CASE REPORT

Surgical Resection after TNFerade™ Therapy for Locally Advanced Pancreatic Cancer

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ABSTRACT

Context Treatment of pancreatic cancer remains a major oncological challenge and survival is dismal. Most patients, present with advanced disease at diagnosis and are not candidates for curative resection. Preoperative chemoradiation may downstage and improve survival in locally advanced pancreatic cancer. This has prompted investigators to look for novel neoadjuvant therapies. Gene therapy for pancreatic cancer is a novel investigational approach that may have promise. TNFerade™ is a replication deficient adenovirus vector carrying the human tumor necrosis factor (TNF)-alpha gene regulated under control of a radiation-inducible gene promoter. Transfection of tumor cells with TNFerade™ maximizes the antitumor effect of TNF-alpha under influence of radiation leading to synergistic effects in preclinical studies. Case report We describe a case of locally advanced unresectable pancreatic cancer treated with a novel multimodal approach utilizing gene therapy with TNFerade™ and concurrent chemoradiation that was followed by successful surgical resection. Conclusion Neoadjuvant TNFerade™ based chemoradiation therapy may be a useful adjunct to treatment of locally advanced pancreatic cancer.

INTRODUCTION

Treatment of pancreatic cancer remains a major oncological challenge and survival is dismal. Due to the poor outcome despite all currently available therapies, there is increasing interest in novel approaches such as gene therapy for locally advanced pancreatic cancer. TNFerade™ (GenVec, Inc., Gaithersburg, MD, USA) is a replication defective adenovirus vector carrying the human tumor necrosis factor (TNF)-alpha gene regulated under control of a radiation-inducible gene promoter. Transfection of tumor cells with TNFerade™ maximizes the antitumor effect of TNF-alpha under influence of radiation leading to synergistic effects in preclinical studies. We describe a case of locally advanced unresectable pancreatic cancer treated with a novel multimodal approach utilizing gene therapy with TNFerade™ and concurrent chemo-radiation that was followed by successful surgical resection.

CASE REPORT

A 56-year-old white female presented to her primary physician with 4-month history of epigastric pain, nocturnal reflux and 6.4 kg weight loss. She was a 37 pack/year smoker with a family history of pancreatic cancer in father. Endoscopic retrograde cholangiopancreatography (ERCP) revealed a large segment stricture of distal common bile duct with pancreatic duct dilatation suspicious for a pancreatic cancer. Biliary stenting was performed. Computed tomography (CT) abdomen and pelvis demonstrated a pancreatic head mass measuring 4.5x3.2 cm that extended to gastric wall and extended to the right border of the superior mesenteric artery. Regional adenopathy was noted (Figure 1a). Small hypodense hepatic lesions were noted and felt to represent potential early metastases. Given the locally advanced pancreatic cancer with questionable liver metastasis, the patient was deemed initially inoperable. Ultrasound guided biopsy of pancreatic mass confirmed the diagnosis of a well-differentiated adenocarcinoma of pancreas. She was considered surgically unresectable and referred for a phase II trial of definitive chemoradiation along with TNFerade™. Complete blood count, serum bilirubin, transaminases, amylase, lipase, hepatitis profile and serum beta-hCG were within normal limits. Carbohydrate antigen 19-9 (CA 19-9) level was 114 U/mL (reference range: 0-37

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U/mL); alkaline phosphatase was elevated at 204 U/L (reference range: 38-126 U/L). Urine and throat culture were found to be negative for adenovirus and tumor necrosis alpha (TNF-alpha) level was 19.1 pg/mL (reference range: 0-8 pg/mL).

After obtaining informed consent, treatment was started with weekly intrapancreatic TNFerade™ injections delivering $4 \times 10^{11}$ Pu of the vector, percutaneously under ultrasound guided biopsy guidance for 5 weeks. Concomitant 5-fluorouracil was administered as a continuous infusion at 200 mg/m²/day, Monday through Friday, weekly. External beam radiation was delivered along with chemotherapy at a total dose of 5,040 cGy over 5.5 weeks. Patient tolerated the therapy well without dose limiting toxicities. She maintained an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1 throughout therapy. Upon completion of therapy, CA 19-9 level improved to 30.9 U/mL and liver function tests were normal. Serial TNF-alpha level during therapy were in the reference range.

Restaging CT of the abdomen and pelvis and diagnostic laparoscopy were performed 3 months later to assess operability. These studies revealed a decrease in size of the pancreatic head mass, with no lymph node involvement or metastasis (Figure 1b). Subsequently, patient underwent definitive resection by pancreaticoduodenectomy (Whipple’s procedure). Perioperatively, she developed hypotension requiring aggressive hydration. No clear etiology was identified. Gross pathologic analysis revealed residual tumor size of 1.4x1.0 cm. On histopathologic evaluation, residual tumor was difficult to appreciate by hematoxylin and eosin staining (H&E) (Figure 2a). Figure 2b shows a cytokeratin AE 1/3 immunohistochemical stain (at 40x) of the same region. Residual tumor cells lining the slit-like spaces seen on H&E stain in the muscularis propria of the duodenum were recognized. Final pathological staging revealed ypT3N0 stage IIA pancreatic cancer with 0/17 positive lymph nodes. Patient had an otherwise uneventful recovery and was discharged home, 12 days post-operatively. Adjuvant chemotherapy with weekly gemcitabine was administered for 12 weeks. Patient remained in good health with normal CA 19-9 levels until 18 months post completion of adjuvant gemcitabine.

**Figure 1.** CT scans of abdomen at the level of pancreatic lesion. **a.** A pancreatic head mass measuring 4.5x3.2 cm with inflammatory changes or neoplastic extension adjacent to the posterior head and along the right border of the superior mesenteric artery is noted (arrow). **b.** Post neoadjuvant chemoradiation therapy with intratumoral TNFerade™ administration. Decreased perfusion is noted. The tumor has reduced size (3.1x3.3 cm) and importantly the prior change along the superior mesenteric artery border is improved (arrow).

**Figure 2.** **a.** H&E staining of the residual tumor in the region of head of pancreas/duodenum. In the lower right portion of the figure there is dense fibrosis due to treatment effect (arrow). Residual tumor is difficult to appreciate. **b.** A cytokeratin AE 1/3 immunohistochemical stain (at 40x) of the same region. One can see that the slit-like spaces seen on H&E stain in the muscularis propria of the duodenum are lined by residual tumor cells (arrow).
DISCUSSION

Pancreatic cancer is the second most common gastrointestinal malignancy and fourth most common cause of adult deaths from cancer in U.S. [1]. Fewer than 15% of newly diagnosed pancreatic cancer patients are eligible for curative resection [2]. Available data suggests that the combination of surgery with postoperative adjuvant chemoradiation improves survival and loco-regional tumor control compared with surgery alone [2]. However, the morbidity and prolonged recovery time associated with pancreaticoduodenectomy hinders timely delivery of postoperative chemoradiation in up to one-fourth of eligible patients. [3] Preoperative chemoradiation may improve negative resection margin rates and decrease incidence of pancreaticojejunal anastomotic fistulae as well as spare unnecessary surgery in patients who have progression despite the therapy [3].

In lieu of the poor outcome despite all currently available therapies, there is increasing interest in novel approaches such as gene therapy for locally advanced pancreatic cancer. The potent antitumor activity of TNF-alpha is well demonstrated in literature; however, severe systemic toxicity has precluded its widespread clinical use [4]. Gene therapy with TNFerade™ aims to maximize the local antitumor effect of TNF-alpha while minimizing systemic toxicity. TNFerade™ is an E1-, partial E3- and E4 deleted replication defective adenovirus 5 vector carrying a radiation-inducible immediate response Egr-1 (early growth response) gene promoter ligated upstream to the transcriptional start site of human TNF-alpha cDNA (Figure 3). This construct allows maximal TNF-alpha gene expression under the regulatory control of locally targeted radiation therapy [5]. Hence, there is a spatial and temporal control of the radio sensitivity and cytotoxicity [6]. Radiation alone has variable effects on the shrinkage of pancreatic cancer. While infusional 5-FU traditionally may cause tumor shrinkage with radiation, the impressive response to therapy in our patient is likely due to TNFerade™. There was a significant decrease in the inflammatory response around the tumor which was in close proximity to the superior mesenteric artery and significant tumor fibrosis on pathologic examination which is a described effect of TNFerade™ therapy.

Available data support synergy between TNF-alpha and ionizing radiation. Locally secreted TNF-alpha increases the level of hydroxyl or other radical products, thereby enhancing the oxidative damage produced by radiation [5]. Other proposed mechanisms include sphingomyelin-ceramide signal transduction pathway mediated endothelial apoptosis as well as enhanced production of angioatin leading to angiogenic effects [5]. Animal studies and phase I trials in humans have revealed decrease in mean tumor volume after treatment with TNFerade™ and radiation [5]. Furthermore, a phase I trial showed that repeated TNFerade™ injections of doses up to 4x10¹¹ Pu were well tolerated without significant local or systemic toxicities [5]. We did not observe any dose limiting toxicities in our case. She experienced mild to moderate side effects including mild nausea, diarrhea and abdominal pain. The peri-operative hypotension episode in our patient was unlikely to be due to TNFerade™ injection. The short half-life of TNF-alpha (20 to 30 min) [5] would exclude its persistence in circulation 4 months after the last TNFerade™ dose. Of note, TNF-alpha was not detected on immunohistochemical testing in pathology specimen from pancreas. This is likely due to the fact that surgery was undertaken 4 months after the completion of therapy and short half-life of TNF-alpha would exclude its presence in the tumor. We believe that TNFerade™ may have contributed to the necrosis and apoptotic changes seen in the pathologic specimen. Interestingly, our patient had neutralizing antibodies to adenovirus at presentation, which increased in titer with therapy. Senzer et al. showed that presence of neutralizing antibody did not have any effect on response to TNFerade™ therapy [5]. McLoughlin et al., in a phase I trial of TNFerade™ with ionizing radiation, demonstrated the feasibility and safety of this combination in various solid tumors [7]. We believe that our experience with this case suggests that intra-pancreatic injection of TNFerade™ may be safe when combined with chemoradiation to optimize the therapy for locally advanced pancreatic cancer. An ongoing randomized trial in locally advanced pancreas cancer is underway designed to answer the added value of TNFerade™ to 5-FU based radiation therapy. Recent data by Murugesan et al. show that addition of TNFerade™ to gemcitabine resulted in significant shrinkage of pancreatic xenografts relative to either agent alone [8]. This may open newer avenues for therapy in patients with pancreatic adenocarcinoma, especially in borderline-resectable cases.

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References


