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PANCREATIC CANCER AND CHRONIC PANCREATITIS: RECENT ADVANCES IN PATHOGENESIS, MOLECULAR BIOLOGY AND SURGERY

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Molecular changes in Chronic Pancreatitis and Pancreatic Cancer

To summarize, the pathogenesis of pain, tissue destruction, inflammation and fibrosis in CP is better understood today than ever before. Recent advances in cellular molecular biology have revealed complex interactions between inflammatory cells and pancreatic parenchyma cells as well as alterations in nerves. It is now clear that nerve changes, well studied and observed in alcoholic CP for over a decade, are also similar in other forms of CP such as tropical and idiopathic CP. Thus the pathobiological pathways responsible for the pain syndrome of CP reach a common final pathway irrespective of underlying etiological form of CP. The NK-1 receptor, critical for the action of the pain neurotransmitter substance P, is now confirmed to be overexpressed in relevant areas of chronic pancreatitis tissues. These findings further confirm the phenomenon of neuroimmune cross talk in CP apart from raising promising possibilities for therapeutic interventions to treat pain of CP. Inflammatory changes in CP, responsible for the morphophological alterations of continuing tissue destruction and fibrosis in this disease, are identical in different forms of CP. It is thus proposed that the disease reaches a “common surgical stage” where the inflammatory changes are similar irrespective of the underlying etiology of CP. Further molecular and cell biology studies will undoubtedly

increase our knowledge of the pathogenesis and pathophysiology of this disease, hopefully resulting in better diagnostic and therapeutic modalities in the future.

In pancreatic cancer, the overexpression of XIAP in pancreatic cancer tissues raises interesting possibilities because XIAP acts fairly downstream in the apoptotic pathway. It remains to be seen whether inhibition of this gene can enhance the therapeutic efficacy of anti-cancer agents and improve prognosis of pancreatic cancer. However, despite our knowledge of the complex interaction of growth factors and growth factor receptors in association with gene mutations and other genetic alterations, yet unknown systems continue to operate and function more efficiently than researchers. But there is no doubt that effective therapeutic intervention for pancreatic cancer will have to apply the molecular knowledge accumulated so far by researchers from around the world. In the coming years, it is expected that an increasing number of therapeutic strategies (for e.g. biologic agents) will develop, which would improve the prognosis of pancreatic cancer.

Pancreatic Surgery for Chronic Pancreatitis and Pancreatic Cancer

In 2005, management of CP should be tailored according to the patient´ symptoms that are assessed by objective tests and by sound radiological imaging that precisely documents the dominant focus and extent of the disease. This information is crucial in the context that pain in small duct CP seems to be more difficult to manage than pain in CP with a dilated main pancreatic duct. Pancreatic resection provides the best results as far as pain management in CP is concerned. These procedures are especially useful when a malignant neoplasm must be excluded in small duct CP with a head dominant mass. Before undertaking resection for what is largely a benign disease, the individual surgeon must assess his or her own abilities and experience since a low risk is a prerequisite. With over 90% long term pain relief and results of randomized trials in favour of DPPHR and its modification, these recent organ preserving procedures should be the benchmark against which all alternative treatment modalities for pain management of CP with head dominant disease should be evaluated. These demanding procedures are best undertaken in high volume, experienced centers with excellent results. The causes of recurrent or persistent pain following drainage procedures are complex, multifactorial, and as yet ill understood. It can be due to inadequate drainage of the head of the gland, failure to drain small ducts and associated perineural inflammation as can happen in the management of pancreas divisum where there is often absence of ductal dilation and a drainage procedure results in failure of pain control. However, acceptable outcomes can still

be achieved in this group of patients by identifying the residual disease and planning a strategy aimed at it.

Procedures which have combined the advantages of resectional surgeries with those of drainage procedures have gained ground in recent times for pain management especially in small duct CP. Pending larger series and long term results, resectional procedures may be tested by procedures such as the longitudinal V-shaped excision of the ventral pancreas, an extensive drainage procedure that offers the benefits of resection without its attendant morbidity.

In pancreatic adenocarcinoma surgical resection offers the best hope for prolonged survival, and major resections have evolved into very safe procedures in experienced centers. PPPD can now be considered to be the standard operation for pancreatic head cancer. A safe pancreatic anastomosis is the most critical step to ensure good outcomes after these major operations which can have potentially serious complications. As our unpublished experience shows, early haemorrhage, another feared complication after pancreaticoduodenectomy, can be managed effectively in centers of excellence thus undermining the need for centralization of these major resectional procedures. If clear established guidelines are followed by the intensive care, endoscopy, radiology, and surgical teams without any confusion, satisfactory outcomes can be achieved more in the event of early haemorrhage rather than in delayed haemorrhage. While experienced high volume centres are likely to yield better results in these emergent situations, clearly the surgeon remains one of the most, if not the most, important prognostic factor in prevention of early haemorrhage after pancreaticoduodenectomy.

Patients with tumors adherent to the PV should have PV resection performed only if negative resection margins can be obtained. Current evidence does not support extended lymphadenectomy as the standard of care, and it should be confined to prospective randomized trials. The recent unpublished experience with resections for pancreatic ductal adenocarcinoma with M1 disease, with survival rates better than all other currently available palliative treatment modalities, raises distinct possibilities to suggest a role for radical resections in highly selected patients.

Chronic Pancreatitis and Pancreatic Carcinogenesis

As far as role of CP in the development of pancreatic cancer is concerned, while the increased risk of cancer developing on a background of CP is established and the pathways better elucidated, the significance of gene mutations such as K-ras or p53 mutations in CP has not

yet been clearly defined. New technologies, such as DNA arrays, provide a systematic way to survey concomitant RNA expression of a large number of genes and could help in understanding and evaluating the pathology of CP. In the future, specific alterations identified by DNA array analysis will serve as targets for new diagnostic strategies in CP. Certain alterations might also enable the clinician to predict the course of the disease at an early stage making it possible to prevent or treat pancreatic cancer more effectively in those at risk.