A phase I and pharmacokinetic study of NK105, a paclitaxel-incorporating micellar nanoparticle formulation.


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This phase I study was designed to examine the maximum tolerated dose (MTD), the dose-limiting toxicities (DLTs), the recommended dose (RD) for phase II, and the pharmacokinetics of NK105, a new polymeric micelle carrier system for paclitaxel (PTX). NK105 was administered as a 1-h intravenous infusion every 3 weeks, without antiallergic premedication. The starting dose was 10 mg/m², and the dose was escalated according to the accelerated titration method. Nineteen patients were recruited. The tumour types treated included pancreatic (n=11), bile duct (n=5), gastric (n=2), and colonic (n=1) cancers. Neutropenia was the most common hematological toxicity. A grade 3 fever developed in one patient given 180 mg/m². No other grades 3 or 4 nonhematological toxicities, including neuropathy, was observed during the entire study period. DLTs occurred in two patients given 180 mg/m² (grade 4 neutropenia lasting for more than 5 days). Thus, this dose was designated as the MTD. Grade 2 hypersensitivity reactions developed in only one patient given 180 mg/m². A partial response was observed in one patient with pancreatic cancer. The maximum concentration (C_max) and area under the concentration (AUC) of NK105 were dose dependent. The plasma AUC of NK105 at 150 mg/m² was approximately 15-fold higher than that of the conventional PTX formulation. NK105 was well tolerated, and the RD for the phase II study was determined to be 150 mg/m² every 3 weeks. The results of this phase I study warrant further clinical evaluation.

Human MUC4 mucin induces ultrastructural changes and tumorigenicity in pancreatic cancer cells.

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MUC4 is a type-1 transmembrane glycoprotein and is overexpressed in many carcinomas. It is a heterodimeric protein of 930 kDa, composed of a mucin-type subunit, MUC4alpha, and a membrane-bound growth factor-like subunit, MUC4beta. MUC4 mRNA contains unique 5’ and 3’ coding sequences along with a large variable number of tandem repeat (VNTR) domain of 7-19 kb. A direct association of MUC4 overexpression has been established with the degree of invasiveness and poor prognosis of pancreatic cancer. To understand the precise role of MUC4 in pancreatic cancer, the authors engineered a MUC4 complementary DNA construct, mini-MUC4, whose deduced protein (320 kDa) is comparable with that of wild-type MUC4 (930 kDa) but represents only 10% of VNTR. Stable ectopic expression of mini-MUC4 in two human pancreatic cancer cell lines, Panc1 and MiaPaCa, showed that MUC4 minigene expression follows a biosynthesis and localisation pattern similar to the wild-type MUC4. Expression of MUC4 resulted in increased growth, motility,
and invasiveness of the pancreatic cancer cells in vitro. Ultra-structural examination of MUC4-transfected cells showed the presence of increased number and size of mitochondria. The MUC4-expressing cells also demonstrated an enhanced tumorigenicity in an orthotopic xenograft nude mice model, further supporting a direct role of MUC4 in inducing the cancer properties. In conclusion, these results suggest that MUC4 promotes tumorigenicity and is directly involved in growth and survival of the cancer cells.

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**Pharmacogenomics of gemcitabine: can genetic studies lead to tailor-made therapy?**

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Gemcitabine is a deoxycytidine analogue that has a broad spectrum of antitumour activity in many solid tumours including pancreatic cancer. The authors have recently carried out a pharmacogenomic study in cancer patients treated with gemcitabine, and found that one genetic polymorphism of an enzyme involved in gemcitabine metabolism can cause interindividual variations in the pharmacokinetics and toxicity of this agent. In this paper, the authors review recent genetic studies of gemcitabine, and discuss the possibility of individualised cancer chemotherapy based on a pharmacogenomic approach.

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**Intense adrenal enhancement in patients with acute pancreatitis and early organ failure.**

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Intense adrenal enhancement has previously been reported in patients with hypovolemic and septic shock. The purpose of this study was to assess whether this computed tomography (CT) finding is also observed in patients presenting with severe acute pancreatitis and early organ failure. A retrospective analysis of a prospectively collected database was performed. Out of 38 consecutive patients with predicted severe acute pancreatitis, 3 patients showed intense bilateral adrenal enhancement on early CT. All patients had early multiple organ failure and subsequently died. In two cases, pathologic correlation was obtained. Intense adrenal enhancement may be a new prognostic indicator in patients with acute pancreatitis, particularly when organ failure is present at the time of CT examination. Further studies are necessary to confirm this observation.

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**Functional polymorphisms of the GSTT-1 gene do not predict the severity of acute pancreatitis in the United States.**

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Acute pancreatitis (AP) is an inflammatory response to pancreatic injury that is clinically classified as mild AP or severe AP, depending on specific criteria. Rahman et al. [Gastroenterology 2004; 126:1312-22] reported that genetic variation in the glutathione S-transferase theta-1 gene (GSTT-1) is associated with susceptibility and severity of
AP in England. The aim of this study was to determine whether the same GSTT-1 polymorphism affects the severity of AP in a population from Pittsburgh, PA, USA. Ninety-one consecutive patients with AP (19 severe) were prospectively evaluated. The GSTT-1 haplotypes were determined by PCR amplification in all patients and 268 controls. The resulting genotypes were classified as functional (GSTT-1*A/*A or *A/null) and nonfunctional (GSTT-1 null/null) phenotypes. The relative frequencies of functional GSTT-1 phenotypes were similar in subjects with severe AP (15 of 19, 78.9%) and mild AP (61 of 72, 84.7%; P=0.54) and in the controls (228 of 268, 85.1%; P=0.66). Furthermore, the GSTT-1 functional and nonfunctional phenotypes were not associated with serum C-reactive protein levels (11.9 vs 7.3 mg/dL; P=0.19), interleukin-6 levels (74 vs. 60 pg/mL; P=0.9), APACHE II scores (7 vs. 9; P=0.26), or 48-hour Ranson scores (1 vs. 1; P=0.63). Functional GSTT-1 phenotypes do not correlate with susceptibility to AP or severity of AP in this patient population.

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Laparoscopic pancreatic resection: the past, present, and future.
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Since the early 1990s, laparoscopic techniques have been applied to a growing number of pancreatic surgeries. Laparoscopic pancreatic resections have been performed in patients with a variety of diseases including chronic pancreatitis, pancreatic trauma, congenital hyperinsulinism, and neoplasms of the pancreas; e.g., insulinoma, mucinous cystic neoplasm, intraductal papillary mucinous neoplasm, etc. Laparoscopic pancreatic resections with an en bloc lymph node dissection have also been performed for invasive carcinomas. However, the long-term results after laparoscopic resections for invasive pancreatic cancer are still not well defined. Laparoscopic distal pancreatectomies with or without spleen preservation may benefit patients with reduced postoperative pain, shorter hospital stay, a quicker recovery to normal activity, and better cosmetic appearances based on retrospective analyses of collective series and case reports. Prospective randomized controlled trials are needed to validate these benefits. In contrast, laparoscopic proximal pancreatectomies with or without duodenum preservation remain controversial. Although a laparoscopic pancreaticoduodenectomy and laparoscopic duodenum-preserving pancreatic head resection are technically feasible, laparoscopic reconstruction after proximal pancreatectomies is not yet generally practicable but limited to personal experiences by highly skilled endoscopic surgeons. To justify the performance of laparoscopic proximal pancreatectomies, it is mandatory to demonstrate the potential clinical benefits and safety of these complicated procedures.

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Laparoscopic distal pancreatectomy with splenic preservation.
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The technique of distal pancreatectomy has been well described, both with en bloc resection of the spleen and with splenic preservation. Splenic preservation during pancreatic tail resection is desirable when oncologically appropriate, yet it is technically challenging, particularly with laparoscopic approaches. Skeletonization of the splenic artery and vein is associated with longer operative times and greater potential for bleeding. The authors report their experience with splenic preservation during laparoscopic
pancreatic resection using ligation of the splenic vessels and preservation of the short gastric vessels. A retrospective chart review was performed for all patients who underwent attempted laparoscopic pancreatic resection at Duke University Medical Center from July 2002 to October 2005. Charts were analyzed for demographic information, length of hospital stay, conversion, splenic preservation, and postoperative complications. A total of 12 laparoscopic distal pancreatic resections were attempted for three men and nine women with a mean age of 55.8 years (range: 33-74 years). All 12 patients underwent distal pancreatectomy, 8 with splenic preservation. The spleen was removed from three patients using splenic hilar lesions that prevented splenic salvage. One patient required splenectomy secondary to more than 50% ischemia of the spleen. No patients with preoperatively diagnosed malignancy underwent splenic salvage. The final pathologic diagnosis included neuroendocrine tumors (n=2), cystic serous (n=4) and mucinous (n=2) neoplasms, intraductal papillary mucinous neoplasm (IPMN) (n=1), pancreatitis (n=2), and adenocarcinoma (n=1). Two patients underwent conversion to open surgery for thickened parenchyma secondary to chronic pancreatitis (17%). There were no other conversions. There were three chemical leaks (25%) diagnosed by elevated drain amylase and low volume output, which were managed with intraoperatively placed drains removed at the initial postoperative clinic visit. There were three higher volume leaks (25%) that required extended or percutaneous drainage, with eventual removal. The average blood loss was 215 mL (range: 50-700 mL). The average operative time was 3 h and 41 min (range: 2 h 15 min to 5 h 58 min). The average length of hospital stay was 4 days (range: 2-7 days). Splenic preservation should be performed when technically possible to decrease the morbidity of laparoscopic distal pancreatectomy. The choice to ligate the splenic vessels allows for shorter operative times with minimal perioperative morbidity and blood loss while maintaining the spleen.

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Recurrent flares of pancreatitis predict development of exocrine insufficiency in chronic pancreatitis.

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The natural history of specific morphologic stages of chronic pancreatitis (CP) is not well defined. The aim of this study was to determine if worsening morphologic stages of CP are associated with poorer clinical outcomes. A retrospective analysis of 159 subjects with CP was performed. The baseline stage of CP was categorized according to the Cambridge classification. Pain was categorized as type A (intermittent acute), B (continuous), or combined. Exocrine failure was defined by steatorrhea; endocrine failure was characterized as diabetes mellitus. Complications were defined clinically. Pancreatic duct (PD) morphology was equivocal in 37.1%, minimal in 12.6%, moderate in 7.5%, and severe in 42.8% of the patients. Over a median follow-up period of 3.7 years, the risk of developing exocrine insufficiency and diabetes was 28% and 19%, respectively. Recurrent acute flares of pancreatitis predicted the development of exocrine insufficiency (P=0.004). Severe PD morphology predicted the likelihood of having persistent pain (P=0.008). Patients with concurrent type A and B pain and older age at diagnosis had a greater likelihood of having persistent pain (P=0.021). The risk of developing bile duct stricture was higher in the advanced morphologic stages of CP (P=0.005). Recurrent flares of pancreatitis predispose to the development of exocrine insufficiency in CP. Patients with complex-type pain, older age at diagnosis, and advanced morphologic stage are more likely to have persistent pain. PD morphology does not correlate with the risk of developing exocrine failure and/or diabetes. Pain does not
necessarily decrease or disappear with the onset of exocrine insufficiency and diabetes.

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In this commentary, the authors offer evidence about the burden of chronic conditions and use diabetes as a case study to reveal the gap between recommended and actual care in Canada. What they found through our research is cause for concern - namely, that the care that Canadians with diabetes receive is simply not good enough (an inconvenient truth) and that the country has tremendous untapped potential to prevent chronic illness and improve the quality of care (a convenient truth). Our work and the work of others help Canadians understand the benefits that will accrue to them from investments to close the gap between what we know and what we do.

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