EDITORIAL

Interventional Endosonography for Pancreatic Cancer

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Endoscopic ultrasound (EUS) was initially developed in the early 1980s as a research tool to overcome limitations of transabdominal ultrasound for an examination of the pancreas caused by intervening gas, bone, and fat. Since its introduction into clinical practice, EUS has revolutionized the diagnosis and treatment of gastrointestinal disorders, particularly pancreatic cancer. The ability to position the transducer in direct proximity to the pancreas via the stomach and proximal duodenum, combined with the use of high-frequency ultrasound, provides detailed high-resolution images of the pancreas that are superior to those of computerized tomography and trans-abdominal ultrasound. The incorporation of fine-needle aspiration (FNA) technique has significantly improved the accuracy of cancer staging and has encouraged a therapeutic capability that may parallel the evolution of endoscopic retrograde cholangiopancreato-graphy (ERCP) from a diagnostic to a therapeutic procedure. Injection with therapeutic agents can also be accomplished under EUS guidance leading to many therapeutic techniques being developed for the treatment of pancreatic cancer.

Pancreatic cancer is the fourth leading cause of cancer-related deaths in the United States. According to the American Cancer Society, estimated 33,730 Americans will be diagnosed with pancreatic cancer in 2006 [1]. The disease is associated with a high mortality rate and the 5-year survival rate is estimated to be only 4% with the median

survival of less than 6 months in untreated patients [1]. Currently, surgical resection is the only opportunity for a cure. However, surgical resection is possible in only 15% of cases - due to the late presentation of the disease - with a 5-year survival of approximately 20% [2, 3]. When the tumor is unresectable, chemotherapy, radiation therapy, or a combination thereof can be used to increase overall survival and to improve the quality of life [4]. Consequently, pancreatic cancer has become a target for novel therapies such as immunotherapy and gene therapy.

This review will focus on the available evidence of EUS as a therapeutic intervention for pancreatic cancer, including EUS-guided fine-needle injection therapy, EUS-guided radiofrequency ablation, EUS-guided photo-dynamic therapy, and EUS-guided celiac plexus neurolysis.

EUS-Guided Fine-Needle Injection Therapy

Locally advanced pancreatic cancer remains a major clinical challenge with limited options of treatment and a very poor prognosis. Because of limited efficacy of systemic chemotherapy with or without radiotherapy with potential systemic side effects, a major effort is underway to develop therapeutic agents that can be locally and directly delivered to the tumor. The advance of this area is based on the ability of EUS to place fine needles precisely within the tumor. Several therapeutic agents have been

proposed, including allogenic mixed lymphocyte culture (cytoimplant) and gene therapy through viral vectors.

The immunologic approach to treatment of tumor is based on the activation of host immune effector cells (cytotoxic T-lymphocyte) by cytokines. Cytokines may be instilled directly within the tumor or can be produced by a mixed lymphocyte reaction generated by the coincubation of host and allogenic donor peripheral blood mononuclear cells [5].

The first phase I clinical trial was reported by Chang *et al*. in 2000 [6]. The early study was conducted in 8 patients with unresectable pancreatic cancer. The feasibility and safety of EUS-guided injection with immunologic therapy was demonstrated. In this study, the allogenic mixed lymphocyte culture (cytoimplant) at the dose of 3, 6, or 9 billion cells was delivered within the tumor by a single injection through a 22-gauge FNA needle. No procedure-related complications or major toxicities were demonstrated. Tumor regression occurred in 3 of the 8 patients, no change in 3 patients, and increased growth in 2 patients. There was no correlation of tumor response with the dose of cytoimplant and survival. The median survival was 13.2 months. Based on these encouraging results from the phase I study, a randomized trial comparing EUS-guided fine-needle injection of cytoimplant with systemic gemcitabine was initiated. Unfortunately, the interim analysis demonstrated that patients who received cytoimplant did worse than the patients who received systemic gemcitabine. Thus, the trial was subsequently suspended [7].

Besides immunologic therapy, gene therapy has also been studied for pancreatic cancer [8, 9]. Gene therapy involves the transfer of genetic constructs, which alter the neoplastic potential of the cancer cells. Once genetic transfer has developed, expression of the gene product may modify the biologic behavior of the tumor. This modification can occur due to blocking transformation of known oncogenes, restoration of tumor suppressor function, or augmentation of the immunologic attack against cancer cells. In addition, viral constructs can be altered to create attenuated viruses that replicate specifically in the tumor and destroy cancer cells without being responsible for an infectious process [10]. An attenuated adenovirus has been proposed as a possible therapeutic vector for pancreatic cancer. Using the similar technique of EUS-guided fine-needle injection, vectors for gene therapy can be directly delivered to the tumor. The first clinical trial of gene therapy was conducted in 21 patients with locally advanced pancreatic cancer to assess the feasibility, safety, and efficacy of such approach [11]. In this study, the patients underwent 8 sessions of EUS-guided injection to deliver viral vectors (ONYX-015) directly within the tumor over 8-week duration and received intravenous systemic gemcitabine at the dose of 1,000 mg/m^2 concomitantly with the final 4 sessions. Significant toxicity and procedure-related complications were demonstrated early in the study. Two patients developed bacterial infections, which were felt to be secondary to the EUS-guided injection. Both infections were easily treated with antibiotics. No further infections were noted after the modification of study protocol which included the administration of prophylactic oral ciprofloxacin. Two patients developed duodenal perforation prior to the study protocol was revised to require all injections to be performed using only transgastric approach. The investigators concluded that repetitive EUS-guided injection therapy is well tolerated if the administration is performed using transgastric approach and with prophylactic antibiotics treatment. However, no convincing evidence proving the efficacy of ONYX-015 for the treatment of pancreatic cancer was found. No objective responses were demonstrated on day 35, following 4 injections of ONYX-015 as a single agent. After combination treatment with virus and gemcitabine, objective partial regressions of more than 50% were seen in 2 of 21 (10%) patients. Eight patients (38%) had stable diseases, and 11 (52%) had progressive disease or had to be removed from the study because of treatment toxicity. The median time to injected tumor

progression was approximately 6 weeks, and 14% of patients were free from local progression at 6 months. The median survival time was 7.5 months.

Several active studies are underway investigating EUS-guided gene therapy for pancreatic cancer. Local gene transfer has the potential to locally deliver high concentration of a therapeutic agent while limiting systemic toxicity. Direct local gene delivery to the tumor cells via EUS-guided injection theoretically maximizes the anti-tumor effect limited to those cells expressing the gene and their local milieu. Phase I and II studies have been completed, confirming the safety, tolerability, and potential efficacy of EUS-guided fine-needle injection with a replication-deficient adenovector containing the human tumor necrotic factor (TNF)-alpha gene (TNFerade[TM], GenVec, Inc., Gaithersburg, Maryland, USA) in patients with locally advanced and unresectable pancreatic cancer undergoing chemoradiation [12]. A phase III multicenter, randomized, controlled study is currently conducted to compare TNFerade[TM] plus standard of care and standard of care [13]. Preclinical and phase I/II studies have demonstrated that tumors transfected with adenovector have a favorable response to radiation with induction of TNF-alpha expression and substantial increases in antitumor activity [12].

EUS-Guided Radiofrequency Ablation

Percutaneous ablative therapies with thermal energy including radiofrequency, microwaves, and laser energy have received much attention as minimally invasive strategies for the management of focal neoplasms [14]. Potential advantages of these techniques are real-time imaging guidance, the ability to ablate tumor in patients with high risk for surgical treatment, reduced morbidity compared to surgical intervention, and the potential to perform the procedure on an outpatient basis.

EUS-guided radiofrequency ablation has been studied in the normal porcine pancreas by Goldberg *et al*. [15]. The study demonstrated the feasibility and safety of using EUS to guide transgastric placement of an endoscopic radiofrequency needle-electrode to induce coagulation necrosis in the pancreas of 13 Yorkshire pigs. The radiofrequency electrode used in the study was a modified 19-gauge biopsy needle. Thus the placement of radiofrequency electrode into the pancreas under EUS guidance was no more challenging than performing EUS-guided pancreatic biopsy with a 19-gauge needle. Radiofrequency current (285±120 mA) was delivered for 6 minutes. The results confirmed the excellent correlation between EUS or computed tomography (CT) and gross pathologic findings for all lesions larger than 5 mm. Three transmural burns extending from the gastric mucosa through the serosa were seen in the first 2 pigs, probably due to incomplete penetration of the gastric serosa, which is significantly thicker in pigs than in humans and frank perforation was not observed. No further burns were seen in the subsequent applications in which the entire distal needle was inserted within the pancreas before and during ablation. No clinical evidence of distress, fever, or pancreatitis was demonstrated following the procedures. The author concluded that EUS-guided radiofrequency ablation of pancreas is feasible and can be used safely to produce discrete zones of coagulation necrosis in the porcine pancreas. Resultant coagulation necrosis is well visualized with EUS or CT with excellent radiologic-pathologic correlation. The technique appears to be well tolerated. Most complications developed in the study were related to initial technical problems or differences between porcine and human anatomy. Potential clinical uses of this technique include management of small neuroendocrine tumors or other focal lesions within the pancreas, liver, spleen, or kidney. In addition, it may be used for palliation of unresectable pancreatic cancers. However, further studies are required to standardize several parameters including duration of radiofrequency application, electrode tip temperature, impedance, and wattage to optimize the diameter of coagulation necrosis in human pancreatic tissue.

EUS-Guided Photodynamic Therapy

Photodynamic therapy (PDT) has emerged as one of the useful methods for the ablation of malignant or benign tumors of epithelial-lined or solid organs [16, 17, 18, 19, 20]. Role of PDT has been previously established for malignancies of the esophagus, stomach, urinary bladder, brain, bronchial tree, and hepatobiliary system [16, 17, 18, 19, 20]. Following the intravenous infusion of a photosensitizing drug, the target tissue is exposed to light of appropriate wavelength. The activated drug interacts with oxygen to generate singlet oxygen, which produces localized tissue necrosis.

Studies of PDT in the pancreas demonstrate that photosensitizing drugs are avidly taken up by pancreatic tissue [21]. In addition, a 7-fold greater concentration of photosensitizing drug has been observed in malignant pancreatic tissue compared to normal tissue [22]. Light exposure with resulting tissue necrosis has not resulted in significant structural damage to the gastroduodenal musculature [23]. Phase I study by Bown *et al*. using PDT for inoperable cancer in the human pancreas demonstrated that light catheters placed percutaneously could produce necrosis in pancreatic cancers with an acceptable morbidity [21]. A study by Chan *et al*. demonstrated the role of EUS to guide the placement of a quartz optical fiber with light diffuser in the pancreas, liver, spleen, and kidney to assess the feasibility and safety of EUS-guided, low-dose laser light delivery to intra-abdominal solid organs [24]. The study was performed in 3 pig models injected with intravenous porfimer sodium (Photofrin®, Axcan Pharma Inc., Mont-Saint-Hilaire, Quebec, Canada) at 1 mg/kg 24 hours before the procedure. Experienced endosonographers encountered no technical difficulty in performing the procedure, including passage of the light delivery fiber into solid tissue and administration of the light dose. There was no immediate or delayed complication in any of the 3 animals. Total of 26 treatment locations were performed in liver (5), pancreas (9), kidneys (9), and spleen (3). The area of PDT-induced necrosis was similar in the pancreas, liver, and kidney, but smaller in the spleen compared to the other organs. The authors concluded that EUS-guided low-dose PDT ablation of the pancreas is feasible and safe. This technique may be applicable to small lesions in the pancreas or liver. PDT can cause a focal necrotic area of 3.6 mm^2 during each application of light (50 J/cm for 120 seconds), thus a lesion with a diameter of 10 mm and a wall thickness of 1 mm could be ablated with 3 light exposures. However, further studies are required to confirm similar results in human pancreas.

EUS-Guided Celiac Plexus Neurolysis

Pain is a significant source of morbidity in the patients with unresectable pancreatic cancer and chronic pancreatitis. Mechanisms of pain production in both conditions have much in common but may also differ [25]. Pancreatic cancer has a predilection for perineural invasion leading to the generation of pain [26]. In addition, increased intrapancreatic or intraductal pressures, ulceration, stretching of the capsule, ductal obstruction, and spread to celiac or other retroperitoneal lymph nodes may also contribute [25, 26]. The majority of pancreatic pain is mediated by sympathetic visceral afferent fibers relaying via the celiac plexus, through the crurae of the diaphragm to the splanchnic nerves, entering the spinal cord at the fifth to ninth thoracic segments. The celiac plexus consists of a variable number of ganglia which lies in front of the diaphragmatic crurae, slightly anterior and cephalad to the celiac trunk.

Celiac plexus neurolysis (CPN) is a chemical splanchnicectomy and has been performed for almost 100 years as a palliative treatment to alleviate pancreatic pain. A variety of techniques, routes, and chemical agents have been used to maximize the efficacy and minimize the complications [27, 28, 29]. CPN has been most commonly performed under fluoroscopic or computerized tomography (CT) guidance using either bilateral posterior or an anterior approach. Recently, a few studies using EUS guidance have confirmed

the similar or probably superior results [30]. EUS-guided approach offers several theoretical advantages over the other routes. The celiac plexus can be clearly visualized from the lesser curvature of the gastric body by tracing the aorta to the origin of the main celiac trunk using curvilinear echoendoscope. The procedure can be performed under real-time guidance with Doppler study to avoid inadvertent injection into blood vessels. EUS-guided FNA to confirm the diagnosis and staging can also be performed at the same time. In addition, the anterior approach avoids the retrocrural space and should minimize the risk of neurological complications from thrombosis or spasm of the anterior spinal artery or artery of Adamkiewicz [30].

There are few prospective studies of EUS-guided CPN in the patients with pancreatic cancer. Gunaratnam *et al*. reported the results of a prospective observational study in 58 patients with pancreatic cancer [31]. EUS-guided CPN provided pain relief in 78% of patients, which was sustained to 24 weeks and independent of changes in analgesic doses or use of adjuvant therapy.

A randomized controlled trial comparing EUS-guided CPN versus sham injection is currently underway to confirm the efficacy at our Institution.

Conclusions

EUS has matured over the past several years as an essential investigation for pancreatic cancer. The capability of EUS to precisely access the tumor has led to the development of therapeutic indications. A better understanding of the molecular biology and events that lead to the development and progression of pancreatic cancer are underway with the anticipation that many potential targets for therapy will be identified. These developments will revolutionize the role of EUS from a purely diagnostic procedure to a powerful therapeutic tool. EUS with fine needle injection in pancreatic cancer therapy represents an approach worth pursuing, given the poor prognosis of this disease and the feeling that survival benefits associated with conventional therapy have nearly maximized.

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