

CASE REPORT

Sirolimus Can Reverse Resistance to Gemcitabine, Capecitabine and Docetaxel Combination Therapy in Pancreatic Cancer

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ABSTRACT

Context Treating patients with metastatic carcinoma of the pancreas can lead to regression of disease, but the tumor becomes resistant to therapy within a few months. If resistance can be reversed or prevented, the chemotherapeutic benefit may be prolonged. **Case reports** Two patients with metastatic pancreatic cancer progressed on gemcitabine, capecitabine and docetaxel (GTX). When sirolimus was added to this regimen at a dosage to achieve a serum level of at least 10 ng/dL at the time of the gemcitabine and docetaxel infusion, their tumors regressed. **Conclusion** This demonstrates that the addition of sirolimus to a gemcitabine/docetaxel containing regimen can reverse tumor resistance in the clinical setting.

INTRODUCTION

Treating patients with metastatic carcinoma of the pancreas can lead to regression of disease, but the tumor becomes resistant to therapy within a few months. If resistance can be reversed or prevented, the chemotherapeutic benefit may be prolonged. In this paper we describe 2 patients who had a response and then progression on the combination of gemcitabine, docetaxel and capecitabine (GTX), a regimen described earlier [1]. They again had regression of the disease when sirolimus (rapamycin) was added to this regimen without other change in therapy.

CASE REPORT

Case 1

A 67-year-old retired bank examiner with a history of 4 pack per day smoking for 25 years, hypertension, coronary artery disease with arterial bypass surgery, type II diabetes mellitus, and pancreatic adenocarcinoma. He began chemotherapy with gemcitabine, docetaxel, capecitabine. After 3 cycles of chemotherapy and radiation therapy to the head of the pancreas, an attempt at resection was made. At the time

of surgery he was found to have progressed with metastatic disease in the gallbladder fossa and the surgery was aborted. Following surgery, the patient accumulated massive ascites thought to be due to portal vein obstruction and developed intractable pain. This time, gemcitabine, docetaxel, capecitabine was resumed with the addition of sirolimus, 14 mg the day before the intravenous portion of the chemotherapy and 6 mg the day after treatment. The sirolimus levels at the time of intravenous chemotherapy were 8 to 16 ng/mL.

The ascites did not improve and a Denver (peritoneal-venous) shunt was placed with improved comfort. A month later, the shunt became obstructed and the ascites recurred. The ascitic fluid was negative for malignancy and it was thought that the ascites was due to portal vein thrombosis. He continued on the chemotherapy regimen. Two months later, he was readmitted for ascites. The Denver shunt was found to be occluded with a thrombus in the subclavian vein. The Denver shunt was replaced with little improvement. The diuretics were increased. A month later, he became hypotensive, developed diffuse intravascular coagulopathy and subsequently died, 8 months after resuming GTX chemotherapy with the addition of sirolimus.

At post-mortem examination, there was no gross evidence of tumor. The liver weighed 1,150 g. The capsule was smooth. The cut surface showed grossly normal architecture. No masses or lesions were identified. A stent was present in the common bile duct extending into the ampulla. The gallbladder was not present. The pancreas was normal in size, shape and location, tan and firm. The parenchyma appeared lobular with firm white irregular fibrotic areas extending throughout the pancreas. No discrete lesion

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Abbreviations GTX: gemcitabine, docetaxel and capecitabine; HIF: hypoxia inducible factor

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was identified. On microscopic examination, the common bile duct revealed extensive fibrosis with foci of adenocarcinoma both in single cells and tubules adjacent to the common bile duct. The pancreas had marked fibrosis and atrophy of the remaining pancreatic parenchyma. Adenocarcinoma both in single cells and tubules were identified in the fibrotic areas. The adenocarcinoma cells and glands were sparse and few in number.

Case 2

A 71-year-old woman presented with a mass in the head of the pancreas and at least 10 hepatic metastatic lesions. She was treated with GTX for 22 months. The CA 19-9 initially fell from 1,608 to 22 U/mL (reference range: 0-37 U/mL) and the hepatic lesions decreased in size. After 17 months, the hepatic lesions started re-growing. The CA 19-9 rose to 97 U/mL. Sirolimus, 14 mg the night prior to the intravenous treatment and 6 mg the day after treatment was added to her regimen. The sirolimus level 12 hours after oral administration and at the time of intravenous gemcitabine and docetaxel was 18.2 ng/mL. She developed more leucopenia that she had with this regimen prior to the addition of sirolimus, but no other evident toxicity. The CA 19-9 fell to 42 U/mL. The MRI scans showed a decrease in the size of the hepatic lesions (Figures 1 and 2). The images show two different sites before and after adding sirolimus.

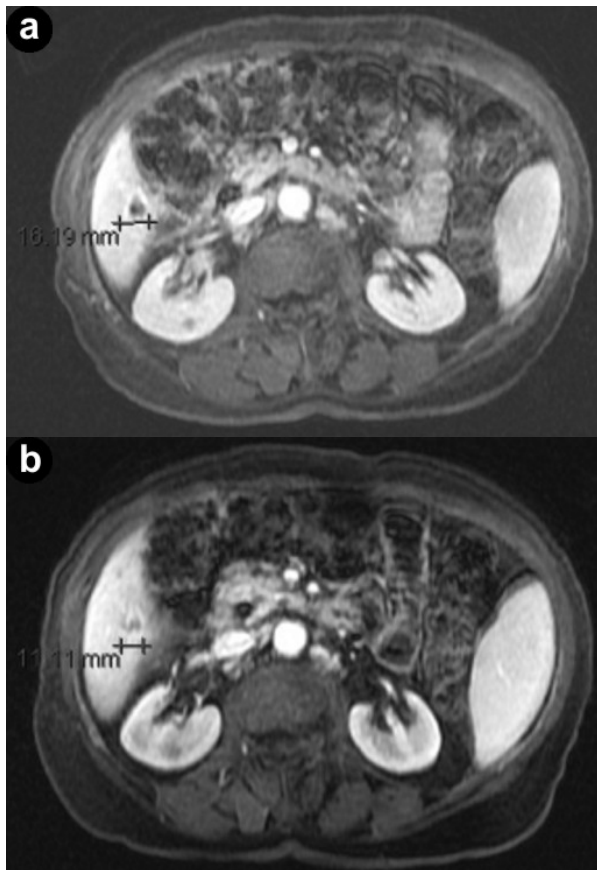


Figure 1. a. Lesion of 16 mm across before addition of sirolimus. **b.** Lesion of 11 mm across after addition of sirolimus. (Case 2).

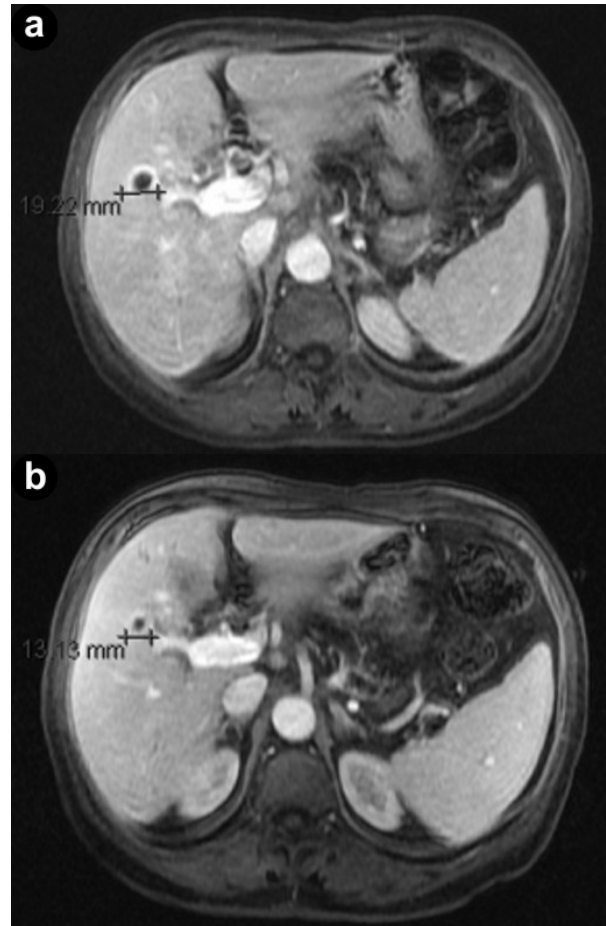


Figure 2. a. Lesion of 19 mm across before addition of sirolimus. **b.** Lesion of 13 mm across after addition of sirolimus. (Case 2).

DISCUSSION

In the first case, there was progression of disease into the gallbladder fossa on GTX. With the addition of sirolimus to GTX, this disease regressed to the degree that it was not grossly evident at post-mortem. The patient died from intractable ascites and diffuse intravascular coagulopathy related to attempts to control the ascites. At the time of death, there were only residual microscopic tumor cells.

The second case progressed after 17 months of GTX therapy. With the addition of sirolimus, the growing lesions regressed along with a decrease in the CA 19-9. This response is still on-going. The only noticeable side-effect is more leucopenia. The response duration for each patient is over 8 months, which is remarkable given that the median survival with gemcitabine in previously untreated patients is only 6.5 months.

Sirolimus has been used since the 1970's to prevent transplant rejection. It is orally available and has a T1/2 of 72 hours. It is primarily hepatically metabolized. By giving sirolimus the night before intravenous gemcitabine and docetaxel, serum levels between 9 and 19 ng/dL at the time of chemotherapy infusion can be achieved with minimal toxicity. This is the range Grewe *et al.* used in tissue culture to maximally down-regulate the effects of TORC1 [2].

Sirolimus blocks the mammalian target of rapamycin. mTOR forms 2 complexes, TORC1 and TORC2. TORC1 is easily inhibited by sirolimus while TORC2 may require longer exposure to be inhibited. TORC1 is activated by akt and then phosphorylates the downstream p70^{s6K}. TORC2, as opposed to TORC1 activates akt.

With respect to cancer cells, TORC1 is part of a cell survival and growth pathway from pTEN through akt, to the mTOR complex to a series of transcription factors including p70^{s6K} and hypoxia inducible factor (HIF). Up-regulation of this pathway seems to protect cancer cells from the effects of various chemotherapeutic agents including gemcitabine [3]. Grewe *et al.* [2] studied effects in the Panc-1 cell line and the MiaPaCa-2 cell line of pancreatic cancer. In each case, therapeutic levels of sirolimus, 10 ng/dL, blocked activation of the downstream target of the mTOR complex, phosphorylation of p70^{s6K}, and blocked expression of cyclin D1. This effect occurred within 30 minutes and persisted for up to 36 hours. Higher concentrations of sirolimus did not further inhibit cell growth. p70^{s6K} may be necessary for some pancreatic cell lines to proliferate [4]. CCI-779, sirolimus derivitized with a side-chain to improve aqueous solubility, suppressed the mTOR pathway in pancreatic cell lines and suppressed proliferation [5]. Therapeutic levels of CCI-779 are similar to sirolimus. Not all pancreatic cell lines respond to the combination of gemcitabine and sirolimus. Okada *et al.* [6] showed that in some cell lines the combination of sirolimus and gemcitabine was synergistic, but not in all cell lines. They found that akt phosphorylation was inhibited, implying that both TORC1 and TORC2 can be inhibited with sirolimus.

The downstream target of TORC1 may ultimately be HIF. HIF is expressed in the pancreatic adenocarcinoma but not in normal pancreatic ductal tissue [7]. Büchler *et al.* [7] studied 4 pancreatic cancer cell lines and fresh human pancreatic cancer tissue for expression of HIF RNA and protein. The cell lines expressed HIF under all conditions, but only expressed VEGF when made hypoxic. The expression of HIF was not increased with hypoxia suggesting that the effect was translocation of HIF to the nucleus under hypoxic conditions. In 83% of surgical specimens, HIF was present in "almost all nuclei in cancerous ducts ... No immunopositivity was found in normal pancreatic tissue" [7].

Blocking TORC has other effects on tumor cells to block uptake of nutrients which may also improve chemotherapeutic sensitivity. Sirolimus can decrease the uptake of radioactive glucose on the PET scan, but has no independent effect of tumor growth and survival [8]. The latter is not surprising as the pTEN-akt-mTOR-p70^{s6K}-HIF-VEGF pathway is permissive for tumor growth and improves tumor survival in the

presence of gemcitabine, but is not a cause of growth of this tumor.

While there are numerous studies showing that blocking mTOR can improve chemotherapeutic sensitivity of pancreatic cancer cell lines [2, 3, 4, 5, 6, 7, 8, 9], these two cases demonstrate that the addition of an mTOR blocker, sirolimus, to a gemcitabine based chemotherapy regimen, can reverse tumor resistance in the clinical setting with minimal additional toxicity. The short course of sirolimus does not seem to be associated with increased risk of infections or serum lipid problems. The only possible adverse effect noted was mildly increased myelosuppression. A randomized trial with the addition of an mTOR inhibitor to gemcitabine-based chemotherapy is needed to assess both beneficial effects in terms of response rates and survival, and possible increased toxicity that may occur when this pathway is blocked.

Conflict of interest The author has no potential conflicts of interest

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