

Pancreatic cancer: chemotherapy and radiotherapy

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Abstract

Pancreatic cancer in many cases appears in a non-curatively resectable stage when the diagnosis is made. Palliative treatment become an option in the patients with advanced stage. The present article reviewed chemotherapy and radiotherapy in various advanced stage of pancreatic cancer.

Keywords: Pancreas, pancreatic cancer, chemotherapy, radiotherapy, adjuvant.

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Neoadjuvants

Gemcitabine plus oxaplatin

Neoadjuvant chemotherapy can facilitate pancreatic resection in patients with initially unresectable pancreatic cancer (PC). It was reported the results of a phase II trial of gemcitabine-oxaliplatin neoadjuvant chemotherapy for patients with locally advanced, nonmetastatic PC. A prospective, phase II clinical trial using neoadjuvant chemotherapy, consisting of gemcitabine (900 mg/m²) and oxaliplatin (60 mg/m²) given as intravenous infusion once a week at day 1 of each treatment cycle (NeoGemOx protocol). Patients received 6-9 cycles of chemotherapy. Those patients with sufficient tumor regression subsequently underwent pancreatic resection and were followed postoperatively to assess long-term survival. A total of 33 patients were eligible and were included in the intent-to-treat and evaluable population. On centralized review of the imaging studies, 18 patients had unresectable disease at inclusion, and 15 patients had borderline resectable PC. Eventually, 13 patients (39 %) had a curative resection after neoadjuvant therapy. The R0 resection rate was 69 percent. Median overall survival of patients who underwent tumor resection was 22 months (95 % confidence interval 14 to 30) compared with 12 months (95 % confidence interval 9 to 15) for those without resection. The median recurrence-free survival rate after resection was 10 months (95 % confidence interval 4 to 17). It was concluded that neoadjuvant gemcitabine plus oxaliplatin is well tolerated and safe. Substantive tumor regression occurs in some patients with locally advanced pancreatic

treated with this neoadjuvant protocol, offering the potential for curative resection and improvement in overall survival [1].

Docetaxel plus radiotherapy

To assess the safety and efficacy of a new neoadjuvant chemoradiation (CRT) docetaxel-based regimen in patients with resectable adenocarcinoma of the pancreatic head or body 34 patients with histologically-confirmed resectable pancreatic adenocarcinoma were included in this prospective two-center phase II study. Radiotherapy was delivered at the dose of 45 Gy in 25 fractions of 1.8 Gy per fractions, 5 days/week, over 5 weeks. Docetaxel was administered as a 1-h intravenous (IV) infusion repeated every week during 5 weeks. The dose was 30 mg/m²/week. All patients were restaged after completion of CRT. Tumor progression was documented in 11 patients (32 %), stable disease was documented in 20 patients (59 %), and partial remission was documented in 3 patients (9 %). 23 patients still with local disease at restaging underwent explorative laparotomy. Of this, 17 patients (50%) had a curative pancreaticoduodenectomy with lymphadenectomy. Morbidity and mortality rates were 29 percent and 0%, respectively. Three patients (17 %) had complete histological responses and 5 patients had minimal residual disease. All resected patients (n=17) underwent R0 resection. The median and five-year survival times for the resected patients were 32 months and 41percent, respectively. Among the resected patients, ten (59 %) died as a result of recurrent pancreatic cancer without local

tumor bed recurrence. It was concluded that the neoadjuvant docetaxel-based chemoradiation is well-tolerated. Resected patients had a prolonged survival time [2].

Adjuvant

Standardization of surgical reports in adjuvant studies

Standardization of surgical and pathologic techniques is crucial to the interpretation of studies evaluating adjuvant therapies for pancreatic cancer (PC). To assess the degree to which treatment administered prior to enrollment of patients in trials of adjuvant therapy is quality controlled, the operative and pathology reports of patients in American College of Surgeons Oncology Group (ACOSOG) Z5031-a national trial of chemoradiation following pancreaticoduodenectomy (PD)-were rigorously evaluated. It was analyzed variables with the potential to influence staging or outcome. Eighty patients reported to have undergone R0 (75 %) or R1 (25 %) pylorus-preserving (38 %) or standard (62 %) PD were evaluated. A search for metastases was documented in 96 percent of cases. The proximity of the tumor to the superior mesenteric vein was reported in 69 percent; vein resection was required in 9 percent and lateral venorrhaphy in 14 percent. The method of dissection along the superior mesenteric artery (SMA) was described in 68 percent, being ultrasonic dissection (17 %), stapler (24 %), and clamp and cut (59 %). SMA skeletonization was described in 25 percent, and absence of disease following resection was documented in 24 percent. The surgeon reported marking the critical SMA margin in 25 percent; inking was documented in 65 percent of cases and evaluation of the SMA margin was reported in 47 percent. A range of 1-49 lymph nodes was evaluated. Only 34 percent of pathology reports met College of American Pathologists criteria. It was thus found that trials of adjuvant therapy following PD suffer from a lack of standardization and quality control prior to patient enrollment. These data suggest areas for improvement in the design of multidisciplinary treatment protocols [3].

Prognostic marker for response to adjuvant gemcitabine

Treatment options for pancreatic ductal adenocarcinoma (PDA) typically includes surgery and/or chemotherapy with gemcitabine. No reliable biomarker exists for prognosis or response to chemotherapy. Two previously proposed prognostic markers, cyclooxygenase-2 (COX-2) and vascular endothelial growth factor (VEGF), are regulated by Hu protein antigen R (HuR), an mRNA binding protein that we have previously demonstrated to be a promising predictive marker of gemcitabine response. One study was designed to evaluate the clinical utility of HuR, COX-2, and VEGF as potential prognostic and predictive biomarkers for PDA. A tissue microarray of 53 PDA specimens from patients who underwent potentially curative pancreatic resection was analyzed. HuR, COX-2, and VEGF status were correlated with clinicopathologic and survival data. It was also performed ribonucleoprotein immunoprecipitation assays using an HuR antibody to assess VEGF and COX-2 mRNA binding to HuR in pancreatic cancer cells. Roughly 50 percent (27/53) of

patients had high cytoplasmic HuR expression. These patients had significantly worse pathologic features as assessed by T staging. Only cytoplasmic HuR status correlated with tumor T staging, whereas VEGF and COX-2 expression did not correlate with T staging. Additionally, HuR status was an unprecedented positive predictive marker for overall survival in patients treated with gemcitabine, pushing median survival over 45 months in the high cytoplasmic HuR expressing patient population compared with less than 23 months in the low cytoplasmic HuR expressing patient group for the low versus high cytoplasmic HuR expressing group. It was also validated that mRNA transcripts for both VEGF and the gemcitabine metabolizing enzyme, deoxycytidine kinase, are specifically bound by HuR in pancreatic cancer cells. It was concluded that HuR is a useful prognostic biomarker for PDA patients as indicated by its association with higher tumor T stage. Additionally, HuR status is a robust predictor of outcome for patients with resected PDA in the setting of adjuvant gemcitabine therapy. Finally, HuR binds to VEGF mRNA implying that HuR, in part, regulates VEGF expression in PDA [4].

Gemcitabine versus 5-fluorouracil plus folinic acid

Adjuvant fluorouracil has been shown to be of benefit for patients with resected pancreatic cancer. Gemcitabine is known to be the most effective agent in advanced disease as well as an effective agent in patients with resected pancreatic cancer. The European Study Group for Pancreatic Cancer (ESPAC)-3 trial, an open-label, phase 3, randomized controlled trial conducted in 159 pancreatic cancer centers in Europe, Australasia, Japan, and Canada. Included in ESPAC-3 version 2 were 1088 patients with pancreatic ductal adenocarcinoma who had undergone cancer resection; patients were randomized between 2000 and 2007 and underwent at least 2 years of follow-up. Patients received either fluorouracil plus folinic acid (folinic acid, 20 mg/m², intravenous bolus injection, followed by fluorouracil, 425 mg/m² intravenous bolus injection given 1-5 days every 28 days) (n=551) or gemcitabine (1000 mg/m² intravenous infusion once a week for 3 of every 4 weeks) (n=537) for 6 months. Primary outcome measure was overall survival; secondary measures were toxicity, progression-free survival, and quality of life. Final analysis was carried out on an intention-to-treat basis after a median of 34 (interquartile range, 27-43) months' follow-up after 753 deaths (69 %). Median survival was 23 (95 % confidence interval 21 to 25) months for patients treated with fluorouracil plus folinic acid and 24 (95 % confidence interval 21 to 26) months for those treated with gemcitabine (hazard ratio, 0.94; 95 % confidence interval 0.81 to 1.08). Seventy-seven patients (14 %) receiving fluorouracil plus folinic acid had 97 treatment-related serious adverse events, compared with 40 patients (78 %) receiving gemcitabine, who had 52 events, which was a statistically significant difference. There were no significant differences in either progression-free survival or global quality-of-life scores between the treatment groups. The authors concluded that compared with the use of fluorouracil plus folinic acid, gemcitabine

did not result in improved overall survival in patients with completely resected pancreatic cancer but was less toxic [5].

Gemcitabine plus radiotherapy

A randomized phase II intergroup study explores the feasibility and tolerability of a gemcitabine-based chemoradiotherapy (CRT) regimen after R0 resection of pancreatic head cancer. Within 8 weeks after surgery, patients were randomly assigned to receive either four cycles of gemcitabine (control arm) or gemcitabine for two cycles followed by weekly gemcitabine with concurrent radiation (50.4 Gy; CRT arm). The primary objective was to exclude a < 60 percent treatment completion and a > 40 percent rate of grade 4 hematologic or GI toxicity in the CRT arm with type I and II errors of 10%. Secondary end points were late toxicity, disease-free survival (DFS), and overall survival (OS). Between 2004 and 2007, 90 patients were randomly assigned (45 to 45). Patient characteristics were similar in both arms. Treatment was completed per protocol by 87 percent and 73 percent in the control and CRT arms, respectively, and grade 4 toxicity was 0 percent and 5 percent, respectively. In the CRT arm, three patients experienced grade 3-related late toxicity. Median DFS was 12 months in the CRT arm and 11 months in the control arm. Median OS was 24 months in both arms. First local recurrence was less frequent in the CRT arm (11% vs 24%). It was concluded that adjuvant gemcitabine-based CRT is feasible, well-tolerated, and not deleterious [6].

Intraoperative radiotherapy

To retrospectively analyze the results of intraoperative radiotherapy (IORT) with or without external beam radiotherapy (EBRT) for resected pancreatic cancer the records of 210 patients treated with gross complete resection (R0: 147 patients; R1: 63 patients) and IORT with or without EBRT were reviewed. One hundred forty-seven patients (70 %) were treated without EBRT and 114 patients (54 %) were treated in conjunction with chemotherapy. The median doses of IORT and EBRT were 25 Gy (range, 20-30 Gy) and 45 Gy (range, 20-60Gy), respectively. The median follow-up of the surviving 62 patients was 26 months (range, 3-91 months). At the time of this analysis, 150 of 210 patients (71 %) had disease recurrences. Local failure was observed in 31 patients (15 %), and the 2-year local control rate in all patients was 84 percent. The median survival time but the 2-year actuarial overall survival (OS) in all 210 patients were 19 months and 42 percent, respectively. Patients treated with IORT and chemotherapy had a significantly more favorable OS than those treated with IORT alone. On univariate analysis, chemotherapy use, degree of resection, CA 19-9, and pathological N stage had a significant impact on OS and on multivariate analysis; these four factors were significant prognostic factors. Late gastrointestinal morbidity of NCI-CTC Grade 4 was observed in 7 patients (3 %). The authors concluded that IORT yields an excellent local control rate for resected pancreatic cancer with few frequencies of severe late toxicity, and IORT combined with chemotherapy confers a survival benefit compared with that of IORT alone [5].

Stereotactic body radiotherapy

The aim of this study was to evaluate the role of stereotactic body radiotherapy (SBRT) as adjuvant therapy for resected pancreatic adenocarcinoma with close or positive margins. Between 2006 and 2010, 24 patients were treated with adjuvant SBRT following surgical resection. Eight (33 %) patients had close margins of 1-2.5 mm to the retroperitoneal, vascular structures, and periduodenal adipose tissue. Sixteen (67 %) patients had positive margins at retroperitoneal margin and vascular structures. Twenty-three patients received 24 Gy (20-24 Gy) in one fraction, and one had 30 Gy in three fractions. The median target volume was 11 cc (4.5-30 cc). Eighteen patients were treated with the Cyberknife® Robotic Radiosurgery System and six patients were treated with Trilogy intensity-modulated radiosurgery. Kaplan-Meier survival analyses were used to estimate freedom-from-local-progression (FFLP), and overall survival (OS) rates. PET/CT or CT was used to monitor disease recurrence following SBRT. The median follow-up for all patients was 13 months (1-40 months), and among surviving patients it was 16 months (2-40 months). The FFLP rates at 6 months, 1 and 2 years were 95 percent, 66 percent, and 44 percent, respectively. Overall, FFLP was achieved in seven (88 %) patients with close margins, and 10 (63 %) with positive margins. After SBRT, 19 patients resumed or started a 6-month course of gemcitabine-based chemotherapy at a median interval of 18 days (range, 9-31 days) post-SBRT. The median OS was 27 months and the 1- and 2-year OS rates were 80 percent and 57 percent, respectively. Of the 24 patients, 12 (50 %) developed distant metastases of whom two (25 %) had close margins and 10 (63 %) had positive margins. Ten patients (42 %) were free of progression at last follow-up (range, 3-40 months). Three patients (13 %) had grade 1-2 acute GI toxicities, and two patients (8 %) had grade 1 and 2 late toxicities. No patients experienced grade 3 or 4 toxicity, including bowel perforation, secondary to SBRT. The data suggest that adjuvant SBRT for resected pancreatic cancer can be achieved with minimal toxicity. This shorter treatment course allowed initiation of systemic chemotherapy shortly after the completion of SBRT [7].

Gemcitabine

Gemcitabine is widely used as first-line chemotherapeutic drug in the treatment of pancreatic cancer. Previous experimental chemotherapy studies have shown that treatment of human pancreatic carcinoma cells with 5-fluorouracil (5-FU) alters the cellular transporter expression profile and that modulation of the expression of multidrug resistance protein 5 (MRP5; ABCC5) influences the chemoresistance of these tumor cells. It was now studied the influence of acute and chronic gemcitabine treatment on the expression of relevant uptake and export transporters in pancreatic carcinoma cells by reverse transcription-polymerase chain reaction (RT-PCR), quantitative RT-PCR, and immunoblot analyses. The specific role of MRP5 in cellular gemcitabine sensitivity was studied by cytotoxicity assays using MRP5-overexpressing and MRP5-silenced cells. Exposure

to gemcitabine (12 nM for 3 days) did not alter the messenger RNA (mRNA) expression of MRP1, MRP3, MRP5, and equilibrative nucleoside transporter 1 (ENT1), whereas high dosages of the drug (20 microM for 1 hour) elicited up-regulation of these transporters in most cell lines studied. In cells with acquired gemcitabine resistance (up to 160 nM gemcitabine), the mRNA or protein expression of the gemcitabine transporters MRP5 and ENT1 was upregulated in several cell lines. Combined treatment with 5-FU and gemcitabine caused a 5- to 40-fold increase in MRP5 and ENT1 expressions. Cytotoxicity assays using either MRP5-overexpressing (HEK and PANC-1) or MRP5-silenced (PANC1/shMRP5) cells indicated that MRP5 contributes to gemcitabine resistance. Thus, the novel data not only on drug-induced alterations of transporter expression relevant for gemcitabine uptake and export but also on the link between gemcitabine sensitivity and MRP5 expression may lead to improved strategies of future chemotherapy regimens using gemcitabine in pancreatic carcinoma patients [6].

Gemcitabine ± cetuximab

There is an article specially discussing the safety, efficacy and pharmacokinetics of nimotuzumab, a humanized monoclonal anti-epidermal growth factor receptor (EGFR) antibody, in patients with locally advanced or metastatic pancreatic cancer [8].

Patients with advanced pancreas cancer present with disease that is poorly responsive to conventional therapies. Preclinical and early clinical evidence has supported targeting the epidermal growth factor receptor (EGFR) signaling pathway in patients with pancreas cancer. One trial was conducted to evaluate the contribution of an EGFR-targeted agent to standard gemcitabine therapy. Cetuximab is a monoclonal antibody against the ligand-binding domain of the receptor. Patients with unresectable locally advanced or metastatic pancreatic adenocarcinoma were randomly assigned to receive gemcitabine alone or gemcitabine plus cetuximab. The primary end point was overall survival. Secondary end points included progression-free survival, time to treatment failure, objective response, and toxicity. A total of 745 eligible patients were accrued. No significant difference was seen between the two arms of the study with respect to the median survival time (6 months or the gemcitabine plus cetuximab arm vs. 6 months for the gemcitabine alone arm; hazard ratio = 1.06; 95 % confidence interval 0.91 to 1.23). Objective responses and progression-free survival were similar in both arms of the study. Although time to treatment failure was significantly longer in patients on gemcitabine plus cetuximab, the difference in length of treatment was only 2 weeks longer in the combination arm. Among patients who were studied for tumor EGFR expression, 90 percent were positive, with no treatment benefit detected in this patient subset. It was concluded that in patients with advanced pancreas cancer, the anti-EGFR monoclonal antibody cetuximab did not improve the outcome compared with patients treated with gemcitabine alone [9].

Study results for patient-reported health-related quality of life (HRQL) outcomes were also reported. Patients completed the Brief Pain Inventory and a measure of emotional well-being (each measured on a 0 to 10 scale) at baseline and at weeks 5, 9, 13, and 17 postrandom assignment. Worst pain status was classified as palliated (worst pain scores < 5 maintained for 2 consecutive cycles) or not palliated (remaining patients). Change in emotional well-being and worst pain (exploratory analysis) were assessed over 17 weeks using generalized estimating equations with inverse probability of censoring weights. Seven hundred twenty of 766 enrolled patients contributed baseline HRQL data. The two treatment arms did not differ statistically in the percentage of patients with successful worst pain palliation. Longitudinal analyses showed significantly improved emotional well-being for patients on both arms by weeks 13 and 17. An exploratory longitudinal analysis of worst pain showed significant decreases at all time points for both arms. Significant treatment arm differences for either worst pain or emotional well-being were not observed at any of the assessment times. It was observed palliated pain and improved well-being for patients on this trial. However, these improvements were similar in both treatment arms, suggesting that the addition of cetuximab did not contribute to improvement in these HRQL outcomes [10].

Gemcitabine ± Bevacizumab

The combination of gemcitabine plus bevacizumab, (Avastin®; rhuMab VEGF), a monoclonal antibody targeting vascular endothelial growth factor (VEGF), produced a 21 percent response rate and a median survival of 9 months in a multicenter phase II trial in patients with metastatic pancreatic cancer. These encouraging data led Cancer and Leukemia Group B (CALGB) to conduct a double-blind, placebo-controlled, randomized phase III trial of gemcitabine/bevacizumab vs. gemcitabine/placebo in advanced pancreatic cancer patients. Eligible patients had no prior therapy for advanced disease, Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2, no tumor invasion of adjacent organs, and no increased bleeding risk. The primary end point was overall survival. Patients were stratified by performance status, extent of disease, and prior radiotherapy. Patients received gemcitabine at 1,000 mg/m² over 30 minutes on days 1, 8, and 15 every 28 days and bevacizumab at 10 mg/kg or placebo on days 1 and 15 every 28 days. Between 2004 and 2006, 602 patients were enrolled onto the study and 535 were treated. Median overall survival was 6 months for gemcitabine/bevacizumab and 6 months for gemcitabine/placebo. Median progression-free survival was 4 and 3 months, respectively. Overall response rates were 13 percent and 10 percent, respectively. Patients with a performance status of 0, 1, and 2 survived a median of 8, 5, and 2 months, respectively. The only statistically significant differences in grades 3 and 4 toxicity occurred for hypertension (10 % vs. 3 %) and proteinuria (5 % vs. 1 %); venous thrombosis grade ≥ 3 was equivalent in both arms (14 % and 15 %, respectively). It was concluded that the addition of bevacizumab to gemcitabine does not

improve survival in advanced pancreatic cancer patients [11].

Bevacizumab has seen increased use in the perioperative treatment of colorectal and pancreatic cancer. Little is known, however, regarding its impact on surgical outcomes in patients undergoing resection. The objective of one review was to examine if the addition of bevacizumab to existing neoadjuvant regimens increases morbidity after cancer resection [12].

Gemcitabine plus Erlotinib

National Cancer Institute of Canada Clinical Trials Group PA.3 (NCIC CTG PA.3) was a phase 3 study (n=569) that demonstrated benefits for overall survival and progression-free survival with the addition of the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) erlotinib to gemcitabine in patients with advanced pancreatic carcinoma (APC). Mutation status of the v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) and EGFR gene copy number (GCN) were evaluated as predictive markers in 26 percent of patients who had tumor samples available for analysis. KRAS mutation status was evaluated by direct sequencing of exon 2, and EGFR GCN was determined by fluorescence in situ hybridization (FISH) analysis. The results were correlated with survival, which was the primary endpoint of the trial. KRAS analysis was successful in 117 patients, and EGFR FISH analysis was successful in 107 patients. KRAS mutations were identified in 92 patients (79 %), and EGFR amplification or high polysomy (FISH-positive results) was identified in 50 patients (47 %). The hazard ratio of death between gemcitabine/erlotinib and gemcitabine/placebo was 0.66 (95 % confidence interval 0.28 to 1.57) for patients with wild-type KRAS and 1.07 (95 % confidence interval 0.68 to 1.66) for patients with mutant KRAS and the hazard ratio was 0.6 (95 % confidence interval 0.34 to 1.07) for FISH-negative patients and 0.90 (95% confidence interval 0.49 to 1.65) for FISH-positive patients. It was concluded that in a molecular subset analysis of patients EGFR gene copy number and KRAS mutation status were not identified as markers predictive of a survival benefit from the combination of erlotinib with gemcitabine for the first-line treatment of APC [2].

Gemcitabine plus Imexone

Imexon is an aziridine-derived iminopyrrolidone which has synergy with gemcitabine in pancreatic cancer cell lines. Gemcitabine is a standard therapy for pancreatic cancer. It was performed a phase I trial of imexon and gemcitabine to evaluate safety, dose-limiting toxicity (DLT), and maximum tolerated dose (MTD) in patients with advanced pancreatic cancer. Patients with untreated locally advanced or metastatic pancreatic adenocarcinoma received therapy in sequential cohorts on regimen A (n=19; imexon 200 or 280 mg/m² intravenously (IV) over 30 min days 1-5, 15-19 and gemcitabine 800 or 1,000 mg/m² IV over 30 min on days 1,8,15 every 28 days) or regimen B (n=86; imexon 280-1,300 mg/m² IV over 30-60 min days 1, 8, and 15 and gemcitabine 1,000 mg/m² IV over 30 min on days 1, 8, and

15 every 28 days). One hundred five patients received 340 treatment cycles (median 2, range 1-16). Patient characteristics: median age 63, 61 percent male, ECOG PS 0/1 50 percent/50 percent, 93 percent metastatic. DLT was abdominal cramping and pain, often with transient, acute diarrhea. Best response was confirmed partial response (PR) in 11 percent, 9 percent unconfirmed PR, and 48 percent with stable disease. There was a dose proportional increase in imexon AUC across the doses tested with terminal half life 69 min at the MTD and no alteration of gemcitabine pharmacokinetics. The recommended phase II dose of imexon is 875 mg/m² with gemcitabine 1,000 mg/m. Dose-limiting toxicity was acute abdominal pain and cramping. Encouraging antitumor responses support further evaluation of this combination in advanced pancreatic cancer [13].

Gemcitabine plus S1

The aim of one study was to investigate the feasibility and efficacy of induction chemotherapy with gemcitabine and S-1 followed by chemoradiotherapy for locally advanced pancreatic cancer. Patients with locally advanced unresectable pancreatic cancer received four cycles of induction chemotherapy consisting of 30-min intravenous infusions of gemcitabine 1,000 mg/m² on days 1 and 8 and oral S-1 40 mg/m² twice daily on days 1-14 of a 21-day cycle. Those without disease progression received chemoradiotherapy of 30 Gy in ten fractions with 250 mg/m² of gemcitabine on days 1 and 8. A total of 20 patients were treated. Median follow-up time was 431 days (range 133-1,014 days). Four cycles of induction chemotherapy were completed in 18 patients, and 16 patients received chemoradiotherapy, which was completed without delay in all. Grade 3-4 toxicities associated with induction chemotherapy were neutropenia (50 %); anemia (20 %); thrombocytopenia (10 %); febrile neutropenia (5 %); nausea (10 %); anorexia (10 %); and vomiting, fatigue, dehydration, stomatitis, and rash (5 %). Grade 3-4 toxicities among those receiving chemoradiotherapy were neutropenia (13%) and anemia (6%). Median progression-free survival was 8 months. Median overall survival was 14 months, with a 1-year survival rate of 54 percent. The regimen of induction chemotherapy with gemcitabine and S-1 followed by chemoradiotherapy used in the present study demonstrated promising activity in locally advanced pancreatic cancer [14].

In a case reported a patient with pancreatic body cancer with multiple liver metastasis in which S-1 plus gemcitabine (GEM) therapy proved to be effective. A 77-year old female was asymptomatic and diagnosed as a pancreatic body cancer with multiple liver metastases at the end of 2008 by periodical ultrasonography. After careful examination, GEM 1,200 mg/body was administered on days 1 and 15, and S-1 was administered orally at 80 mg/day for two weeks, followed by two weeks rest. Currently, at the end of the 10th course, tumor size has been reduced from 27 mm to 19 mm, and two of the five liver metastatic lesions have disappeared, while the remaining three liver lesions have been revealed as scars by CT

examination. Tumor marker levels have been remarkably decreased. Ten months from the initial diagnosis, there has been no side effect and chemotherapy is being continued [15].

Gemcitabine plus Radiotherapy

To accurately determine the maximal tolerated dose, feasibility, and antitumor activity of concurrent chemoradiotherapy including twice-weekly gemcitabine in patients with unresectable pancreatic adenocarcinoma all eligible patients with histologically proven adenocarcinoma of the pancreas were included in a phase I trial. Radiotherapy was delivered to a total dose of 50 Gy. Concurrent chemotherapy with twice-weekly gemcitabine was administered during the 5 weeks of radiotherapy, from an initial dose of 30 mg/m². The gemcitabine doses were escalated in 10 mg/m² increments in a three-plus-three design, until dose-limiting toxicities were observed. A total of 35 patients were included in the trial. The feasibility of chemoradiotherapy was high, because all the patients received the planned total radiation dose, and 26 patients (74 %) received ≥ 70 percent of the planned chemotherapy dose. The mean total delivered dose of gemcitabine was 417 mg/m² (i.e. 77% of the prescribed dose). The maximal tolerated dose of twice-weekly gemcitabine was 70 mg/m². Of the 35 patients, 13 had a partial response (37 %) and 21 had stable disease (60 %). Overall, the median survival and the 6-, 12-, and 18-month survival rates were 11 months and 82 percent, 31 percent, and 11 percent, respectively. Survival was significantly longer in patients with an initial performance status of 0 or 1. According to the authors these mature data have indicated that gemcitabine doses can be increased ≤ 70 mg/m², when delivered twice-weekly with concurrent radiotherapy. This combination shows promises to achieve better recurrence-free and overall survival [16].

Docetaxel

No therapeutic standard of care exists for patients who have progressed following first-line treatment with a gemcitabine-based regimen with advanced pancreatic cancer. Approximately half of the patients failing upfront treatment present with ECOG PS 1-2 and are willing to undergo further treatment. Docetaxel activity against pancreatic cancer is reported both in the preclinical and clinical setting. One study retrospectively evaluated the role of docetaxel as second-line therapy in patients with gemcitabine-refractory disease. Between 2006 and 2009, 17 patients (median age of 61 years) with advanced pancreatic adenocarcinoma, after receiving gemcitabine-containing chemotherapy as first-line median ECOG performance status 1 and with adequate organ function, were treated with either weekly docetaxel at 25 mg/m² or 3-weekly docetaxel regimen (docetaxel at 75 mg/m² or docetaxel-gemcitabine-capecitabine or docetaxel-gemcitabine) until progressive disease. Serum CA19-9 levels were measured every 3/4 weeks and CT scans performed after every eight/nine weeks. Docetaxel dose intensity was 90 percent in the patients who received weekly docetaxel, 85% in docetaxel-erlotinib regimen and 65% in 3-weekly regimen

(docetaxel-gemcitabine-capecitabine, docetaxel-gemcitabine). Only one objective response (6%) to treatment was obtained (docetaxel-gemcitabine), while 5 patients achieved stable disease (weekly docetaxel). Median progression-free survival was 8 weeks (range: 3-16 weeks) and median survival was 4 months (range: 2-7 months). No toxicity with grade >3 associated with docetaxel was observed. Thus, docetaxel seems to have mild activity in the treatment of gemcitabine-resistant metastatic pancreatic cancer [17].

S-1

112 patients with pancreatic cancer who received chemotherapy between 2001 and 2007 were divided into 2 groups: PreS-1 (53 patients who started chemotherapy before 2005) and PostS-1 (59 patients who started chemotherapy after 2005, the time of S-1 introduction). Patient characteristics and clinical outcomes were compared, and prognostic factors were analyzed. Patient characteristics did not significantly differ between the 2 groups. S-1 was administered as a second-line monotherapy in 6 percent of the PreS-1 group and combined with gemcitabine as a first-line therapy in 27 percent or as second-line monotherapy in 24 percent in the PostS-1 group. Both progression-free survival and overall survival improved after introduction of S-1 (median progression-free survival, 4 and 5 months which was a significant difference; median overall survival, 10 and 13 months; which also was significant in PreS-1 and PostS-1 groups, respectively). Multivariate analysis revealed that the PostS-1 group (hazards ratio, 0.52), performance status, and carcinoembryonic antigen were significant prognostic factors for survival. It was concluded that the introduction of S-1 may improve the prognosis of Japanese patients with advanced pancreatic cancer [18].

It was investigated the impact of S-1 on the prognosis of patients with gemcitabine-refractory pancreatic cancer. A total of 108 patients with gemcitabine-refractory pancreatic cancer were divided by the time of S-1 introduction in the institution: 47 patients who experienced progressive disease before 2005 (pre-S-1 group) and 61 patients showed progressive disease after 2005 (post-S-1 group). Introduction rates of second-line chemotherapy and survival were compared. Introduction rates of second-line chemotherapy were 13 percent in the pre-S-1 group and 46 percent in the post-S-1 group. Second-line chemotherapy was administered to 34 patients: 29 using S-1, 4 using 5-fluorouracil-based chemoradiation and 1 using 5-fluorouracil. The objective response rate, progression-free survival and overall survival for second-line chemotherapy with S-1 were 17 percent, 3 and 8 months, respectively. By the introduction of S-1 in the institution, residual survival was prolonged from 3 months in the pre-S-1 group to 7 months in the post-S-1 group, which was a significant increase. Overall survival from the initiation of gemcitabine was 9 months in the pre-S-1 group and 11 months in the post-S-1 group. Multivariate analysis identified the post-S-1 group (hazard ratio, 0.43), gender, performance status, liver metastasis, and lactate

dehydrogenase and C-reactive protein levels at progressive disease for gemcitabine to be prognostic factors for residual survival. The authors concluded that the introduction of S-1 might improve the prognosis of patients with gemcitabine-refractory pancreatic cancer [19].

A 65-year-old man suffering from acute pancreatitis underwent MRI scanning, which revealed a low signal on the T1 and T2 sequences, and hypovascularity in arterial phase in the head of the pancreas. This corresponded to the area showing the absence of the lower common bile duct. FDG-PET was highly suggestive of pancreatic cancer (T4N1M0, Stage IVa) with lymph node metastasis. He was treated with systemic chemotherapy using gemcitabine (GEM) followed by radiotherapy. His symptoms gradually improved with a reduction in size of the primary lesion. The patient has been receiving systemic chemotherapy using S-1 without recurrence [20].

Breath test for prediction of effect

S-1 is an oral anticancer drug containing tegafur (FT), a pro-drug of fluorouracil, combined with two modulators, 5-chloro-2,4-dihydropyridine and potassium oxonate (Oxo), at a molar ratio of 1:0.4:1. CYP2A6 genetic polymorphism and dihydropyrimidine dehydrogenase (DPD) inhibition are important for the antitumor effect of S-1. Exploiting the usefulness of the 2-¹³C-uracil breath test (UrBT) as an indicator of DPD activity, it was examined whether the results of CYP2A6 genetic polymorphism analysis and UrBT could be used to predict the antitumor effect of S-1. Thirty-four patients with advanced or recurrent cancer (15, 16 and 3 with gastric, colorectal and pancreatic cancer, respectively) were orally administered 40 mg/m² S-1 twice daily in the morning and evening. Eighteen patients with a complete response (CR)/partial response (PR) (2 with CR, 16 with PR) and 16 with progressive disease (PD) were compared with respect to CYP2A6 genetic polymorphisms (1- vs 2-allele mutation), UrBT results, and plasma FT and 5-fluorouracil levels at 3 h after S-1 ingestion in the morning. On multivariate analysis between the CR/PR and PD groups, only the UrBT results was an independent factor of CR/PR to S-1 (95 % confidence interval 1.02 to 1.10). These results suggest that the anticancer effect of S-1 can be predicted by performing UrBT 3 h after the initial oral S-1 administration [21].

Ipilimumab

New and effective therapies are needed for pancreatic ductal adenocarcinoma. Ipilimumab can mediate an immunologic tumor regression in other histology. This phase II trial evaluated the efficacy of Ipilimumab for advanced pancreatic cancer. Subjects were adults with locally advanced or metastatic pancreas adenocarcinoma with measurable disease, good performance status, and minimal comorbidities. Ipilimumab was administered intravenously (3.0 mg/kg every 3 weeks; 4 doses/course) for a maximum of 2 courses. Response rate by response evaluation criteria in solid tumors criteria and toxicity were measured. Twenty-seven subjects were enrolled (metastatic disease: 20 and locally advanced: 7) with median age of 55

years (27 to 68 y) and good performance status (26 with Eastern Cooperative Oncology Group performance status 0 or 1). Three subjects experienced \geq grade 3 immune-mediated adverse events (colitis 1, encephalitis 1, hypophysitis 1). There were no responders by response evaluation criteria in solid tumors criteria but a subject experienced a delayed response after initial progressive disease. In this subject, new metastases after 2 doses of Ipilimumab established progressive disease. But continued administration of the agent per protocol resulted in significant delayed regression of the primary lesion and 20 hepatic metastases. This was reflected in tumor markers normalization, and clinically significant improvement of performance status. Single agent Ipilimumab at 3.0 mg/kg/dose is ineffective for the treatment of advanced pancreas cancer. However, a significant delayed response in one subject of this trial suggests that immunotherapeutic approaches to pancreas cancer deserve further exploration [22].

Chemoradiotherapy

The optimal management for patients with unresectable locally advanced adenocarcinoma of the pancreas (LAPC) is unclear. The aim of this study was to determine the outcome of patients treated with chemoradiotherapy (CRT) with or without induction chemotherapy. It was conducted a multi-centre retrospective analysis of 48 patients with biopsy-proven LAPC treated with CRT in four regional oncology centres in the UK between 2000 and 2007. The prescribed radiotherapy dose was 4500-5040 cGy in 25-28 fractions and was given concurrent with gemcitabine (n=37), gemcitabine/cisplatin (n=9), 5-fluorouracil (n=1) or capecitabine (n=1). Four patients (8.3%) did not complete the intended treatment due to CRT-related toxicities. The disease control rate (Objective response rate (ORR) and stable disease (SD)) was 81 percent. The median overall survival was 17 months (range 5-66 months). In subgroup analysis, a trend towards improved survival was seen in patients who completed the intended treatment (17 months vs. 11 months) and in patients undergoing surgery (27 months vs. 16 months). This is the largest reported series from the UK focusing on patients who received CRT for pancreas cancer. It shows that it is possible to deliver pancreatic CRT with acceptable toxicity. Induction chemotherapy followed by gemcitabine-based CRT shows promising activity and should be evaluated in phase III studies [23].

Stereotactic Radiosurgery

Locally advanced unresectable pancreatic adenocarcinoma is characterized by poor survival despite chemotherapy and conventional radiation therapy (RT). Recent advances in real-time image-guided stereotactic radiosurgery (SRS) have made it possible to treat these cancers in two to four fractions followed by systemic chemotherapy. The aims of one study included to obtain local control of the disease, to improve the survival of these unresectable patients, to evaluate the toxicity of SRS and to report results of the largest series from a single center. Pancreatic SRS involves

delivery of high doses of accurately targeted radiation given non-invasively in two to four fractions. It was treated 85 consecutive patients with locally advanced and recurrent pancreatic adenocarcinoma from 2004 to 2009. It was 80 adenocarcinoma, three islet cell, two other. Pre-SRS staging: T(3-4) 85; N(+) 16, N(x) 57, N(0) 12; M(0) 64, M(1) 21. All patients were unresectable at the time of SRS. Seventy-one had no prior surgical resection, and 14 had local recurrence after prior surgical resection. Twenty-nine patients had progression of disease after prior conventional RT. Location of the tumor: head, 57; body and tail, 28. Pre-SRS chemotherapy was given in 48 patients. All patients received gemcitabine-based chemotherapy regimen after SRS. Median tumor volume was 60 cm³. PET/CT scans done in 55 patients were positive in 52 and negative in three patients. Average maximum standard uptake value was 6.9. Pain score on a scale of 1-10 was: 0-3 in 54, 4-7 in 18, and 8-10 in 13 patients. SRS doses ranged from 15 to 30 Gy with a mean dose of 26 Gy delivered in 3 days divided in equal fractions. Mean conformality index was 1.6, and mean isodose line was 80 percent. Complete, partial, and stable disease were observed in 78 patients for the duration of 3-36 months with median of 8 months. Pain relief was noted in majority of patients lasting for 18-24 weeks. Most of the patients died of distant disease progression while their primary tumor was controlled. Overall median survival from diagnosis was 19 months and from SRS it was 9 months. For the group of 35 patients with adenocarcinoma without prior surgical resection or RT and no distant metastases, the average and 1-year survival from diagnosis was 15 months and 50 percent, respectively, and from SRS it was 11 months and 31 percent, respectively. A total of 19 (22%) patients developed grades III/IV GI toxicity including duodenitis, 12 (14 %); gastritis, 11 (13%); diarrhea, three (4 %); and renal failure was noted in one (1%). Three patients had both gastritis and duodenitis. Toxicity was significantly more prevalent in the first 40 patients compared with the last 45 patients (33 vs. 14%). It was concluded that SRS for unresectable pancreatic carcinoma can be delivered in three fractions with minimal morbidity and a local tumor control rate of 92 percent. The survival is comparable or better than the reported results for advanced pancreatic cancer, specifically for the group of previously untreated patients with unresectable tumors. Development of distant metastases remains a significant factor [24].

CyberKnife® is a newly developed technology in the field of stereotactic radiosurgery/radiotherapy (SRS/SRT). Compared with conventional SRS/SRT, there are many advantages for CyberKnife in terms of treating tumors that move with respiration, being real-time image-guidance, frameless, high accurateness, and so on. Recently, it has been used to treat different types of malignant carcinoma including intracranial and caudomedial tumors. One study was designed to evaluate the short-term efficacy and toxicity of the CyberKnife radiotherapy for locally advanced pancreatic cancer. A total of 20 patients with locally advanced (stage II-III) pancreatic cancer treated with CyberKnife were recruited in 2009. Of 20 patients, 13

were with cancer located at the pancreatic head and 7 were located at the pancreatic body and tail. The planning target volume (PTV) was defined as gross tumor volume (GTV) plus 2-3 mm, and more than 95 percent PTV should be covered by 75 percent isodose surface. The median of PTV was 47 cm³ (26-64 cm³). The median total prescription dose was 40 Gy (32-55 Gy) at 3-6 fractions. During treatment delivery, X-Sight Spine Tracking System was used in 5 patients to track movement of the tumor. Another 15 patients were implanted fiducials in the tumors to track movement of the tumor and patient breathing patterns. The median follow-up time was 7 months (3-11 months). All patients had finished the treatment and 19 were alive by the last follow-up. Slight fatigue was the most common complain. Evaluated by CT scan, 6 were complete response, 9 were partial response, 3 were stable disease, and 1 was progression; 1 was dead. There were 6 patients with grade I granulocytopenia, 7 with grade I nausea, and 5 with grade II vomiting. The authors concluded that CyberKnife radiosurgery for the locally advanced pancreatic cancer shows a high rate of local control and minimal toxicity, but long-term follow-up is necessary to evaluate the survival and late toxicity [25].

External Radiotherapy

To analyze retrospectively the results of postoperative external beam radiotherapy (EBRT) for resected pancreatic adenocarcinoma the records of 47 patients treated with gross complete resection (R0: 24 patients, R1: 23 patients) and post-operative EBRT were reviewed. The median dose of EBRT was 50 Gy (range, 12-60 Gy), and chemotherapy was used in 37 patients (79 %). The median follow-up period for all 47 patients was 14 months (range, 1-68 months). At the time of this analysis, 24 patients (51 %) had disease recurrence. Local failure was observed in 10 patients (21 %), and the 2-year local control (LC) rate in all patients was 69 percent. Patients treated with EBRT and chemotherapy had a significantly more favorable LC (2-year LC rate: 76 %) than those treated with EBRT alone (2-year LC rate: 40 %). The median survival time and the 2-year actuarial overall survival (OS) in all 47 patients were 30 months and 55 percent, respectively. Patients treated with EBRT and chemotherapy had a significantly more favorable OS (2-year OS rate: 62 %) than those treated with EBRT alone (2-year OS: 25 %). On univariate analysis, chemotherapy use alone had a significant impact on OS, and on multivariate analysis, chemotherapy use also was a significant prognostic factor. There were no late morbidities of NCI-CTC Grade 3 or greater. It was concluded that post-operative EBRT with chemotherapy yields a favorable LC rate for resected pancreatic adenocarcinoma, and EBRT combined with chemotherapy confers a survival benefit compared to EBRT alone [26].

Radiotherapy planning

Intensity-modulated radiotherapy (IMRT) allows for improved sparing of organs at risk (OARs) in advanced pancreatic cancer. A planning study evaluated if volumetric modulated arc therapy (RapidArc [RA]) could be used as an alternative to IMRT in such cases. In ten patients, five-field

IMRT (5f-IMRT) plans with fixed gantry positions were compared to RA plans using similar constraints for planning target volume (PTV) and OARs. PTV coverage, conformity indices (CI), and OAR doses were compared. One patient was treated using RA and calculated dose distributions were measured in coronal planes in a solid-water phantom. It was concluded that RA planning achieved superior CI for pancreatic tumors compared to 5f-IMRT, and modestly reduced OAR doses. Fast treatment delivery using RA may decrease the risk of intrafractional organ motion [27].

New Therapeutic Options

Pancreatic cancer (PC) is a highly lethal disease with complex etiology involving both environmental and genetic factors. Although cigarette smoking is known to explain 25 percent of cases, data from recent studies suggest that obesity and long-term type II diabetes are two major modifiable risk factors for PC. Furthermore, obesity and diabetes seem to affect the clinical outcome of patients with PC. Understanding the mechanistic effects of obesity and diabetes on the pancreas may identify new strategies for prevention or therapy. Experimental and epidemiologic evidence suggests that the antidiabetic drug metformin has protective antitumor activity in PC. In addition to insulin resistance and inflammation as mechanisms of carcinogenesis, obesity and diabetes are linked to impairments in endothelial function and coagulation status, which increase the risks of thrombosis and angiogenesis and, in turn, the risk of PC development and progression. The associations of the ABO blood group gene and NR5A2 gene variants with PC discovered by recent genome-wide association studies may link insulin resistance, inflammation, and thrombosis to pancreatic carcinogenesis. These exciting findings open new avenues for understanding the etiology of PC and provide opportunities for developing novel strategies for prevention and treatment of this disease [28].

High-intensity focused ultrasound ablation

The aim of one study was to evaluate the safety and efficacy of ultrasound-guided high-intensity focused ultrasound therapeutic ablation of solid tumors in difficult locations. A procedure was performed with a focused ultrasound tumor therapeutic system which provides real-time ultrasound guidance. All patients underwent MDCT or MRI, and some patients underwent PET/CT. From 2007 through 2009, 31 patients with 38 lesions of the liver and pancreas in difficult locations were treated. Six patients had hepatocellular carcinoma, 13 patients had hepatic metastasis from colorectal cancer, two had hepatic metastases of breast cancer, two had hepatic metastasis of neuroendocrine tumors, one patient had lymph node metastasis of breast cancer at the hepatic hilum, six patients had pancreatic cancer, and one patient had a neuroendocrine tumor. Difficult location was defined as tumor adjacent to a main blood vessel, the heart, the gallbladder and bile ducts, the bowel, or the stomach. The mean diameter of tumors was 2.7 ± 1.4 cm. PET/CT, MDCT, or both on the day after one session of high-intensity focused ultrasound treatment

showed complete response in all six patients with hepatocellular carcinoma, the patient with lymph node metastasis, and 22 of 24 patients with hepatic metastasis. The symptoms of all seven patients with pancreatic cancer or neuroendocrine tumors were palliated, and PET/CT or MRI showed complete response of six of seven lesions. Portal vein thrombosis occurred after high-intensity focused ultrasound ablation in one patient with pancreatic cancer. No other side effects were detected in a median follow-up period of 12 months. According to the short- and long-term follow-up results, ultrasound-guided high-intensity focused ultrasound ablation can be considered a safe and feasible approach to the management of solid tumors in difficult locations [29].

Curcumin

Curcumin (diferuloylmethane), a derivative of turmeric is one of the most commonly used and highly researched phytochemicals. Abundant sources provide interesting insights into the multiple mechanisms by which curcumin may mediate chemotherapy and chemopreventive effects on cancer. The pleiotropic role of this dietary compound includes the inhibition of several cell signaling pathways at multiple levels, such as transcription factors (NF- κ B and AP-1), enzymes (COX-2, MMPs), cell cycle arrest (cyclin D1), proliferation (EGFR and Akt), survival pathways (β -catenin and adhesion molecules), and TNF. Curcumin up-regulates caspase family proteins and down-regulates anti-apoptotic genes (Bcl-2 and Bcl-X(L)). In addition, cDNA microarrays analysis adds a new dimension for molecular responses of cancer cells to curcumin at the genomic level. Although, curcumin's poor absorption and low systemic bioavailability limits the access of adequate concentrations for pharmacological effects in certain tissues, active levels in the gastrointestinal tract have been found in animal and human pharmacokinetic studies. Currently, sufficient data has been shown to advocate phase II and phase III clinical trials of curcumin for a variety of cancer conditions including multiple myeloma, pancreatic, and colon cancer [30].

Genistein

Oxaliplatin (OxP) has been used in combination therapy with gemcitabine for the treatment of pancreatic cancer (PC) but the beneficial effect was marginal, which is believed to be due to de novo and acquired drug-resistance of PC. It was reported in vitro and in vivo preclinical evidence in support of chemo-sensitization of drug-resistant cells by a non-toxic chemopreventive agent (genistein). Genistein pretreatment together with low concentration of OxP showed significant reduction in cell viability and colony formation concomitant with increased apoptosis, which was highly synergistic. Drug-resistance of PC is allegedly linked with both constitutive and OxP-induced activation of NF- κ B, and it was found that inactivation of NF- κ B by genistein prior to treatment of cells with OxP was required for cell killing, which was consistent with the down-regulation of NF- κ B and its downstream anti-apoptotic genes (Bcl-2 XIAP's, survivin). Most importantly, the in vivo

experiments using orthotopic mouse model showed significant reduction in tumor size and reduction of locoregional lymph node metastasis by combination treatment. These results were also consistent with inactivation of NF-kappaB and the down-regulation of NF-kappaB downstream genes, decreased proliferation marker (Ki-67), and increased apoptosis (TUNEL) in tumor remnants, all of which was consistent with in vitro findings. From these results, it was concluded that genistein sensitizes drug-resistant PC to OxP, which is mechanistically linked with inactivation of NF-kappaB signaling, resulting in greater anti-tumor effects [31].

Etoposide particles

Amphiphilic diblock copolymers composed of methoxy poly ethylene glycol (MePEG) and poly epsilon caprolactone (PCL) were synthesized for the formation of micelles by ring opening mechanism using stannous octoate as a catalyst. The effects of the molecular weight of MePEG and the copolymer ratio on the properties of micelles were investigated by Nuclear Magnetic Resonance (¹H-NMR), Fourier Transform Infrared Spectroscopy (FT-IR), and Gel Permeation Chromatography (GPC). The diblock copolymers were self-assembled to form micelles and their hydrophobic core was used for the encapsulation of the anti-cancer drug (etoposide) in aqueous solution. The sizes of micelles were less than 250 nm with a narrow size distribution with monodispersed unimodal pattern. Differential Scanning Calorimetric (DSC) thermogram was done for etoposide-loaded micelles to understand the crystalline nature of the drug after entrapment. A drug loading capacity up to 60 percent (w/w) with an entrapment efficiency of 68% was achieved as determined by reverse phase high performance liquid chromatography (RP-HPLC). In vitro release kinetics showed a biphasic release pattern of etoposide for 2 weeks. The cytotoxic efficacy of the etoposide-loaded micelles demonstrated greater anti-proliferative activity (IC₅₀=1.1 microg/mL) as compared to native drug (IC₅₀=6.3 microg/mL) in pancreatic cancer cell line MIA-PaCa-2. Thus, etoposide-loaded MePEG/PCL block copolymeric micelles can be used as an efficient drug delivery vehicle for pancreatic cancer therapy [32].

Interferons

Clinical trials on pancreatic cancer demonstrated that interferons (IFN) improve the therapeutic index of combined radio- and chemotherapy. This is believed to be due to radiosensitisation of cells, which, however, needs experimental verification. It was therefore compared the survival response of ten pancreatic tumor cell lines following ionising radiation (IR), interferon-alpha (IFN-alpha), interferon-beta (IFN-beta) and combined treatment. The effect of combination treatment on apoptosis induction was also determined. In most cell lines IFN treatment on its own exerted cytotoxicity, which was independent of the expression level of the IFN receptor on the cell surface. Three cell lines showed a radiosensitisation effect while two showed radioprotection. Although IFN-alpha is commonly used in the clinic, IFN-beta

induced a stronger cytotoxic response than IFN-alpha in vitro. The likely mechanism of enhancement of radiosensitivity in the responsive cell lines was shown to be an increase of the radiation-induced apoptotic response by IFN pretreatment. Given that the in vitro data do not conform to the impressive clinical results observed after combined radio- and chemotherapy with IFN-alpha, it is reasonable to conclude that the sensitising effect of IFN is not mediated through modulating the intrinsic radiosensitivity of pancreatic cancer cells [33].

Nanoparticles with cetuximab

Gold and carbon nanoparticles absorb nonionizing radio frequency (RF) energy and release heat. Solid gold nanoparticles are delivered to cancer cells via conjugation with targeting antibodies. Here, 20-nm gold particles were conjugated to cetuximab, which is an epidermal growth factor receptor-1 (EGFR-1) antibody. A pancreatic carcinoma cell line that highly expresses EGFR-1, Panc-1, and Cama-1, which is a breast carcinoma cell line that minimally expresses EGFR-1, were treated with 100-nmol/L cetuximab-conjugated gold nanoparticles for 3 h (n=4). Thirty-six hours later, the dishes were placed in an RF field with a generator power of 200 W for 5 min. After another 36 h, cell injury and death were evaluated with flow cytometry. The targeted cell line Panc-1 had a viability of 46 % ± 12 %, whereas the Cama-1 cell had a viability of 92 % ± 2 % after RF field exposure, which was a significant difference. Transmission electron microscopy showed gold nanoparticle uptake in Panc-1 cells but negligible uptake by Cama-1 cells. Nontargeted cells do not internalize a sufficient amount of antibody-conjugated gold nanoparticles to induce injury in a noninvasive RF field. It was concluded that this technique could be useful in cancer treatment if a cancer-specific antibody is used to localize gold nanoparticles to malignant cells [34].

References

1. Sahara K, Kuehrer I, Eisenhut A, et al. NeoGemOx: Gemcitabine and oxaliplatin as neoadjuvant treatment for locally advanced, nonmetastasized pancreatic cancer. *Surgery* 2010 Sep 2 [Epub ahead of print].
2. da Cunha Santos G, Dhani N, Tu D, et al. Molecular predictors of outcome in a phase 3 study of gemcitabine and erlotinib therapy in patients with advanced pancreatic cancer: national Cancer Institute of Canada Clinical Trials Group Study PA.3. *Cancer* 2010 Sep 7 [Epub ahead of print].
3. Katz MH, Merchant NB, Brower S, et al. The American College of Surgeons Oncology Group. Standardization of surgical and pathologic variables is needed in multicenter trials of adjuvant therapy for pancreatic cancer: results from the ACOSOG Z5031 trial. *Ann Surg* 2010 Sep 1 [Epub ahead of print].
4. Richards NG, Rittenhouse DW, Freydn B, et al. HuR status is a powerful marker for prognosis and response to gemcitabine-based chemotherapy for

- resected pancreatic ductal adenocarcinoma patients. *Ann Surg* 2010; 252: 499-505.
5. Ogawa K, Karasawa K, Ito Y, et al. JROSG Working Subgroup of Gastrointestinal Cancers. Intraoperative radiotherapy for resected pancreatic cancer: a multi-institutional retrospective analysis of 210 patients. *Int J Radiat Oncol Biol Phys* 2010; 77: 734-742.
 6. Hagmann W, Jesnowski R, Löhr JM. Interdependence of gemcitabine treatment, transporter expression, and resistance in human pancreatic carcinoma cells. *Neoplasia* 2010; 12: 740-747.
 7. Rwigema JC, Heron DE, Parikh SD, et al.. Adjuvant stereotactic body radiotherapy for resected pancreatic adenocarcinoma with close or positive margins. *J Gastrointest Cancer* [Epub ahead of print].
 8. Strumberg D, Schultheis B, Scheulen ME, et al. Safety, efficacy and pharmacokinetics of nimotuzumab, a humanized monoclonal anti-epidermal growth factor receptor (EGFR) antibody, in patients with locally advanced or metastatic pancreatic cancer. *Int J Clin Pharmacol Ther* 2010; 48: 473-475.
 9. Philip PA, Benedetti J, Corless CL, et al. Phase III study comparing gemcitabine plus cetuximab versus gemcitabine in patients with advanced pancreatic adenocarcinoma: Southwest Oncology Group-directed intergroup trial S0205. *J Clin Oncol* 2010; 28: 3605-3610.
 10. Moinpour CM, Vaught NL, Goldman B, et al. Pain and emotional well-being outcomes in Southwest Oncology Group-directed intergroup trial S0205: a phase III study comparing gemcitabine plus cetuximab versus gemcitabine as first-line therapy in patients with advanced pancreas cancer. *J Clin Oncol* 2010; 28: 3611-3616.
 11. Kindler HL, Niedzwiecki D, Hollis D, et al. Gemcitabine plus bevacizumab compared with gemcitabine plus placebo in patients with advanced pancreatic cancer: phase III trial of the Cancer and Leukemia Group B (CALGB 80303). *J Clin Oncol* 2010; 28: 3617-3622.
 12. Cheon EC, Small W Jr, Strouch MJ, et al. The effects of bevacizumab on postoperative complications in patients undergoing colorectal and pancreatic cancer resection. *J Surg Oncol* 2010 Sep 1 [Epub ahead of print].
 13. Cohen SJ, Zalupski MM, Modiano MR, et al. A phase I study of imexon plus gemcitabine as first-line therapy for advanced pancreatic cancer. *Cancer Chemother Pharmacol* 2010; 66: 287-294.
 14. Nakachi K, Furuse J, Kinoshita T, et al. A phase II study of induction chemotherapy with gemcitabine plus S-1 followed by chemoradiotherapy for locally advanced pancreatic cancer. *Cancer Chemother Pharmacol* 2010; 66: 527-534.
 15. Fukui H, Kou C, Matsumoto T, Matsumoto M. S-1+gemcitabine (GEM) therapy effective in a case of pancreatic body cancer with multiple liver metastasis. *Gan To Kagaku Ryoho* 2010 Sep 37: 1775-1778.
 16. Girard N, Mornex F, Bossard N, Ychou M, Chauffert B, Wautot V. Estimating optimal dose of twice-weekly gemcitabine for concurrent chemoradiotherapy in unresectable pancreatic carcinoma: mature results of GEMRT-01 Phase I trial. *Int J Radiat Oncol Biol Phys* 2010; 77: 1426-1432.
 17. Saif MW, Syrigos K, Penney R, Kaley K. Docetaxel second-line therapy in patients with advanced pancreatic cancer: a retrospective study. *Anticancer Res* 2010; 30: 2905-2909.
 18. Nakai Y, Isayama H, Sasaki T, et al. Impact of S-1 on the survival of patients with advanced pancreatic cancer. *Pancreas* 2010; 39: 989-993.
 19. Nakai Y, Isayama H, Sasaki T, et al. Impact of S-1 in patients with gemcitabine-refractory pancreatic cancer in Japan. *Jpn J Clin Oncol* 2010; 40: 774-780.
 20. Hisama S, Kimura M, Nishimura T, et al. A case of pancreatic cancer treated by gemcitabine with sequential radiotherapy. *Gan To Kagaku Ryoho* 2010; 37: 1337-1339.
 21. Ishii Y, Suzuki S, Takahashi Y, Takayama T, Asai S. Can the 2-(13)C-uracil breath test be used to predict the effect of the antitumor drug S-1? *Cancer Chemother Pharmacol* 2010; 66: 333-343.
 22. Royal RE, Levy C, Turner K, et al. Phase 2 trial of single agent ipilimumab (Anti-CTLA-4) for locally advanced or metastatic pancreatic adenocarcinoma. *J Immunother* 2010; Sept 13 [Epub ahead of print].
 23. Gillmore R, Laurence V, Raouf S, et al. Chemoradiotherapy with or without induction chemotherapy for locally advanced pancreatic cancer: a UK multi-institutional experience. *Clin Oncol* 2010; 22: 564-569.
 24. Elliott DW, Zollinger RM, Moore R, Ellison EH. The use of human serum albumin in the management of acute pancreatitis. *Experimental and clinical observations. Gastroenterology* 1955; 28: 563-587.
 25. Shen ZT, Wu XH, Li B, Wang L, Zhu XX. Preliminary efficacy of CyberKnife radiosurgery for locally advanced pancreatic cancer. *Chin J Cancer* 2010; 29: 802-809.
 26. Ogawa K, Shibuya H, Uchida N, et al. Postoperative external beam radiotherapy for resected pancreatic adenocarcinoma: impact of chemotherapy on local control and survival. *Anticancer Res* 2010; 30: 2959-2967.
 27. Eppinga W, Lagerwaard F, Verbakel W, Slotman B, Senan S. Volumetric modulated arc therapy for advanced pancreatic cancer. *Strahlenther Onkol* 2010; 186: 382-387.
 28. Li D, Abbruzzese JL. New strategies in pancreatic cancer: emerging epidemiologic and therapeutic concepts. *Clin Cancer Res* 2010; 16: 4313-4318.
 29. Orsi F, Zhang L, Arnone P, Orgera G, et al. High-intensity focused ultrasound ablation: effective and safe therapy for solid tumors in difficult locations. *Am J Roentgenol* 2010; 195: W245-252.
 30. Shehzad A, Wahid F, Lee YS. Curcumin in cancer

- chemoprevention: molecular targets, pharmacokinetics, bioavailability, and clinical trials. *Arch Pharm* 2010; 343: 489-499.
31. Banerjee S, Kong D, Azmi AS, et al. Restoring sensitivity to oxaliplatin by a novel approach in gemcitabine resistant pancreatic cancer cells in vitro and in vivo. *Int J Cancer* 2010 Sep 7 [Epub ahead of print].
 32. Mohanty AK, Dilnawaz F, Mohanty C, Sahoo SK. Etoposide-loaded biodegradable amphiphilic methoxy (poly ethylene glycol) and poly (epsilon caprolactone) copolymeric micelles as drug delivery vehicle for cancer therapy. *Drug Deliv* 2010; 17: 330-342.
 33. Jöst E, Roos WP, Kaina B, Schmidberger H. Response of pancreatic cancer cells treated with interferon-alpha or beta and co-exposed to ionising radiation. *Int J Radiat Biol* 2010; 86: 732-741.
 34. Glazer ES, Massey KL, Zhu C, Curley SA. Pancreatic carcinoma cells are susceptible to noninvasive radio frequency fields after treatment with targeted gold nanoparticles. *Surgery* 2010; 148: 319-324.