

Conclusion: AFP–endostatin shows comparable in vitro effectivity to rh-endostatin. Efficacy in tumour therapy is significantly higher compared to rh-endostatin (100 mg/kg/24h rh-endostatin versus 1.2 mg/kg/72h AFP-endostatin for an inhibition rate of 80%) published in the literature. The application frequency could be reduced with AFP-endostatin, which leads to better patients compliance and reduced therapy costs.

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POSTER

Non-resectable esophageal cancer treated with chemotherapy and radiotherapy of multiple 3D beams

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Purpose: The objective of this study is to evaluate the feasibility of treatment in non-resectable esophageal cancer with high dose radiotherapy by multiple 3D beams.

Methods: From July 2005 to February 2007, 18 patients with non-resectable esophageal cancer were treated in our institution with radical intention. Stage distribution was 3p. (17%) T4 N1 M0, 2p. (11%) T4 N0 M0, 4p (22%) T3 N1 M0, 3p (17%) T3N1M1a, 3p (17%) T3 N0 M0 and 3p (17%) T1-T2 N0 (non operable by comorbidity). Esophagus sublocation were: 3p (17%) Cervical, 8 p (44%) Upper-esophageal, and 7 p. (39%) were distal. We administered four cycles of chemotherapy (CDDP 80 mg/m²/day iv × 1 day + 5 FU 800 mg/m²/day iv × 5 days the first and the fourth week radiotherapy) in 11p. (61%). Gross tumour volume (GTV) was defined according to CT Scan-PET images. Clinical tumour volume (CTV) was defined by GTV with a 3 cm cranial-caudal and 1 cm radial expansion. PTV was defined by CTV with a 1 cm around. Boost dose tumour was defined by GTV with a 1 cm around. A "combined" plan was created to treat the PTV receiving 44 Gy in 22 fractions using 3D planning, followed by a boost until final dose at 66 Gy in 11 fractions. Treatment planning goals were spinal cord max dose <46 Gy, lung dose restricted to a combined V20 <35% and heart dose restricted to V60 <30%.

Results: Our doses in critical organs were: the mean of maximum dose received in spinal cord was 40.9 with standard deviation (sd) of 5.9 and 17 p. (94.4%) received doses lower than 46.2 Gy. In heart V60 mean was 4.02% (sd, 7.43, range 0.02–24) and irradiated heart volume was less than 24% in all cases. Finally V20 mean for lung was 23.96 (sd 9.09, range 11–37) and 17 p. (94.4%), V20 was less than 36%. No high grade acute complications were observed during the treatment course.

Conclusions: The irradiation with multiple 3D beams in non-resectable esophageal cancer is a good option for radical treatment, achieving high doses in PTV. However, though we didn't have acute complications, the maxim dose in critical organs is not negligible. Late complications should be analyzed during the follow up of this cohort.

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POSTER

Interleukin-13 exerts autocrine growth promoting effects in human pancreatic cancer and its expression correlates with a propensity for lymph node metastases

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Background: Pancreatic cancer cells express receptors for interleukin-13 (IL-13). It is not known, however, whether IL-13 modulates pancreatic cancer cell growth and spread.

Materials and Methods: Cell growth and signaling were analyzed by cell counting, MTT assays, FACS, and kinase activity assays. IL-13 expression and secretion were determined by Northern blot analysis and ELISA, respectively. Localization of IL-13 and IL-13 receptors (IL-4R and IL-13R) in primary pancreatic ductal adenocarcinoma (PDAC) was characterized by immunohistochemistry.

Results: IL-13 significantly enhanced the growth of ASPC-1, CAPAN-1, and COLO-357 pancreatic cancer cells. This was associated with enhanced p44/42 MAPK phosphorylation. In contrast to p44/42 MAPK, IL-13 also induced PI-3 kinase activity in IL-13 unresponsive MIA PaCa-2, PANC-1, and T3M4 cells. All tested cell lines expressed and secreted IL-13.

Neutralizing IL-13 antibodies inhibited the growth of ASPC-1 and CAPAN-1 cells. High IL-13 (30/70) and IL-4R (28/70) immunoreactivity was present in PDAC tumor samples. Fifteen of 16 specimen (94%) exhibiting high levels of both IL-13 and IL-4R displayed lymph node metastases, while only 30 of the remaining 54 samples (56%) had positive lymph nodes (p = 0.0134).

Conclusions: IL-13 may be an autocrine growth factor in PDAC. Moreover, endogenous expression of IL-13 in conjunction with IL-4R in the cancer cells may facilitate lymph node metastasis by modulating the interactions between tumor cells and immune cells.

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POSTER

Altered expression of hepatocyte nuclear factors in pancreatic ductal adenocarcinoma cell lines, varying on the level of differentiation

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The work is devoted to the analysis of the impact of hepatocyte nuclear factors (HNFs) in the control of pancreatic cell lines proliferation and differentiation.

HNFs were identified as the main regulators of liver development and differentiation. We have previously identified the essential role of the dysfunction of HNFs network in the progression of hepatocellular carcinoma. The central player of HNFs network in the liver is HNF4a, which is downregulated in highly malignant tumors. Restoration of HNF4a expression in dedifferentiated hepatocellular carcinoma can promote the reversion of tumors toward a less invasive highly differentiated slow-growing phenotype.

While HNFs were first discovered in the liver, they are expressed in different combinations in the epithelium of other organs including pancreas and clearly participate in gene regulation and tissue differentiation together with other tissue-specific factors. Being derived from the common ontogenetic precursor, the liver and pancreas demonstrate very similar patterns of HNFs expression. The most significant difference in HNF set between the liver and pancreas is substitution of "adult" HNF4a1 isoform of by "embryonic" HNF4a7 one driven by the alternative promoter.

On the basis of these facts we decided to analyze the role of HNFs in differentiation and malignant transformations in the pancreas. For this study we used four cultures derived from pancreatic ductal adenocarcinomas: Capan-2, Panc1, AsPC-1 and MIA PaCa-2. These cultures were arranged by their level of differentiation: first consists of typical epithelial cells, able to form well-defined monolayer and three-dimensional structures resembling ducts and acini, and last – of poor differentiated fibroblastoid single cells, therefore presenting an interesting model for investigation of EMT in the process of malignisation.

Using semi-quantitative RT-PCR we have found that HNF4a7 and vHNF1 expression correlates with the level of differentiation. On the contrary the expression of OC2 and CEBPa in differentiated cell cultures is minimal and increases towards the less differentiated ones. Forced expression of HNF4a7 in dedifferentiated cell culture MIA PaCa-2 reduced the cell proliferation and altered the expression of differentiation markers in this pancreatic cell line.

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POSTER

Cisplatin is more cytotoxic than oxaliplatin in oesophageal adenocarcinoma cells demonstrated by Expression of ERCC1 and XPA

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Background: Xeroderma Pigmentosum protein A (XPA), recognises DNA damage, its low levels with decreased expression of Excision Repair Cross Complementing 1(ERCC1), an endonuclease of Nucleotide excision repair pathway, were found responsible for pronounced cisplatin sensitivity. While increased levels of XPA and ERCC1 has demonstrated cisplatin resistance. We want to compare the levels of XPA and ERCC1 gene expression in oesophageal adenocarcinoma cells (OE33) after treating them with cisplatin and oxaliplatin.

Methods: Lethal doses 50 (LD50) of oxaliplatin and cisplatin in OE 33 cells for 24 hours were determined by the alamarBlue assay. Cells were treated with that LD50 at 2, 4, 6 and 24 hours. Using RT-PCR and specific primers, expression of ERCC1 and XPA gene levels with cisplatin and oxaliplatin treatments were compared at 2, 4, 6 and 24 hours interval, by Syngene Gene Tools programme.

Results: XPA was undetectable with cisplatin treatment, while it was overtly expressed with oxaliplatin treatment at all time intervals. Small amounts of ERCC1 were seen in 2, 6 and 24 hours with below detectable levels at

4 hours after cisplatin treatment. In contrast, it was over expressed with oxaliplatin treatment at all time intervals

Conclusions: XPA and ERCC1 were over expressed with oxaliplatin treatment while in cisplatin treatment they were nearly undetectable. These findings suggest that cisplatin is more toxic in oesophageal adenocarcinoma cells than oxaliplatin.

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POSTER

Report of safety analysis in a randomized phase III study comparing S-1 alone with S-1 plus CDDP in advanced gastric cancer (The SPIRITS trial. TS-1 Advanced Gastric Cancer Clinical Trial Group)

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Background: The oral fluoropyrimidine S-1 (TS-1®) is based on the biochemical modulation of 5-fluorouracil, and is widely used as a single agent and in combination therapies for advanced gastric cancer (AGC) in Japan. A phase III study comparing S-1 alone with S-1 plus CDDP was conducted to evaluate the efficacy and feasibility of the S-1 plus CDDP combination as first-line therapy of AGC in Japan. Its result will be presented at ASCO 2007 as oral presentation. Analysis of safety and continuity will be presented at ECCO.

Material and Methods: Patients (Pts) were randomized to one of two treatment arms by multicenter. Arm S: S-1 was administered orally 40 mg/m² twice daily for 28 days, followed by 14 days rest as one cycle. Arm SP: S-1 was administered orally 40 mg/m² twice daily for 21 days followed by 14 days rest, while CDDP was administered intravenously 60 mg/m² on day 8 as one cycle. Pts were required to have unresectable/recurrent AGC. Primary endpoint was overall survival (OS). Secondary endpoints were RR, time to treatment failure (TTF) and toxicity.

Results: 305 pts (Arm S/SP, 152/153) were randomized between Mar 2002 and Nov 2004. The eligible pts were 299 (Arm S/SP, 150/149). The MST of Arm S/SP were 335.5 days (95% CI: 292–402)/396.0 days (95% CI: 342–471), respectively. The OS for Arm SP was superior to Arm S (log-rank p = 0.0366, hazard ratio: 0.774, 95% CI: 0.608–0.985). RR of Arm S/SP was 31.1%/54.0%. Median TTF of Arm S/SP were 119.0 days (95% CI: 91–136)/145.0 days (95% CI: 112–162). Pts received a median of 3.0 cycles (range, 1–12) for Arm S and 4.0 cycles (range, 1–11) for Arm SP of chemotherapy. The percentage of compliance for Arm S in 4th cycle and Arm SP in 5th cycle was 92.4% and 76.1%. The most common reason of study-off was progression of disease in both arms. The overall percentage of grade 3/4 toxicity was 24.7% (Arm S) and 66.9% (Arm SP). Grade 3/4 toxicities that occurred more than 10% with one of both arms were leucopenia (Arm S/SP: 2.0%/11.5%), neutropenia (Arm S/SP: 10.7%/39.9%), Hb decreased (Arm S/SP: 4.0%/25.7%), anorexia (Arm S/SP: 6.0%/30.4%) and nausea (Arm S/SP: 1.3%/11.5%). Treatments related death was not observed in this study.

Conclusions: It could be regarded that combination therapy of S-1 plus CDDP is useful, which does not have any problem in continuity and compliance. Accordingly, the combination therapy was active and well tolerated as one of the first line standard treatment of AGC.

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POSTER

The novel biomarker (HOXB2) predicts response to pancreatectomy for pancreatic cancer

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A current challenge in the treatment of cancer is identifying biomarkers of response to therapies in order to tailor optimum treatment to individual patients. Pancreatic Cancer (PC) is the fourth leading cause of cancer death in Western societies with a 5-year survival rate of less than 10%. Pancreatectomy is the only therapeutic intervention that offers the chance

of long term survival, however, only 10 to 20% of patients who undergo pancreatectomy survive >3 years with prognostic factors only determined after pathological examination of the resected specimen. Identification of a biomarker of response to surgical resection that can be determined preoperatively offers the potential to significantly improve survival and quality of life for patients with PC by improving patient selection for pancreatectomy.

We examined the aberrant expression of over 20 genes identified using transcript profiling or known to be important in carcinogenesis using immunohistochemistry and in-situ hybridisation in a cohort of 124 patients with pancreatic cancer to identify potential biomarkers of prognosis and response to operative resection.

Aberrant expression of p53, p21WAF1/CIP1, p27KIP1, p16INK4A, cyclin D1, cyclin E, DPC4/Smad4, EGFR, beta-catenin, sfrp4, HER2, LMO4, HOXB2, c-myc, LRAT, S100P, S100A6, S100A2, RAI3 and CRBP1 were identified in a significant proportion of PC. Multivariate analysis of clinicopathological variables (tumor size, differentiation, subtype, lymph node metastases, perineural invasion and vascular space invasion), treatment parameters (margin involvement, adjuvant therapy, resection type), and aberrant expression of the above candidate biomarkers identified that HOXB2 expression and resection margin involvement by tumor were the only 2 independent prognostic factors. Patients who had absent HOXB2 expression and had clear margins after pancreaticoduodenectomy (48%) had an actual survival of 42% at 3 years and 21% at 5 years, compared to those with HOXB2 expression and/or positive surgical margins who had all died by 28 months.

HOXB2 expression may represent a surrogate marker of advanced disease, can potentially be assessed preoperatively using FNAB, and is currently the best predictor of outcome and response to operative resection to be reported. Preoperative assessment of HOXB2 expression has potential clinical utility in predicting response to operative resection for PC to allow better selection of patients for operative intervention.

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POSTER

Cetuximab with Irinotecan/FA/5-FU as first-line treatment in advanced gastric cancer: Preliminary results of a non-randomized multicenter AIO phase II study

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Background: Since cetuximab had promising activity in irinotecan-based therapies in colorectal cancer and irinotecan has shown to be effective with 5-FU/FA in advanced or metastatic gastric cancer, we evaluated tolerability and efficacy of cetuximab with irinotecan/5-FU/FA as first-line treatment in patients with unresectable locally advanced or metastatic gastric cancer.

Methods: Patients (pts) with previously untreated adenocarcinoma of stomach, the esophagogastric junction or distal esophagus, with an ECOG Performance status (PS) <2, measurable lesions and adequate organ functions were eligible. Pts received cetuximab at an initial dose of 400 mg/m² followed by weekly 250 mg/m² over 60 min, irinotecan 80 mg/m² over 90 min and sodium folinate 200 mg/m² plus 5-FU 1500 mg/m² over 24 hours on days 1, 8, 15, 22, 29 and 36 (one week rest). Cycles were repeated on day 50. Treatment was continued until disease progression. Tumor assessments were performed every other cycle, i.e. every 14 weeks.

Results: From August 2006 – April 2007, 41 of 50 enrolled pts were included into a preliminary analysis: 75.6% were males, median age 63 years (range 35–77); median PS 0 (70.7%); 66% had gastric and 34% had esophagogastric or Barrett carcinomas. The median treatment duration was 7 weeks (range 0–28). Common grade 3/4 toxicities were diarrhoea 7.3%, skin toxicities 7.3%, leucopenia 4.9%; other serious adverse events seen in 1 patient were non-fatal lung embolism, acute coronary syndrome and hypersensitivity reaction to cetuximab, respectively. Among 20 evaluable patients, complete or partial remissions were seen in 45% and tumor control (remission or stable disease) was obtained in 85%. No early death occurred.

Conclusion: Cetuximab combined with irinotecan/FA/5-FU can be safely administered and is effective in advanced gastric cancer. Updated results will be presented at the meeting.