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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

the appropriate sequence and use of radiation and chemotherapy in both respectable and locally advanced disease. These refinements have great potential to improve disease control.

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How do we choose new molecular targets for clinical exploitation?

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The recent expansion of our knowledge of new molecular targets for cancer therapy provides an exciting opportunity to introduce a new generation of molecular biological response modifiers (MBRM) in clinical studies. Encouraging clinical results using for example epidermal growth factor receptor blockers, angiogenesis inhibitors and signal transduction modulators are the product of basic science translating this increased understanding of molecular biology to an improved clinical care for cancer patients. However, many of these inhibitors of growth factors and signal transduction are cytostatic and, as single agent, not sufficient to eradicate all malignant cells. The advantage of combining these MBRM with radiation lies in the interaction between both treatment modalities, leading to increased and sometimes synergistic cytotoxicity. Moreover, high-dose high-precision radiotherapy will add another dimension to this approach by enhancing cytotoxicity selectively at the tumor site while sparing normal tissues. *How do we choose new molecular targets for clinical exploitation?* There are many aspects that need to be considered to guide a promising MBRM from its molecular identification through preclinical models into phase I-III trials. For example, in the first *in vitro phase* of this process, characterization of the *type of interaction* between a candidate MBRM and radiation is crucial, since it may provide a first indication about the chance of a successful application *in vivo*. Additive cytotoxicity may simply be not enough to improve therapeutic results. The choice of the *appropriate in vitro assays* should be dictated by properly predefined endpoints/read-outs, because almost no compound exhibits absolute target specificity and biological effects develop over time. As most *in vitro* assays focus on one particular cell type, they fail to take into account relevant *microenvironmental influences*, like survival signals, hypoxia and normal cell interactions. The next *in vivo phase* of the process provides a better approximation of the physiological state and habitat of primary tumors. In this context, transgenic animal models for *spontaneous tumorigenesis* offer many advantages over xenograft tumor systems since they allow studying the impact of specific genes on treatment sensitivity. Collectively, these preclinical *in vitro* and *in vivo* results should form the basis for the rational design of new clinical trials for combined modality treatment.

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p53 signaling and novel mechanisms for targeted radiosensitizers

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Objective: p53 protein can induce growth arrest, apoptosis and cell senescence upon stress stimulation including ionizing radiation. P53 mutations are common and occur in more than 50% of human malignancies. P53 mutations, abnormal sub-cellular localization, subsequent dysfunction (e.g. abnormal cytoplasmatic sequestration) and downstream defects in the p53 signaling pathway have been reported in radio-resistant human cancer. Therefore both better mechanistic insight into tissue specific p53 signaling and tumour specific defects in p53 signaling are needed. P53 independent radiosensitizers are of clinical interest if they re-sensitize radio-resistant human tumours with a known intrinsic/acquired defect in p53 signaling and if they maintain a large therapeutic index given concurrently with low dose fractionated ionizing radiation (IR). Our group is focusing on various strategies to overcome clinically relevant tumor specific defects in p53 signaling.

Results: Overall the screening for p53 "independent" radiosensitizers lead to the following preclinical results: 1)Taxol was among the first compounds identified in a p53 mouse sarcoma system but with a small therapeutic window 2) The PKC inhibitor, PKC-412, did no longer induce apoptotic cell death if combined with IR in p53 dysfunctional tumours but induced a G2 cell cycle arrest in combination with IR. This effect was supra-additive and well tolerated in vivo. An intact PI3K/AKT pathway is required for this combination. 3) The transcription factor E2F1 and specific genetically engineered mutants of E2F1 are potent radiosensitizers if combined with IR in tumour cells lacking p53. However "gene replacement" is still far from clinical application. 4) Anti-angiogenic agents like inhibitors of the VEGF receptor tyrosine kinase (e.g. PTK 787/ ZK222548) are of interest, because combined treatment with IR primarily targets the p53 wildtype angiogenic tumour system. 5) Recent screening identified recombinant Lectin I (one of the main compounds of mistletoe) as a novel radiosensitizer in p53-mutated tumour cell lines.

Conclusion: Both better mechanistical understanding of p53 tissue- and tumour specific signaling and novel radiosensitizers with a broad therapeutic index targeting the p53 signaling pathways are required.

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EGF-receptor inhibition and radiotherapy

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Background: The epidermal growth factor receptor (EGFR) is overexpressed in many human tumours and plays a major regulative role in cell proliferation. The EGFR may be activated by irradiation leading to a proliferative response. This might be an important component of accelerated repopulation of clonogenic tumour cells during fractionated radiotherapy. Furthermore activation of the EGFR may increase intrinsic cellular radioresistance. From these findings combination of radiotherapy with EGFR inhibition appears to be a promising strategy in cancer treatment.

Materials and methods: Preclinical experiments on combination of radiotherapy and EGFR inhibition are reviewed.

Results: Investigations in vitro showed an antiproliferative effect and increased radiosensitivity in several tumour cell lines after inhibition of the EGFR. Experiments on tumour models in vivo demonstrated that EGFR inhibitors can prolong growth delay (GD) compared to irradiation alone. GD and local tumour control (TCD50 assay) after single dose irradiation were evaluated in one tumour model. The enhancement ratio was significantly lower in the TCD50 than in the GD assay. In own experiments GD and TCD50 were investigated for fractionated irradiation combined with the selective EGFR-TK-inhibitor BIBX1382BS. As in the experiments reported by others GD was significantly enhanced after simultaneous combined treatment, however, this did not translate into improved local tumour control. In a further experiment the same finding was obtained for adjuvant EGFR inhibition after radiotherapy.

Conclusions: To fully utilize the potential of combining EGFR-inhibitors with irradiation, further investigations are necessary that explore the mechanisms of action and the efficacy of the approach.

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The PI3K/AKT pathway: a target for new chemo-radiation approches?

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Phosphoinositide 3-Kinase (PI3K) catalyze the production of specific inositol lipids that have been implicated in a plethora of cell functions. One of the best-characterized targets of PI3K lipid products is the serine/threonine protein kinase AKT (PKB). Activation of the PI3K/AKT pathway can suppress the apoptotic response, undermine cell cycle control, enhance cell survival and proliferation. The PI3K/Akt signal transduction cascade has been investigated extensively for its roles in oncogenic transformation. Compelling evidence suggests that members of PI3K family can be considered as oncogenes because they control cell cycle progression, differentiation, survival, invasion and metastasis as well as angiogenesis. The activity of fundamental growth factor receptors like PDGFR, EGFR and IGFR are blocked by the specific PI3Ks inhibitor wortmannin, leading to the conclusion that the PI3Ks/AKT pathway is critical for cell signaling. Response to ionizing radiation is also regulated through the PI3K/AKT signaling pathway by distinct mechanisms. When transiently expressed a constitutively active PI3K gene can induce radioresistance. It has been suggested that the phosphorylated active form of AKT could be a significant predictor for local control in head and neck cancer patients after radiation therapy. PTEN, which is a lipid phosphatase frequently inactivated in cancers, acts as an inhibitor of the PI3K/AKT pathway. Restoration of the PTEN gene can sensitize malignant cells to irradiation. The PI3K/AKT pathway is involved in cell cycle control, activated AKT overrides G2/M. checkpoint induced by irradiation. This pathway is also regulating survival of vascular endothelial cells after irradiation. Enhancement of endothelial cell viability after irradiation. occurs through the PI3K/Akt signal transduction pathway. Interestingly, the use