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Biweekly treatment with Docetaxel-Gemcitabine and Erlotinib in patients with metastatic and/or unresectable pancreatic cancer offers a survival benefit

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Background: Pancreatic cancer represents 2% of all cancers as the 4th leading cause of cancer-related deaths worldwide. Patients (pts) with unresectable and metastatic pancreatic adenocarcinoma had a median survival no longer than 2 months. This is a treatment challenge due to poor outcomes with current treatment modalities.
Materials and Methods: Chemotherapy naïve pts with histologically confirmed unresectable pancreatic cancer and documented extrapancreatic metastases, received docetaxel 75 mg/m^2 on day 1, gemcitabine 1250 mg/m^2 on day 1and daily erlotinib 100 mg p.o., in a biweekly schedule cycle. Pts were monitored every 4 cycles with CT scans and monthly serum CA19−9 measurements. 23 pts (14 males, 9 females, median age 71 years, range 41−80, ECOG PS: 0−2) were enrolled; all pts were eligible for the study. Pts received a total of 146 cycles with a median of 8.33 cycles (2−22).
Results: 8 pts remain alive and undergoing the study treatment. 10 pts discontinued therapy, 7 pts died due to disease progression and 3 pts due to cumulative grade III asthenia. Fatigue had 9/23 pts (36%), cumulative fluid retention edema had 11/203 pts (44%) docetaxel-related that resolved with diuretics and corticosteroids. Onycholyshis 10/23 (40%). Skin toxicity (rash) 15/23 pts (60%) after 6 cycles. Nausea and vomiting 4/23 (16%). 10/23 (40%) had improvement in their pain control and stop to take analgesics after a mean of 6 cycle of chemotherapy. 9/23 (39.1%) had amelioration of their performance status. 1 patient (5.5%) achieved CR, 3 (16.6%) PR and 4 (22.2%) showed stabilization in measurement disease. The median progression-free survival was 4 (2−13) months and the median survival was 8.4 (2−49+) months.
Conclusions: Biweekly chemotherapy with docetaxel, gemcitabine and daily erlotinib is effective for pain control and amelioration of the quality of life in pts with inoperable and/or metastatic pancreatic cancer and offered a median survival of 8.4 (2−49+) months and a reduction >50% in the CA19−9 in 50% of the pts.

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A phase II study of erlotinib plus gemcitabine in Japanese patients with unresectable pancreatic cancer

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Background: In PA.3, erlotinib plus gemcitabine (E+G) improved survival and progression-free survival (PFS) over gemcitabine alone in patients (pts) with unresectable pancreatic cancer (PC) (Moore et al. JCO 2007). We conducted a phase II study (JO20302, closed, CHUGAI Pharmaceutical Co.) to evaluate the safety and efficacy of E+G in Japanese pts.
Materials and Methods: Eligible pts were aged 20−80 years with histologically proven PC and ECOG performance status (PS) 0−2. Pts entered a two-step study to assess safety (dose limiting toxicity [DLT] in $\leqslant$2 pts) and PK in step 1 (6 pts), and to confirm efficacy and safety in step 2 (94 pts). E at 100 mg/day (p.o.) +G at 1000 mg/m^2 (i.v., days 1, 8, 15) were administered in a 28-day cycle. The primary endpoint was safety, and efficacy endpoints were also evaluated.
Results: 106 pts were treated with E+G. In step 1, a DLT (grade 3 diarrhea) occurred in one patient; the study therefore continued to step 2. Baseline characteristics were: median age 62 years (range 36−78); male/female 53/47%; stage IVa/IVb (Japanese Pancreas Society) 15/85% and ECOG PS 0/1/2 75/25/0%. The most common adverse event (AE) was RASH (rash, acne, exfoliative rash, dermatitis acneiform, erythema, eczema, dermatitis and pustular rash) in 93.4% (grade 1/2/3, 30.2/57.5/5.7%). Other grade 3/4 AEs were neutrophils (34.0%), WBC (28.3%), γ-GTP (17.9%), amylase (15.1%), anorexia (15.1%), haemoglobin (14.2%), lymphopenia (14.2%) and ALT (13.2%). Treatment-related interstitial lung disease (ILD)-like events occurred in nine pts (8.5%; grade 1/2/3, 3.8/2.8/1.9%): most were grade 1 or 2; two were grade 3. There were no grade 4/5 ILD-like events and all pts recovered or improved. There was one treatment-related death due to gastrointestinal haemorrhage. The incidence of erlotinib discontinuation due to AEs was 23.6%, that of erlotinib dose reduction was 14.2% and that of erlotinib dose interruptions longer than 7 and 14 consecutive days was 33.0% and 14.2%, respectively. Median overall survival was 9.2 mos (95% CI: 8.3−10.8 mos), with a 1-year survival rate of 33% (95% CI: 24−42%) and the median PFS was 3.5 mos (95% CI: 2.6−3.8 mos). The response rate was 20.3% (95% CI: 11.3−32.2%) for 64 evaluable pts.
Conclusions: This study shows a promising efficacy and safety profile of E+G in Japanese pts with unresectable PC.

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The role of PET/CT imaging in patients with suspected recurrence of pancreatic cancer

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Background: The goal of the study was to determine the value of ^{18}F-FDG PET/CT in patients (pts) with suspected recurrence of pancreatic cancer.
Materials and Methods: Twenty pts (M/F = 10/10, age 44−81, median 63 y) with increasing levels of CA 19−9 and/or CEA during follow-up and negative or equivocal CT scan were included. Sixteen pts were asymptomatic and 4 pts had mild symptoms. Previous treatment included pancreaticoduodenectomy in 14 pts and distal pancreatectomy in 6 pts. Adjuvant chemoradiation was given to 9 pts and was planned for additional 6 pts, while 5 pts were on follow-up. Tumor markers first increased 1 to 24 months after the operation. CT scan was done within one month later in all pts, and found to be normal in 12 pts and equivocal in 8 pts. PET/CT was then performed within one month (12 pts), 2 months (5 pts) and 3 months (3 pts). A final diagnosis of recurrence was confirmed by histopathology or by further clinical and radiologic follow-up.
Results: Of the 20 pts, 17 exhibited PET/CT findings consisted with recurrent cancer. Increased tracer uptake fused with anatomical CT findings were found in 10 pts in whom previous CT scan was defined as normal. Main sites of recurrence were tumor bed – 3 pts and distant (liver, bone and omentum) – 7 pts. PET/CT was also positive in 7 pts with equivocal CT findings (4 in tumor bed, 2 in omentum and 1 in liver+cervical lymph node). Chemotherapy was instituted for 19 pts following PET/CT findings. It was followed by radiation therapy and surgery in 3 and 1 pts with local recurrence, respectively. One pt underwent resection of an isolated abdominal recurrence. In 4 of the 6 pts planned for adjuvant chemoradiation the treatment was changed to systemic chemotherpy after the demonstration of distant metastases by PET/CT. Three pts had false negative PET/CT test, as proved by the clinical course of progressive recurrent disease.
Conclusions: PET/CT is a useful tool for detecting recurrent pancreatic cancer, and has an impact on patient management as well. Its value regarding the clinical course of the recurrent disease should be further evaluated.

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Prognostic model to predict outcomes in pancreatic adenocarcimoma patients who received surgical resection with curative intent

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Purpose: To identify prognostic factors for long term survival of pancreatic adenocarcinomas and devise a prognostic model based on clinical parameters in single centre's experience.
Patients and Methods: Between 1995 and 2007, 292 patients who had undergone surgery for pancreatic adenocarcinoma with curative intent,

were analyzed retrospectively. Indolent tumor types (acinar cell carcinoma and mucinous cystadenocarcinoma) were excluded from the analysis.
Results: Of 292 patients who receivedsurgical resection with curative intent, 234 had curative (R0) and 58 had incomplete resection (R1/2). The median survival duration of all patients was 21.7 months. Multivariate analysis revealed that positive resection margin, CA 19−9>90, no postoperative CCRT, moderate or poorly differentiated histological grade and abnormal range of glucose level as significant independent prognostic factors for decreased OS ($p < 0.05$). OS was estimated on the basis of each prognostic factor: zero and one (good prognostic group), two and three (intermediate prognostic group), and over than four (poor prognostic group). The median OS for good (n = 49), intermediate (n = 204) and poor prognostic groups (n = 39) were 67.8, 24.4, and 11.0 months, respectively ($p < 0.001$). In subgroup analysis of 234 patients with R0 resection, postop CCRT was the only significant prognostic factor for decreased OS at multivariate level; CA 19−9>90, moderate or poorly differentiated histological grade and the presence of perineural and blood vessel invasion predicted reduced disease free survival (DFS) ($p < 0.05$).
Conclusion: The prognostic model based on readily available clinical data would be useful to predict the prognosis and to facilitate decision in clinical practice. The postop (adjuvant) CCRT was the only common independent prognostic factor for OS in patients after RO or R0+R1/2 resection of adenocarcinoma of the pancreas.

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A phase II study of combination chemotherapy with gemcitabine, 5-fluorouracil, and cisplatin for advanced pancreatic cancer

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Background: Gemcitabine alone has been the standard regimen, but the median survival of the patients with advanced pancreatic cancer on it is only 5 months, needing more effective regimen desperately.
The combination of gemcitabine and 5-fluorouracil (5-FU) results in better response rate than gemcitabine alone, but the survival gain has not been demonstrated. The combination of gemcitabine/cisplatin was better than gemcitabine alone in the response rate and possibly in survival in a study. Gemcitabine has synergy with 5-FU and with cisplatin; 5-FU has synergy with cisplatin, making these 3 drugs have triple-synergy. They also have different dose-limiting toxicities. We hypothesized that this synergistic combination of these 3 active agents may be more active than gemcitabine alone.
Materials and Methods: Forty seven patients with pathologically proven adenocarcinoma of pancreas in stage III/IV were treated with the following regimen every 3 weeks: Gemcitabine 800 mg/m^2 IV on day 1 and 8, 5-FU 1 g/m^2/day IV in a 24 hour continuous infusion from day 1 to 4, and cisplatin 60 mg/m^2 IV on day 2, 24 hours after start of gemcitabine.
Results: The median age was 62 and male:female ratio was 33:14. A total of 158 cycles were administered with a median of 3 cycles per patient (range, 1−14 cycles). Among 37 patients evaluable for the response, 5 (13.5%) patients had a partial response (95% Confidence interval: 2.3−24.7%), and 21 patients (56.8%) a stable disease. The median duration of progression free survival and overall survival of all the enrolled patients were 189 days (95% CI:47–331) and 302 days (95% CI: 149–455), respectively. Grade 3/4 leucopenia, neutropenia and thrombocytopenia occurred in 20.3%, 27.9% and 28.5% of all the cycles, respectively. Grade 3/4 mucositis and nausea/vomiting were seen in 2.2% and 3.3%, respectively. No treatment related mortality was observed.
Conclusions: The regimen of gemcitabine, 5-FU and cisplatin has activity and good safety profiles for the treatment of advanced pancreatic cancer. A phase III study comparing with gemcitabine alone is warranted.

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Phase II study of gemcitabine as a fixed dose rate infusion and S-1 combination therapy (FGS) in gemcitabine-refractory pancreatic cancer patients

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Background: Gemcitabine (GEM) monotherapy or GEM-containing chemotherapy is the standard first-line therapy for advanced pancreatic cancer (PC), but there is no standard regimen for treatment after disease progression. In a previous phase II trial conducted on GEM-refractory PC patients S-1 was found to exhibit marginal efficacy, and the results showed a response rate of 15%, a median progression-free survival (PFS) of 2.0 months, and a median overall survival time (OS) of 4.5 months (Cancer Chemother Pharmacol. 2009; 63(2):313−9). GEM administration by fixed dose rate (FDR) infusion of 10 mg/m^2/min would maximize the intracellular rate of accumulation of GEM triphosphate and might improve clinical efficacy. A previous phase I trial determined the recommended dose of biweekly FDR-GEM and S-1 (FGS) in a phase II trial (C. Morizane et. al ECCO14, #3544). The present multicenter phase II study was conducted to confirm the efficacy and toxicity of FGS therapy in patients with GEM-refractory PC.
Materials and Methods: GEM-refractory patients with histologically or cytologically proven unresectable or metastatic PC were enrolled. GEM was given intravenously at a dose of 1200 mg/m^2 over 120 min on day 1, and S-1 was given orally at a dose of 40 mg/m^2 twice daily from day 1 to day 7, repeated every 2 weeks until disease progression. The primary end point of the study was objective response, and the secondary end points were toxicity, PFS, and OS.
Results: Forty patients from four institutions were enrolled between August 2006 and March 2009. A partial response has been confirmed in four patients (10%), and 22 patients (55%) have stable disease. Median OS and median PFS are 7.0 months and 2.3 months, respectively. Thirty-five patients are currently available for evaluation of toxicity in this ongoing trial. Grade 3 and 4 toxicities (%pts) have been fatigue (3%), rash (3%), and leukopenia (23%), neutropenia (34%), and anemia (3%).
Conclusion: The preliminary results have demonstrated safety and marginal activity of FGS therapy in GEM-refractory metastatic PC. The efficacy and toxicity analyses are ongoing. The final results will be presented at the meeting.

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Combination of gemcite & cisplatin chemotherapy in unresectables pancreatic cancer

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Background: Adenocarcinoma of the pancreatic accounts for approximately 2% of all malignant neoplasm. Though surgical resection is the treatment of choice, majority of the cases are unresectable. Different chemotherapeutic agents including 5Flurouracil, Mytomycin C, Cisplatin and Doxurobicin have been tried single or in combination. Partial response lasting from weeks to several months have been observed only in about 15%-20% of the cases and the median survival for patients with pancreatic cancer is approximately 4 months. Gemcitabine is a pyrimydine analogue of Deoxycytidine and has shown strong anti tumour activity in a variety of solid tumours. Cisplatin has synergistic activity with Gemcitabine. The aim of our study was to determine the response rate of Gemcitabine and Cisplatin combination in unresectable pancreatic cancer and to see the tolerability in Indian-Asian pollution.
Materials and Methods: During period from November 2004 to December 2008 we selected 102 consecutive patients with histologically proven unresectable measurable pancreatic cancer. The inclusion criteria were performance status more than 60% (Kornofsky) and normal liver (bilirubin <2) and kidney function (creatinine <2) function. All patient received Gemcitabine (1000 mg/m^2 intravenously over 30 minute) on day 1 and day 8 and Cisplatin total (100 mg/m^2 divided D1 to D3) every 21 days. Response assessment was done by CT scan after 3 cycles of chemotherapy. All 84 patients are eligible for efficacy and toxicity analysis.
Result: There were 17 (16.66%) complete responders, 37 (36.66%) partial responders, 27 (26.66%) with stable disease and 20 (20%) shows disease progression. The median time to progression was 22 weeks (range 12−30 weeks). The median duration of response was 15 weeks (range 5.6−60 weeks). The median over all survival was 22 weeks (range 11−32 weeks) with 1 year survival rate of 20%. WHO grade III or IV anaemia was seen in 19 (18.33%) patients. Fifteen (15%) patients experienced grade III or IV neutropenia while grade III or IV thompocytopenia was seen in 9 patients (8.33%).
Conclusion: The present study showed the Gemcitabin & Cisplatine combination was very useful in advanced unresectable pancreatic cancer. It was well tolerated by the patients.