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POSTER

### Phase II trial of high-dose gemcitabine in patients with metastatic pancreatic adenocarcinoma

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**Purpose:** Although gemcitabine has shown superior antitumour activity than 5-FU in advanced pancreatic cancer (PC), further improvements are warranted. To investigate if this goal might be achieved by dose intensification, the present phase II study was initiated.

**Methods:** Between 08/97 and 09/98, 38 consecutive patients with metastatic PC were entered in this trial. Treatment consisted of gemcitabine 2200 mg/m<sup>2</sup> given iv every 2 weeks for a duration of 6 months unless there was prior evidence of progressive disease.

**Results:** 28 pts (11 female, 17 male) are currently evaluable for response and toxicity assessment. Their median age is 65 (46–75) years, and their median Karnofsky performance status (KPS) 70% (50–100%). 20 (71%) were symptomatic at the time of initiating therapy.

A "clinical benefit response" (defined as a  $\geq 50\%$  reduction in pain intensity,  $\geq 50\%$  reduction in daily analgetic consumption, or  $\geq 20\%$  KPS score improvement for  $\geq 4$  weeks) was achieved in 7/20 (35%) symptomatic pts, and stabilization was noted in 6 (30%). Objective tumour responses (as assessed by serial CT-scans) occurred in 8 pts (28%), and 10 (36%) had stable disease. Median time to progression ( $\geq 4.5$  mos) and median survival ( $\geq 6.5$  mos) have not been reached yet. Therapy was generally well tolerated with a low incidence of severe (WHO grade 3) haematologic (21%) or other organ toxicities (11%).

**Conclusions:** Our findings suggest that high-dose gemcitabine is a tolerable and palliatively effective regimen for the treatment of pts with this otherwise chemorefractory fatal disease.

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### Preoperative chemotherapy with weekly cisplatin plus continuous infusion of fluorouracil and hyperfractionated radiation for esophageal cancer

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**Purpose:** In esophageal cancer, preoperative concurrent chemoradiotherapy is a promising approach, and accelerated hyperfractionated radiation increases local tumor control compared to standard radiation (Nishimura, 1994). We designed a phase II study to test cisplatin plus continuous infusion of fluorouracil plus concurrent hyperfractionated radiotherapy in squamous esophageal cancer.

**Methods:** From October 1996 to July 1998, 18 patients (p) were included. 15 were male and 3 female; mean age 58 (42–76). 3 p (16%) had  $>10\%$  weight loss. Esophageal ultrasound-based staging revealed 4 p with stage II and 14 p with stage III. Treatment consisted of: cisplatin 30 mg/m<sup>2</sup>, days 1, 8, 15; fluorouracil 300 mg/m<sup>2</sup> daily, continuous IV, days 1–21; radiation, 1.5 Gy bid, days 1–21, total dose 45 Gy. Resection was performed 3–5 weeks after chemoradiotherapy.

**Results:** All patients completed planned preoperative treatment. Grade 3/4 toxicities included esophagitis in 11 p (61%) and neutropenia in 3 p (16%); 9 p were hospitalized during the treatment and 5 p required parenteral nutrition. Of the 14 p eligible for curative resection, 13 p (72%) had all gross tumor removed. Six of 14 p (42%) had pathologic complete response, and 2 p had only microscopic residual. There were no treatment-related deaths. With a median follow-up of 17 months (range, 8–28), median survival has not been reached. 1- and 2-year survival rates are 70% and 58%. To date, 10 p (55%) remain alive without relapse.

**Conclusions:** In spite of a high incidence of esophagitis, this chemoradiotherapy combination has demonstrated a substantial activity with an encouraging 2-year survival in patients with resectable squamous esophageal cancer.

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### Proliferative index and DNA content in precancerous conditions and adenomatous polyps of stomach

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**Purpose:** Gastric carcinogenesis is a multistep process, which develops on a background of precancerous conditions. The most prevalent precancerous condition is chronic atrophic gastritis, followed by intestinal metaplasia. Hyperplastic polyps are usually considered as non-neoplastic. Adenomatous lesions (flat and polyps) have been considered the only precursor lesions of gastric carcinoma. We evaluated the proliferative index and DNA content in these precancerous conditions and compared the results with those obtained in adenomatous polyps.

**Methods:** The immunohistochemical study of PCNA and evaluation of DNA content by image cytometry, were performed in 20 samples of normal gastric mucosa, 20 cases of superficial chronic gastritis, 20 cases of chronic atrophic gastritis with intestinal metaplasia, 8 hyperplastic polyps and 8 adenomatous polyps.

**Results:** In superficial chronic gastritis and atrophic gastritis, we observed a "superficialization" of cell proliferation. In intestinal metaplasia type III and in hyperplastic polyps we detected a high cellular proliferative index and some aneuploid cells. We found that the percentage of aneuploid cells in hyperplastic and adenomatous polyps (2.8% + 2.1% and 9.3% + 2.9%, respectively) was significantly higher ( $p < 0.01$ ) than in normal gastric mucosa (0.1% + 0.3%). Similarly, the labelling index of PCNA was significantly higher ( $p = 0.0001$ ) in hyperplastic and adenomatous polyps (47.6 + 8.9 and 63.9 + 7.6 respectively) than in normal gastric mucosa (14.3 + 4.8).

**Conclusion:** We found evidence supporting that the precancerous conditions share similar proliferative indexes and DNA content alterations as adenomatous polyps but less intense.

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### Clinical pathway for the management of gastric cancer with peritoneal seeding

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**Background:** Patients evaluated for primary gastric cancer may have peritoneal carcinomatosis as a manifestation of stage IV disease. Strategies are needed to optimally palliate these patients and allow for an evolution of improved treatments. The purpose of this abstract is to review the information available in the literature and formulate a clinical pathway.

**Methods:** All papers and abstracts published over the last 30 years in the English literature were surveyed.

**Results:** Thirteen reports were reviewed concerning the results of treatment of patients undergoing palliative gastrectomy (1888 patients). Mean survival in months was more than doubled in all papers when patients underwent distal or total gastrectomy as compared to bypass or exploration only. Three papers included data regarding peritonectomy of peritoneal implants in addition to gastrectomy (120 patients). There was a statistically significant improvement in 5-year survival with complete cytoreduction in all reports. Eight reports focused on the use of perioperative intraperitoneal chemotherapy for patients having gastrectomy (714 patients). Patients with resectable stage IV disease had an increased likelihood to survive at 3 years after surgery with an odds ratio of 3.3 (confidence interval 1.7–11.0) and there were occasional prolonged survivors.

**Conclusion:** The gastric cancer literature suggests that palliative treatment of gastric cancer with peritoneal seeding may be improved by combining gastrectomy, peritonectomy, and perioperative intraperitoneal chemotherapy.

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### Preoperative short-term radiotherapy of resectable gastric cancer: Complete 20-years follow up of a randomized trial

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**Purpose:** To determine the impact of preoperative short-term radiation therapy with a dose of 20 Gy given during 5 consecutive days on survival in gastric cancer patients, a prospectively randomized clinical trial was performed from 1974 to 1978.

**Methods:** One hundred and three patients entered into the study. The experimental group received preoperative radiation therapy (n = 49), the control group-surgery alone (n = 54).

**Results:** Similar overall survival was observed in patients of the experimental and the control groups: median survival was 40 and 48 months, 3 year survival rate (YSR)  $54 \pm 7\%$  and  $54 \pm 8\%$ , 5 YSR  $46 \pm 8\%$  and  $44 \pm 7\%$ , 10 YSR  $41 \pm 8\%$  and  $31 \pm 7\%$  respectively. When various subgroups of patients were analyzed the results showed significant difference. The most impressive advantage of the combined treatment modality was seen when N positive cases were compared: median survival was 37 and 17 months, 3 YSR  $50 \pm 11\%$  and  $35 \pm 10\%$ , 5 YSR  $45 \pm 11\%$  and  $10 \pm 6\%$ , 10 YSR  $28 \pm 8\%$  and  $10 \pm 6\%$  respectively.

**Conclusion:** Adjuvant radiation therapy can improve surgical results in selected groups of patients with resectable gastric cancer.

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### The influence of trypsin, chymotrypsin and papain on the growth of human pancreatic adenocarcinoma transplanted to *nu/nu* mice

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**Purpose:** The aim of the study as presented was to investigate the influence of protease mixture in a model of transplanted human pancreatic carcinoma based on our previous results in mice syngenic tumor models.

**Material and Methods:** After the 2 weeks of postransplant latency, total of 18 *nu/nu* mice (CD-1 prone) bearing subcutaneous human pancreatic adenocarcinoma were as random divided into two equal groups. The 1<sup>st</sup> one (enzyme group) was administered with trypsin, chymotrypsin and papain solution rectally. The 2<sup>nd</sup> one (control group), was administered with saline by the same way. The tumour growth in both groups was measured daily for following 30 days and the tumor mass was calculated from their extents.

**Results:** Along the presented study, protease mixture retards growth of human pancreatic adenocarcinoma in *nu/nu* mice. In the enzyme group, the tumor mass increased up only to 47.6% of the control volume in the 30<sup>th</sup> day.

**Conclusion:** Although, the proteases were expected to have mainly the antimetastatic effect in cancer progression, these results confirm growth inhibition of primary tumor by trypsin, chymotrypsin and papain solution.

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### Gemcitabine (G) in combination radiationtherapy (RT) in stage III-IV pancreatic cancer: First results of a current Phase I study

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The purpose of the study was to determine the maximal tolerated dose (MTD) of G. in combination with radiation in patients with stage III/IV pancreatic cancer since it is known that G. is a potent radiation sensitizer of human pancreatic cells in vitro (Int. J. Radiat. Oncol. Biol. Phys. 34: 867, 1996). Also it has been reported, that dose of G. of 500 mg/m<sup>2</sup> might be a tolerable dose when G. was delivered concurrently to radiation (C.J. Mc Ginn ASCO 1998, Abstr. 1014).

**Material and Method:** The therapy encompassed a radiation of the primary tumor region and the lymphatic drainage paths up to the hilar region of the liver. A total dosage of 50.4 Gy was targeted based on a single dose per day of 1.8 Gy. The radiation was carried out on all patients on the basis of a continuous course and with a three-field-box technique. The volume of treatment amounted to 1–1.5 liters. G. was applied on days 1, 8, 15, 22 and 29. The radiation therapy followed one hour after the G. application (30 minute iv infusion.). The dose escalation started from 200 mg/m<sup>2</sup> and increased in 50 mg/m<sup>2</sup> steps, up to 350 mg/m<sup>2</sup>. At each dose level a cohort of three patients were treated and increased to 6 patients when grade 3/4 hematological and non hematological toxicities appeared, except nausea, vomiting and hair loss.

**Results:** 16 patients have been entered the study so far. No grade 3/4 toxicity was found at dose level 1 of G. 200 mg/m<sup>2</sup> and at dose level 2, G 250 mg/m<sup>2</sup>. Because of lack of significant toxicity it has been decided to enroll 2 patients on dose level 2. However, at dose level 3 (300 mg/m<sup>2</sup>), grade 3 leukopenia was found in 2 out of 6 patients. Beside the hematological toxicity grade 1/2 nausea and vomiting was observed and 1 patient with grade 4 toxicity of ALT and AST.

**Efficacy:** At dose level of 200 mg/m<sup>2</sup> one patient was found as stable disease (SD), 2 patients progressed during therapy. 1 patient at this dose level is still alive after 8 month. At dose level 2 (250 mg/m<sup>2</sup>) one patient progressed and one patient is still alive after completing the therapy. At dose level 3 (300 mg/m<sup>2</sup>) all patients developed SD. Progression have been seen after 4 month, 3 month and 1 month respectively and 2 patients are still stable disease.

Currently 6 patient are enrolled on dose level 3 (350 mg/m<sup>2</sup>). At this is dose level 2 patients developed Grade 3 and grade 4 leukopenia.

**Conclusion:** G. in combination with radiation shows a different MTD when given 1 hour before radiation. The study is still ongoing.

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### Gastric carcinoma: A phase II study of capecitabine with new dosing regimen in patients with advanced/metastatic gastric carcinoma

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**Purpose:** Capecitabine is a fluoropyrimidine carbamate with anti-neoplastic activity. It is an orally administered systemic prodrug of 5'-deoxy-5-fluorouridine (5'-DFUR) which is converted to 5-FU. We investigated efficacy and toxicity of capecitabine in advanced/metastatic gastric carcinoma patients.

**Methods:** Capecitabine was administered at a daily dose of 1657 mg/m<sup>2</sup> for 3-weeks followed by a 1-week rest period and given as 4-week cycles. This treatment dosing regimen was determined from its MTD (2510 mg/m<sup>2</sup>) in continuous dosing of a phase 1 study in Japan. Eligibility criteria were as follows: 1) histologically/cytologically confirmed gastric carcinoma with measurable and/or evaluable lesions, 2) PS 0–2, 3) age <75, 4) prior chemotherapy no more than 1 regimen, 5) adequate bone marrow, liver, renal and cardiac functions, 6) written informed consent.

**Results:** Totally, Thirty-two patients were entered into a multi-center phase 2 study from July 1996 to December 1997. One patient was ineligible due to prior chemotherapy violation. Patient characteristics in 31 eligible cases were 22 males, 9 females, median age 61 (range 36–74). The number of treatment cycles ranged from 1 to 9. Overall response rate was 19.4% (95%CI 7.5–37.5%) in 31 eligible cases, and the response rate in patients without prior chemotherapy (including no chemotherapy in the adjuvant setting) was 24% (6/25). Only one NCIC CTC grade 3/4 related adverse event, increase in total bilirubin (grade 3, 6.3%) occurred in >5% of patients. Other related grade 3 adverse events were skin rash, increase in GOT, increase in blood sugar, decrease in hemoglobin & hematocrit, and increase in creatinine (each 3.1%). There was no other related grade 4 adverse events. Median survival time in eligible cases was 246 days (95%CI: 193–306+ days).

**Conclusion:** Oral administration of Capecitabine with the dose of 1657 mg/m<sup>2</sup> for 3-weeks-on and 1-week-off exhibits anti-tumor activity with a favorable safety profile and warrants further investigation.

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### Phase II study of gemcitabine (GEM) combined with radiation therapy (RT) in localized, unresectable pancreatic cancer

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**Purpose:** To evaluate the efficacy and safety of GEM combined with RT in patients (pts) with localized, unresectable pancreatic cancer.

**Methods:** Weekly GEM at a dose of 1000 mg/m<sup>2</sup> for seven weeks was given initially, in order to provide clinical benefit (CB) and to select non-progressing pts for entering into the chemoradiotherapy (CRT) phase of the treatment. This consisted of GEM 400 mg/m<sup>2</sup> weekly  $\times$  3 every 28 days for 2 cycles, delivered concurrently with RT to a total dose of 50.4 Gy in 1.8 Gy daily fractions. GEM dose was re-escalated to 1000 mg/m<sup>2</sup> after completion of RT.

**Results:** Between 8/97 and 12/98, 15 pts entered this study. Their median age was 65 y (38–84 y) and median performance status (PS) was 2 (1–3). Seven pts (46%) achieved positive CB response, measured by pain relief, improvement in PS or weight gain, and one pt was stable. Objectively, they had no tumor progression and thus enrolled to the CRT phase, followed by GEM alone. Five of them (33% of all pts) are alive and asymptomatic 10 m+ to 19 m+ after start of treatment, having objective partial response (2), minimal response (1) and no change (2). Overall median survival was