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Status on anti-angiogenesis trials

Abstract not received.

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Biology of pancreatic cancer and implications for clinical management

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Since in the normal state cells of the pancreas show a very low rate of proliferation, entering the cell cycle is assumed to be the initial event during tumorigenesis. So-called checkpoints monitor cell cycle progression and guarantee the proper duplication of the entire genome.

Loss of one or more checkpoints causes subsequent accumulation of genetic alterations, which finally results in cancer. Cancer cells are characterized by unrestricted growth, invasion into adjacent tissue and metastasis. All these features can be explained in terms of genetic changes and the functional consequence of these changes. Recent advances have uncovered genetic events characteristic for human pancreatic cancer. The vast majority of pancreatic tumors show activation of the

K-RAS proto-oncogene and inactivation of the INK4a tumor suppressor gene locus. In addition, the P53 and SMAD4 genes are deleted and/or mutated in a very high percentage. Genes altered in lower frequency include

AKT2, BRAC2, LKB1/STK11, and mismatch repair genes. In addition to structural alterations, a great variety of growth factor receptors and their ligands are overexpressed in pancreatic cancer. The progression model of pancreatic cancer proposes pancreatic intraepithelial neoplasia

(PanIN) to be the precancerous lesions although the origin of pancreatic cancer is still a matter of debate. Functional evidence reveals that islet as well as acinar cells habor the potential to develop into ductal pancreatic cancer cells. A preferred genetic pathway is in progress of development. Germ-line mutations in specific genes are responsible for cases in which there is a familial predisposition to pancreatic cancer.

Gemcitabine remains the standard therapy, but has limited activity.

Clinical trails show that biologicals have promising activity including compounds directed against growth factors, their tyrosine kinase receptors, G-proteins as well as intracellular kinases.

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Adjuvant treatment for pancreatic cancer

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The results from pancreatic ductal adenocarcinoma appear to be improving with increased resection rates and reduced post-operative mortality reported by specialist pancreatic cancer teams. There are now five adjuvant randomized controlled trials. GITSG showed in resection margin negative patients a median survival of 20 months for adjuvant chemoradiotherapy (radiosensitisation with 5-FU) and maintenance weekly bolus 5-FU versus 11 months for controls. In the EORTC trial (104 patients) there was no significant difference in median survival with adjuvant chemoradiotherapy vs controls (12.6 and 17.1 months) a similar finding to the ESPAC 1 trial (546 patients; 15.5 vs 16.1 months respectively). The Norwegian trial of 47 patients with pancreatic/ampullary tumours showed a better median survival (23 months) with FAM (5-FU, doxorubicin, mitomycin C) compared with controls (11 months) but not 3-year survival. A Japanese trial in 173 patients (curative resections=92) showed a median survival of 12 months in both the chemotherapy (oral 5-FU) and control arms. The ESPAC 1 trial however, showed a median survival of 20.7 months for chemotherapy (weekly bolus 5-FU/folinic acid) versus 15.9 months for no chemotherapy (a highly significant difference). The balance of evidence shows a beneficial survival effect for adjuvant chemotherapy but not chemoradiotherapy. The ESPAC-3 (Europe, Canada and Australasia) pancreas cancer adjuvant trial has recruited around 300 of 990 patients targeted and is comparing 5-FU/folinic acid and gemcitabine (Cancer Research UK).

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Current status of investigational chemoradiotherapy regimens in pancreatic cancer

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Clinical trials investigating gemcitabine based chemoradiotherapy regimens remain under active investigation for the treatment of patients with pancreatic cancer. These trials are based, in part, on the activity of gemcitabine as a single agent and preclinical studies which demonstrate radiosensitization of human pancreatic cancer cell lines. The majority of these phase I trials have investigated gemcitabine dose escalation with radiation therapy regimens (i.e., dose, fractionation and treatment volumes) previously utilized with concurrent 5-FU. An early multicenter trial investigated weekly gemcitabine concurrent with 50.4 Gy (1.8 Gy/fraction). Both hematologic and gastrointestinal toxicity were found to be dose limiting above 600 mg/m^2. A similar trial recommended 440 mg/m^2 with 55.8 Gy[1]. The delivery of weekly gemcitabine with accelerated fractionation (30 Gy in 10 fractions) has found that doses >400 mg/m^2 are not well tolerated[2]. Twice weekly gemcitabine with 50.4 Gy has also been studied, in attempt to maximize radiosensitization. A phase II CALGB trial prescribed 40 mg/m^2 (Mon/Thurs). The toxicity was judged to be manageable, although only 26% of patients completed therapy without treatment breaks or dose reductions[3]. Gemcitabine based combination chemotherapy during radiation therapy has been investigated as well, with further gemcitabine dose reduction required for toxicity[4-6]. In each of these trials, the inclusion of regional nodal basins in the radiation treatment volumes may have contributed to the toxicity observed. An alternative strategy has been developed to maximize systemic drug effect while providing local control through sensitization of a modest radiation dose[7]. In the ongoing phase II trial, gemcitabine is delivered weekly (x 3) at 1000 mg/m^2, concurrent with 36 Gy in 15 fractions. The radiation fields are planned with a conformal 3D technique, to cover the gross tumor volume only (i.e., no elective nodal irradiation). The relative lack of toxicity observed with this approach suggests that the radiation treatment volume is the most critical variable in the design of gemcitabine based chemoradiotherapy regimens. This experience also highlights the need to fully consider the design of these trials in the context of both local and distant disease control, given the radiosensitizing and systemic activity of gemcitabine. As newer agents are integrated into these combined modality regimens, these considerations become even more critical, such that the novel agents can be incorporated to maximize their therapeutic potential.

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New paradigms in pancreas cancer management

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The treatment of adenocarcinoma of the pancreas remains a formidable therapeutic challenge. Compared to other malignancies, this disease is frequently diagnosed late in its course and has an unusual predisposition for early invasion and metastases. In addition, pancreatic carcinoma has been considered to be relatively resistant to conventional cancer therapies. Recently, the nucleoside analogue gemcitabine has been shown to have modest effectiveness in controlling symptoms and improving survival. Through a better understanding of the pharmacodynamics of gemcitabine, it has been possible to improve the activation of this pro-drug resulting in better therapeutic efficacy. Based on the known genotypic and phenotypic alterations in pancreatic adenocarcinoma further advances in therapy are anticipated by the application of a rational approach to drug discovery. Although the potential menu of targets is still unfolding, some attractive new agents are available and poised for application in this disease. In addition, pancreatic adenocarcinoma displays a number of host-tumor interactions suggesting that this malignancy can co-opt its environment to enhance progression, invasion, and metastasis. These additional cell-cell interactions may provide new avenues for therapeutic intervention. Finally, multimodality approaches to pancreatic cancer are under new scrutiny with regard to the timing of adjuvant therapy in respectable disease and