

CASE REPORT

Metastatic Pancreatic Adenocarcinoma and Renal Cell Carcinoma Treated with Gemcitabine and Sunitinib Malate. A Case Report

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ABSTRACT

Context Pancreatic adenocarcinoma and renal cell carcinoma are relatively frequent cancers that have been rarely reported as synchronous primary malignancies. When present simultaneously, they pose a therapeutic challenge given the many available targeted agents with reported efficacy in renal cell cancer and limited options for metastatic pancreatic cancer. **Case report** We report the case of a 43-year-old Caucasian gentleman diagnosed simultaneously with metastatic pancreatic adenocarcinoma and localized renal cell carcinoma treated with combination chemotherapy, consisting of gemcitabine and sunitinib. Patient had a radiographic response and prolonged progression free survival of twenty six weeks; side effects were manageable and included grade 3 neutropenia and grade 2 hypertension. **Conclusion** This encouraging response, safety profile and progression free survival response suggest that we should further examine this and other such regimens to improve clinical outcomes for maximum efficacy with minimal side-effects.

INTRODUCTION

Synchronous primary malignancies at presentation are a recognized yet unusual phenomenon. It is more frequently seen in individuals with hereditary or familial cancer syndromes, such as those associated with colon, breast and ovarian cancers. Von Hippel-Lindau disease [1] and Birt-Hogg-Dube syndrome [2] are autosomal dominant disorders where individuals have a genetic predisposition for renal cell carcinoma. Patients with Von Hippel-Lindau disease may manifest with pancreatic abnormalities such as cysts, serous cystadenomas, and neuroendocrine tumors however they do not have an increased risk of pancreatic adenocarcinoma [3].

Renal cell carcinoma has nonetheless been shown to be associated with a higher risk of a second primary malignancy, which can be antecedent, synchronous or subsequent [4, 5]. The cancers that are most commonly associated with this tumor include cancers of the prostate, bladder, lung, breast, colon and rectal cancer,

malignant melanomas and non-Hodgkin's lymphomas [4, 6]. Renal cell carcinoma is the ninth most frequent cancer in the United States with a 2008 projected incidence of 54,390 and mortality of 13,010.

Pancreatic cancer carries a more dismal prognosis as the estimated new cases and deaths from pancreatic cancer for 2008 is 37,680 and 34,290 respectively [7]. While both cancers are common entities in their own right, it is unusual for renal cell carcinoma and pancreatic adenocarcinoma to be present simultaneously. There are only a handful of case reports of patients with synchronous renal cell carcinoma and pancreatic ductal adenocarcinoma, and as they were not metastatic on diagnosis were able to undergo surgical resection [8, 9].

Alexakis *et al.* described two patients with renal cell carcinoma of which one had a synchronous and two had metachronous pancreatic cancer. The patient was a 67-year-old man who presented with obstructive jaundice and CT scan revealed a mass in the head of the pancreas as well as a 6.5 cm left renal mass. He underwent left nephrectomy for a stage 1 clear cell carcinoma and 6 weeks later underwent Whipple pancreaticoduodenectomy (R1 resection) for the pT3N1b pancreatic adenocarcinoma. He expired fifteen months later due to pancreatic cancer recurrence [8]. Olgay *et al.* presented a case report of a 72-year-old woman who was diagnosed with synchronous renal cell carcinoma and pancreatic adenocarcinoma who successfully underwent distal pancreatectomy,

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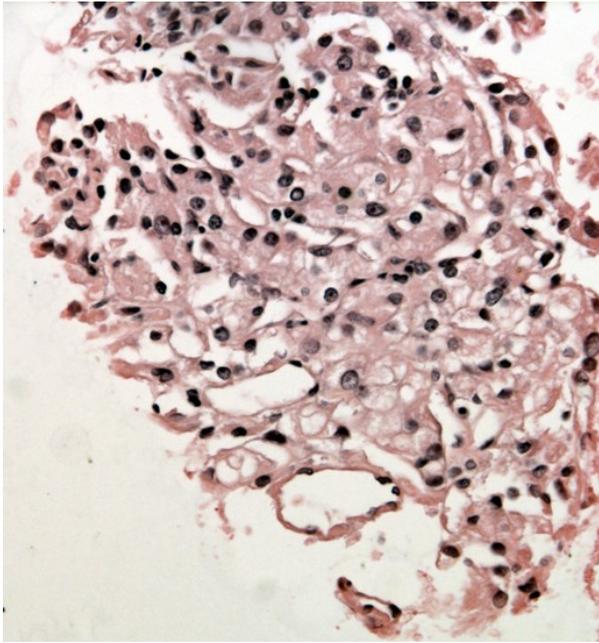


Figure 1. Kidney needle core biopsy: This photomicrograph shows a renal cell carcinoma. (Magnification 200x).

splenectomy and nephrectomy followed by chemotherapy and was well at 6 months' follow-up [9]. We report the first case of a patient with concurrent metastatic pancreatic adenocarcinoma and localized renal cell carcinoma treated with standard chemotherapy along with a novel agent.

CASE REPORT

A 43-year-old Caucasian gentleman presented to a local emergency room in April, 2006 with sudden onset right upper quadrant abdominal pain and jaundice. CT scan of the abdomen revealed a 2.2 cm mass in the head of the pancreas and a 3.2x2.7 cm necrotic right renal mass, suspicious for carcinoma. Total bilirubin was elevated at 8.4 mg/dL (reference range: 0.2-1.3 mg/dL) and CA 19-9 was 310 U/mL (reference range: 0-35 U/mL). An endoscopic retrograde cholangiopancreatogram (ERCP) was performed with placement of a temporary biliary stent for decompression. Bile duct brushings at the time

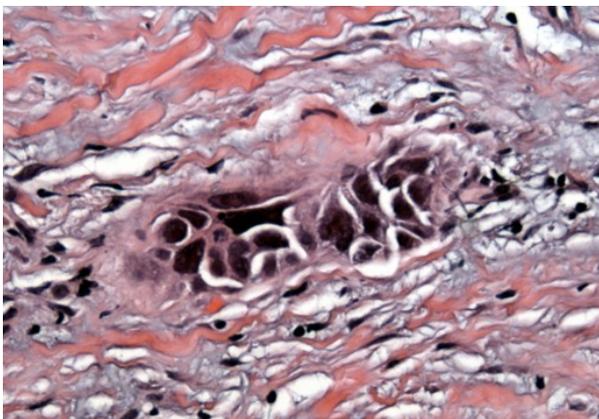


Figure 2. Pancreas needle core biopsy: This photomicrograph shows a ductal carcinoma within dense fibrous stroma. (Magnification 200x).

of ERCP demonstrated marked atypical cells. This was followed by a magnetic resonance cholangiopancreatography (MRCP) that revealed biliary ectasia and a 2 cm common bile duct obstruction, with a mass at the head of the pancreas. There was evidence of intra and extra-hepatic biliary ductal dilatation terminating at the 2 cm pancreatic head mass. The MRI also noted the right renal mass. Ultrasound guided needle biopsy of the renal mass was performed and pathology was consistent with Fuhrman's grade 2, clear cell type renal cell carcinoma (Figure 1). Subsequent restaging CT scans of the chest, abdomen, and pelvis also identified a small 5 mm lesion in the liver and increase in size of the pancreatic mass to 4x3 cm, with stable right kidney hypervascular mass. Due to the extracapsular extension of the pancreatic mass and the hypodense liver lesion the patient underwent a diagnostic laparoscopy in May 2006. Intra-operative biopsy of the pancreatic head mass and liver lesion was performed; the pathology from both was consistent with invasive moderately to poorly differentiated adenocarcinoma (Figures 2 and 3). This confirmed the diagnosis of metastatic pancreatic cancer with a concurrent second primary of renal cell carcinoma, thereby excluding surgical resection as a therapeutic option.

The patient then started treatment with systemic chemotherapy consisting of gemcitabine and sunitinib, as it was felt that this would regimen would simultaneously control both the malignancies. The dose of gemcitabine planned was 750 mg/m² intravenously days one, eight and fifteen repeated on a twenty-eight-day cycle; and the dose of sunitinib was 37.5 mg orally four weeks on followed by two weeks off. These doses were based on selected planned phase I studies of this combination. Dose intensity was maintained for the first two cycles, and restaging CT scan after two cycles showed an almost complete resolution of the liver lesion, with no change in the size of the pancreatic mass, consistent with stable disease and decrease in the size of the renal cell carcinoma, consistent with partial response per Response Evaluation Criteria In Solid Tumors (RECIST) criteria (Figure 4) [10].

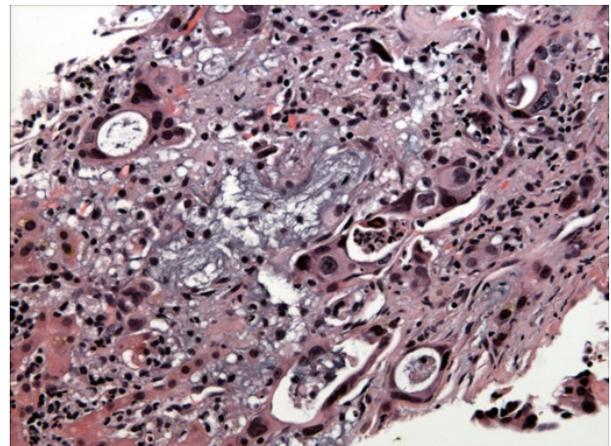


Figure 3. Liver needle core biopsy. Metastatic pancreatic ductal carcinoma (middle to upper right) to the liver (lower left). (Magnification 200x).

Subsequently however patient had three interruptions secondary to grade 3 neutropenia, and four delays due to patient preference. Growth factors were not used in keeping with the American Society of Clinical Oncology (ASCO) guidelines [11]. Dose intensity could not be maintained despite dose reduction of gemcitabine to 700 mg/m², and in total patient received fourteen doses of gemcitabine over twenty-five weeks. He also had an episode of hyperbilirubinemia and migration of biliary stent, requiring a repeat ERCP. He tolerated the sunitinib fairly well, but did develop grade 2 hypertension, and restaging CT scan after three cycles of this regimen continued to show stable disease.

Unfortunately repeat CT of the chest, abdomen, and pelvis in November 2006 revealed multiple new liver metastases. The CA 19-9, which had decreased initially with chemotherapy from 764 U/mL to 479 U/mL, started to trend upwards and at this time was 12,219 U/mL. He thereafter developed small bowel obstruction due to invasion of the duodenum by the pancreatic mass and had a rapid decline in his performance status, and received no further chemotherapy and quickly succumbed to his disease in December 2006.

DISCUSSION

Gemcitabine is standard of care first line therapy for patients with metastatic pancreatic adenocarcinoma with a median overall survival of 5.65 months,

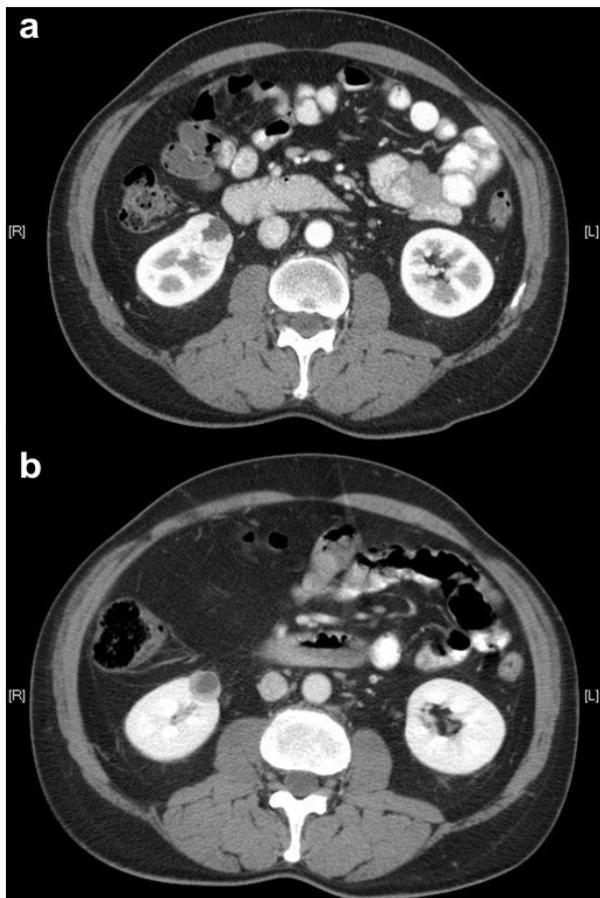


Figure 4. CT scan showing kidney mass at diagnosis (a.) and after 2 months of therapy (b.).

progression free survival of 9 weeks and a clinical benefit response of 23.8% [12]. Our patient had prolonged progression free survival of 26 weeks that may be attributable to the addition of sunitinib. Overall survival was as expected for patients receiving single agent gemcitabine and was similar to that reported from other clinical trials of combination therapy with a targeted molecular agent in addition to traditional chemotherapy in pancreatic malignancy [13, 14].

Erlotinib is the only oral epidermal growth factor tyrosine kinase inhibitor that has been shown to prolong overall survival in patients with advanced pancreatic cancer, although the benefit appears to be modest. It was approved by the Food and Drug Administration (FDA) in 2005, in combination with gemcitabine for treatment of patients with locally advanced, unresectable or metastatic pancreatic carcinoma [15].

Sunitinib malate is an oral multi-kinase inhibitor targeting several receptor tyrosine kinases (PDGFRalpha and PDGFRbeta; VEGFR1, VEGFR2 and VEGFR3; KIT, FLT3, CSF-1R and RET) that was approved by the FDA in 2006 for treatment of metastatic renal cell carcinoma. In a randomized phase III trial, sunitinib prolonged median progression-free survival (11 months) in comparison to interferon-alpha (5 months); corresponding to a hazard ratio of 0.42 (95% confidence interval: 0.32 to 0.54; P<0.001) for patients with advanced renal cell cancer. Sunitinib was also associated with a higher objective response rate than interferon-alpha (31% vs. 6%; P<0.001) [16]. However, the majority of patients (48%) had stable diseases and it also was not shown to improve overall survival. Our patient too, had disease stabilization of his renal cell carcinoma.

Clinical trials involving other tyrosine kinase inhibitors and anti-angiogenic agents in pancreatic cancer are currently ongoing. Results of the Cancer and Leukemia Group B (CALGB) 80603 phase II clinical trial of sunitinib in patients with previously-treated pancreatic adenocarcinoma, which was recently presented at the ASCO 2008 annual meeting, showed that sunitinib has definite value in pancreatic carcinoma; with a response rate of 21% (1% complete response and 20% stable disease) [17].

The rationale for combining gemcitabine with sunitinib in our patient was to exploit the anti-angiogenic and anti-proliferative effect of sunitinib to control both the renal cell carcinoma and pancreatic carcinoma. Gemcitabine was used in addition as it is the accepted standard of care for pancreatic cancers and has also been shown to have increased anti-tumor activity when incorporated with a targeted molecular therapy [15].

The potential efficacy and safety of combination chemotherapy with sunitinib in addition to gemcitabine is currently being tested in a number of phase I and II clinical trials, but at the time that our patient was treated with gemcitabine and sunitinib these trials were unavailable as they had not been initiated. The preliminary results of phase I study of sunitinib malate

continuously dosed and standard-infusion gemcitabine in solid tumors (NCT00462553) also presented at the ASCO 2008 annual meeting indicate that this combination has significant promise for the treatment of pancreatic cancer, as at the dose level 1 (gemcitabine 800 mg/m² intravenously weekly x3 every 28 days and sunitinib 25 mg orally daily) two of the four patients with advanced pancreatic cancer had confirmed partial response, and the treatment was fairly well tolerated [18]. Our patient's response to this regimen is certainly in accordance with this study, although the doses that he received were different.

The combination of gemcitabine and sunitinib has also shown efficacy in a number of clinical trials for renal cell carcinoma. A phase I study of sunitinib and gemcitabine in advanced renal cell carcinoma and other solid tumors explored two different dosing schedules: 1) sunitinib given 4 weeks on, followed by 2 weeks off (4/2); and 2) two weeks on, followed by 1 week off (2/1) with gemcitabine administered i.v. over 30 min on days 1, 8, 22, and 29 on schedule 4/2 and days 1 and 8 on schedule 2/1. Nineteen patients from the total of 34 had renal cell carcinoma and had significant response to this therapy especially those with poor-risk or high-grade renal cell carcinoma (doses: sunitinib 37.5 mg plus gemcitabine 750 mg/m²; sunitinib 37.5 mg plus gemcitabine 850 mg/m²; sunitinib 37.5 mg plus gemcitabine 1,000 mg/m²) [19]. Gemcitabine was also shown to delay disease progression in some patients with renal cell carcinoma who developed resistance to sunitinib alone. Gemcitabine was administered 750 mg/m² i.v. on days 1 and 8 and sunitinib was given at a dose of 37.5 mg/day on days 2-15 over a 21 day cycle. Of the nine patients treated with this regimen one patient had a partial response, four patients had stable disease and four patients had progressive disease documented per RECIST criteria [20].

The results of these and other ongoing clinical trials will help us to refine this regimen and determine the optimum doses and cycle length, for the most favorable results with minimum toxicities.

CONCLUSION

Gemcitabine and sunitinib combination chemotherapy led to a radiographic response and produced a prolonged progression free survival in this patient with metastatic pancreatic cancer and primary renal cell cancer, which is unusual for metastatic pancreatic carcinoma. The toxicities were as expected and manageable, although optimal dosing to maintain dose intensity needs to be determined. Gemcitabine and erlotinib is now an FDA approved regimen for patients with metastatic pancreatic cancer and the success of this combination merits exploration of other targeted therapies such as sunitinib, sorafenib and mTOR inhibitor such as temsirolimus which have established efficacy in renal cell carcinoma in combination with chemotherapy for patients with pancreatic and renal cell cancer. While the search for the best gemcitabine

based backbone for advanced pancreatic cancer continues, studies of anti-angiogenic agents alone or in combination with traditional chemotherapy should be undertaken as they may improve overall survival in this group of poor prognosis patients.

Conflict of interest The authors have no potential conflicts of interest

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