab-paclitaxel 70 mg/m², both administered on day 1, 8 and 15, every 28 days. Due to mildly abnormal serum transaminases the treatment program was initiated at reduced dosages.

Cycle 1 of nab-paclitaxel and gemcitabine was reasonably well tolerated with moderately well controlled pain in the epigastric area (reportedly, the patient did not follow his pain regimen as indicated). Weight gain was noted. A gastroenterology evaluation was completed for biliary ductal dilatation. Stent replacement was performed. The patient was also seen by Interventional Radiology and was not considered to be a suitable candidate for chemoembolization at that point in time.

In view of the excellent tolerance to the gemcitabine/nab-paclitaxel chemotherapy regimen, improvement in liver function tests and hematology parameters, a decision was made to increase the gemcitabine dose to 900 mg/m² and the nab-paclitaxel dose to 100 mg/m². During this time the patient received hematological growth factor prophylaxis. After 3 cycles of gemcitabine/nab-paclitaxel repeat imaging and tumor markers again demonstrated evidence of a favorable response. The CA19-9 level was markedly decreased from 90,200 U/ml to 4,830 U/ml and the CT of chest/abdomen revealed less compression of the portal vein compared to the previous study.

There was overall good tolerance to the gemcitabine/nab-paclitaxel regimen. The patient continued to gain weight while on treatment. At this point in time he had an ECOG performance status of 0. The patient subsequently continued treatment with this regimen at an outside facility, eventually experiencing progression of the disease process. In summary, and of considerable interest, our patient lived for a total period of 2 years after his initial diagnosis of metastatic pancreatic carcinoma.

Discussion

Pancreatic cancer is one of the most lethal tumors of the gastrointestinal tract. The ability to predict which patients would benefit most from surgical intervention and/or chemotherapy would be a great clinical advance. Considerable research has focused on identifying molecular events in pancreatic carcinogenesis, and the correlation with clinicopathological variables of pancreatic tumors and survival.

For the most part, the evidence regarding the application of biomarkers as prognostic indicators in this malignancy is conflicting. The advent of gene microarray and mass spectrometric protein profiling offers the potential to examine many different biomarkers simultaneously. This work may allow researchers to develop accurate and reproducible predictors of survival based on genetic signatures [4].

Genetic and pharmacokinetic testing were not performed in our patient, but his exceptional response to chemotherapy treatments may lead to the conclusion that this patient's pancreatic tumor may have had a unique genetic and molecular makeup.

Highlights of this case report are a dramatic clinical, radiographic and serologic (tumor markers) response observed with each chemotherapy regimen administered, as well as significant improvement of the performance status and quality of life for our patient, secondary to chemotherapy treatment. Evidence supports the suggestion that treatment with gemcitabine/oxaliplatin is superior to gemcitabine alone in terms of response rate, clinical benefit rate and progression-free survival, but the differences did not reach the significant level for overall survival [5].

Data for second-line therapy with gemcitabine-based regimens after first-line gemcitabine treatment have been published. The combination of gemcitabine, docetaxel and capecitabine (GTX) is an active regimen in patients previously treated with gemcitabine for metastatic pancreatic cancer. Better performance status and >75% drop in pretreatment CA19-9 were associated with longer survival. The number of prior regimens did not predict for survival duration [6]. GTX has a promising survival benefit of greater than 1 year in patients with advanced pancreatic adenocarcinoma when compared to studies using single agent gemcitabine or other combination chemotherapies. Randomized controlled studies in pancreatic cancer with GTX are warranted [7].

Following second line with GTX our patient experienced a significant response to a third-line gemcitabine-based regimen (gemcitabine and nab-paclitaxel). Gemcitabine plus nab-paclitaxel has promising antitumor activity in unresectable and borderline resectable pancreatic cancer patients [8].

Pancreatic cancer cells and surrounding stroma are known to overexpress SPARC (secreted protein acid rich in cysteine), which is associated with poor clinical outcomes. Nab-paclitaxel, an albumin-bound nanoparticle form of paclitaxel, increased tumor accumulation of paclitaxel through binding of albumin to SPARC. A disease-specific phase 1 study was designed to evaluate the safety and efficacy of gemcitabine + nab-paclitaxel and the correlation of response with tumor SPARC and serum CA19-9 levels. The combination of nab-paclitaxel and gemcitabine was generally well tolerated and had substantial enough antitumor activity in patients with pancreatic cancer to warrant a phase III clinical trial. SPARC+ status in these patients was associated with higher response rate and longer PFS [9].

A number of possible hypotheses can be advanced for why our patient exhibited this unexpected degree of persistent sensitivity to gemcitabine-based chemotherapy, including an inability to repair chemotherapy-induced DNA damage and a role for the glutamine supplementation he received during his treatment regimen. Hopefully, future research in this area will elucidate the reasons for such relatively favorable outcomes.

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Table 1. Chemotherapy-related details and evolution of serologic response

Date	Before presen- tation 3/24/ 2009	4/15/ 2009	4/23/ 2009	5/14/ 2009	7/7/ 2009	9/1/ 2009	9/30/ 2009	10/20/ 2009	12/9/ 2009	2/18/ 2010	2/23/ 2010	5/11/ 2010	8/16/ 2010	10/7/ 2010	10/21/ 2010	1/5/ 2011	3/31/ 2011
CA19-9 value, U/ml	2,408	5,590	–	6,270	707	130	–	55	125	7,730	–	493	155	–	264	90,200	4,830
CEA value, U/ml	2.8											3.0	3.3	–	–	240	–
Chemo regimen	None	<i>GemOx (8 cycles):</i> Gemcitabine 850 mg/m ² D1, 8 Oxaliplatin 100 mg/m ² D2 q 21 days								<i>GTX (8 cycles):</i> Gemcitabine 600 mg/m ² D1, 8 Docetaxel 30 mg/m ² D4, 11 Capecitabine 1,000 mg p.o. b.i.d. D1–14						(>3 cycles) Gemcitabine 700 mg/m ² D1, 8, 15 Nab-Paclitaxel 700 mg/m ² D1, 8, 15 q 28 days	