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A prospective randomized phase III trial of 5-fluorouracil and cisplatin (FP) versus epirubicin, cisplatin, and 5-fu (ECF) in the treatment of patients with previously untreated advanced gastric cancer (AGC)

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Purpose: Combination chemotherapy of ECF regimen has known one of the active regimens in AGC. But, to date, no standard regimen for AGC has existed. We conducted a randomized phase III study to evaluate the efficacy and toxicities of FP and modified ECF regimen with previously untreated advanced AGC with measurable lesion.

Methods: Patients were allocated to receive either FP (5-FU 1,000 mg/m2 IV for 6 hours on days 1 to 5, and cisplatin 60 mg/m2 IV on day 1) or ECF (epirubicin 50 mg/m2 on day 1, cisplatin 60 mg/m2 on day 1, and 5-FU 1,000 mg/m2 IV for 6 hours on days 1 to 5) every 4 weeks.

Results: From Mar 1997 to Apr 2000, total 121 patients (pts) were enrolled in this study; 60 pts were randomly assigned to FP and 61 to ECF group. One pt was ineligible. The main pts characteristics were comparable between groups FP and ECF: median age 56.5 vs. 55 years, male/female 42/18 vs. 45/15, performance status 0-1 88.3% vs. 90%, locally advanced diseases/metastatic disease 3/57 vs. 3/57, and liver metastasis 47% vs. 53%. Total number of completed cycles was 199 (192 evaluable) in FP and 214 (208 evaluable) in ECF arm. Response was evaluabe in 53 pts in both arm and was observed in 20 pts (20 PR; RR 37.7%) for FP arm and in 22(22 PR; 41.5%) for ECF arm (p=0.66). There were no significant differences between the FP and ECF arms in the time to progression (median 3.9 vs. 4.4 months) or overall survival (median 7.3 vs. 8.5 months). Toxicity grade 3-4 for FP vs. ECF group included leukopenia (10.0% vs. 25.5% pts; p=0.02), thrombocytopenia (6.7% vs. 12.5%; p=0.31), mucositis (3.3% vs. 33.8%; p=0.01), nausea/vomiting (11.6% vs. 16.9%; p=0.41), and diarrhea(2% vs. 2%), respectively.

Conclusion: This trial showed that a combination of modified ECF regimen with this schedule did not showed any advantage over FP regimen in terms of response, survival and toxicity profiles.

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Treatment of locally advanced hepatocellular carcinoma (HCC) by hepatic intra-artery-chemotherapy (IACT): a pilot study

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Purpose: This study was done to assess whether IACT may be helpfull in locally advanced HCC.

Methods: 24 patients (pts) (mean age 69 range 48-80) with biopsy proven HCC and Child-Pugh A or B stages liver cirrhosis were enrolled. 18 had HCV related liver cirrhosis, 2 HBV related, 3 alcohol related and 1 cryptogenic form. 14 pts had no other treatment before IACT because of late diagnosis. All had US and spiral TC and underwent surgery for cholecistectomy and to implant a port a cath into gastroduodenal artery after angiografy. Treatment: 2 weeks interval schedule (8 pts): Folinic acid was infused (100 mg/mq) over 2 hours, followed by 5-FU 300 mg/mq in bolus and then by 5-FU 500 mg/mq infusion over 22 hours. Each course was repeated starting from a dose of 350 mg/mq and increasing until a maximun of 550 mg/mq. 1 Week interval schedule (16 pts): Folinic acid 100 mg/mq over 2 hours followed by 5-FU 250 mg/mq and increasing the dose until 550 mg/mq. Treatment was repeated when had good tolerability and until no evidence of disease or progression. No difference in response or toxicity were shown between these two schedules.

Results: Complication and toxicity were due mainly to surgery and handling of the port a cath. Overall median survival estimated from the diagnosis was 26,5 months (range 8-117) and 19 months (range 4-83) from the beginning of therapy. The response rate was: 13/19 evaluable pts had a major rsponse (2CR, 11PR) (54%) with a median time to progression of 15 months, 4 pts showed PD, 2 pts had SD. There was a significant advantage for pts with cirrhosis stage A as compared with those in stage B (p<0.005) considering the overall survival either from the biginning of chemotherapy or from diagnosis.

Conclusion: This pilot study shows that pts with locally advanced HCC and liver cirrhosis can be treated successfully with folinic acid and 5 FU by intrahepatic artery infusion.

1162 POSTER

Comparison of the efficacy and tolerability of ZD9331 with gemcitabine in locally advanced or metastatic pancreatic cancer: phase II/III trial

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Introduction: Novel chemotherapeutic agents are required to improve the survival and progression outcomes of patients with pancreatic cancer. This study compares the efficacy and tolerability of ZD9331, a novel antifolate, with gemcitabine, the current standard treatment for this tumour type.

Methods: A total of 55 chemonaive patients with histologically or cytologically proven locally advanced or metastatic pancreatic cancer were enrolled in the trial. Patients (pts) were randomised to receive ZD9331 (n=30) or gemcitabine (n=25). ZD9331 (130 mg/m2) was given as a 30-min iv infusion on days 1 and 8 of a 21-day cycle. Gemcitabine (1 g/m2, iv infusion) was given once-weekly for 7 weeks (wks), followed by 1 wk rest, then on days 1, 8 and 15 of a 28-day cycle. The primary endpoint of the study was time to death (TTD). Secondary endpoints included tolerability and objective tumour response.

Results: The median survival time was longer for pts receiving ZD9331 compared with gemcitabine treatment (TTD, 152 and 109 days, respectively), with a higher proportion of ZD9331 pts alive at the end of the trial (13.3% vs 8% for gemcitabine). The median time to progression was also longer for pts receiving ZD9331 (70 vs 58 days for ZD9331 vs gemcitabine pts). Partial responses were confirmed in 1 ZD9331 pt and 2 gemcitabine pts. However, a higher proportion of ZD9331 pts had stable disease (33.3% vs 24% for gemcitabine treatment). Overall, more ZD9331 pts than gemcitabine pts withdrew from therapy due to adverse events (AEs) (33.3% and 20%, respectively). The most common AEs with ZD9331 were nausea/vomiting and asthenia but these were generally mild to moderate: grade 3/4 adverse events were uncommon and comprised neutropenia (5 pts), thrombocytopenia (4) and leucopenia (3). Three patients receiving gemcitabine had grade 3/4 anaemia. Three ZD9331 pts and 2 gemcitabine pts died due to AEs. Two of the deaths in the ZD9331 group were considered to be drug-related (sepsis and myelosuppression, respectively) and this led to the early termination of the trial at the data summary stage.

Conclusions: Although there was a higher withdrawal rate from ZD9331 therapy due to toxicity, the promising preliminary efficacy data indicate that ZD9331 treatment may have a role in the treatment of locally advanced or metastatic pancreatic cancer.

1163 POSTER

Effect of extensive lymph node dissection in surgical treatment of early gastric cancer

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Purpose: Early gastric cancer (EGC) has been defined as a gastric carcinoma confined to mucosa or submucosa, regardless of lymph node status (T1NX). Our objective was to evaluate the long-term benefit of extensive lymph node dissection in the treatment of EGC patients.

Method: From 1987 to 2000 we had surgically treated 169 patients with EGC (Tis-32, T1m-66, T1sm-71). Limited resection was performed in 2 patients, 2/3 gastric resection in 2, subtotal resection in 104 (proximal-4, distal-100), gastrectomy-59, gastrectomy of gastric stamp-2. 111 patients were operated with D0 (n=8) and D1 (n=103) lymph node dissection, 18±D2 resection, 21-D2 resection with dissection of lymph node of hepatoduodenal zone (D2 +_12), 19-with D3 lymph node dissection.

Results: Hospital mortality rate was 1.2% (2 patients died in D1 group). Postoperative morbidity rate was 28.8% in D0-D1 group and 30.2% in D2-D3 group (p>0.05). Lymph node metastases were revealed in 14 patients (8.28%). There are no lymph node metastases of EGC Tis; the incidence of EGC T1m metastases is 4.55%, EGC T1sm-15.49%. 11 patients had metastases only in the perigastric regional node (N1); 3 had metastases in extraperigastric nodes in group _8, 10, 12; 1 of this 3 patients had metastases at the lymph node _12 (N3), the N1 and N2 nodes were clear. Higher metastatic incidence was in D2-D3 group (12.7%) compared with D1 group (6.3%). 5-year survival was statistically higher in N(-) EGC patients compared with N(+) patients (89.26±2.84%

and 64.05±10.90% respectively, p<0.05, Kaplan-Mayer's method) and in D2-D3 group compared with D1 group (97.50±2.47% and 85.87±3.65% respectively, p<0.01). Survival rate didn't depend on hystologic type of tumor. 5-year survival of mucosal cancer (Tis, T1m) was 92.47±2.97% and of submucosal cancer (T1sm) - 81.80±5.95% (p>0,05).

Conclusion: Reasons to extensive D2-D3 lymph node dissection for EGC are 1) the higher survival rate of patients in D2-D3 group with the absence of increasing postoperative mortality and morbidity; 2) difficulty in assessment the accuracy of modern technologies in diagnosing and staging of EGC. D2 resection is radical for the most EGC patients, but we propose more aggressive method, combined D2 resection with lymph node dissection node _12 group.

1164 POSTER

Docetaxel and 5-FU continuous infusion (DF) versus epirubicin, cisplatin and 5-FU (ECF) for advanced gastric adenocarcinoma; a randomized phase II study

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Purpose: Docetaxel shows promising activity as single agent against gastric cancer. To develop a combination chemotherapy (DF) for an ambulant setting we initiated this study. We used a randomized trial design comparing DF with ECF, one of the best investigated regimens, serving as an internal control arm to avoid selection bias. Eligibility: Metastatic or locally advanced gastric adenocarcinoma; PS 0-2; no prior chemotherapy. Methods: Patients (pts) are randomized to receive either ECF (Epirubicin 50mg/sqm d1, Cisplatin 60mg/sqm d1, 5-FU 200mg/sqm d1-21, q3w) or DF (Docetaxel 75mg/sqm d1, 5-FU 200mg/sqm d1-21, q3w).

Results: 55 pts are randomized so far. The study is ongoing. Baseline data is available of 48 pts: M/F 36/12; age 32-75 yrs (median 62); ECOG PS 0:18pts, 1:29pts, 2:1pt. 46pts are evaluable for toxicity: ECF 24pts, DF 22pts. Toxicity [%of pts, worst grade] ECF: Grade 1/2: nausea 71%, emesis 58%, asthenia 58%, diarrhoea 25%, stomatitis 33%, hand-foot 17%, paraesthesia 33%, neutropenia 13%, renal 8%. Grade 3/4: nausea 4%, emesis 4%, stomatitis 4%, hand-foot-syndrome 4%, neutropenia 54%, neutropenic fever 8%, non neutropenic fever 4%, renal toxicity 4%. 1 toxic death occurred in the ECF arm due to renal failure as part of a hepatorenal syndrome. DF: Grade 1/2: nausea 59%, emesis 27%, asthenia 73%, diarrhoea 45%, stomatitis 55%, hand-foot 36%, paraesthesia 36%, neutropenia 32%, renal 5%. Grade 3/4: asthenia 5%, diarrhoea 5%, stomatitis 5%, hand-foot-syndrome 5%, neutropenia 50%, no neutropenic fever, skin tox. 5%, cardiac tox. 5%, thrombosis 5%. 40 pts are evaluable for response (ECF 20 pts, DF 20 pts): ECF: CR 1/20, PR 9/20, NC 4/20, PD 6/20; DF: CR 2/20, PR 7/20, NC 4/20, PD 7/20. Tumor control rate (CR+PR+NC) is 70% for ECF and 65% for DF.

Conclusion: These preliminary results show that DF is a feasible combination which can safely be given in a fully ambulant setting. DF seems to be at least as tolerable as ECF and shows promising efficacy. The study is ongoing.

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Changes in circulating dendritic cells in metastatic or locally advanced pancreatic carcinoma patients during chemotherapy

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Purpose: Since dendritic cells (DC) are the most potent antigen-presenting cells required for the initiation and maintenance of an effective anti-tumor response, the present study was performed to explore the possible relationship between the efficacy of the chemotherapy and changes in circulating DC in metastatic or locally advanced pancreatic carcinoma patients (pts).

Methods: We studied 12 pts, 9 male and 3 female (age range 51-84); 5 of them underwent medical treatment with 5-FU continuous infusion for 6 weeks, Cisplatin weekly and Gemcitabine on days 1-8-28-35. Controls were programmed every two months. DC were generated by culturing peripheral blood adherent cells from pts and normal subjects in granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin-4 (IL-4) for 7 days, and characterized by flow cytometric analysis, capacity to release IL-12, and ability to stimulate eterologous T-cell proliferation and IFN-gamma production.

Results: DC from pts exhibited high levels of CD14 and lower levels of CD1a and CD40 expression as compared with those from healthy volunteers (p=0.02). CD40L-induced IL-12 p40 production of DC was generally increased in pts compared with controls (p=0.02), while bioactive IL-12 p70 was decreased (p=0.04). The T-cell stimulatory activity of DC was lower in pts than in controls (p=0.01), as well as the IFN-gamma production by T cells (p=0.04). After 2-4 months from chemotherapy, a slight increase in CD1a positive DC were found, together with an increase in IL-12 p70 (p=0.04) and a decrease in IL-12 p40 (p=0.02) production in response to CD40-L. In 50% of treated pts, DC increased their ability to induce IFN-gamma by T cells. However, in general, no significant changes in T cell stimulatory activity was observed.

Conclusion: These preliminary results suggest that DC from metastatic or locally advanced pancreatic carcinoma pts are functionally defective and that chemotherapy seem to be effective in modulating their biological activity.

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A phase II study of weekly docetaxel and concurrent radiation in patients (pts) with unresectable esophageal cancer

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Background: The prognosis of patients (pts) with unresectable esophageal cancer treated with radiotherapy alone is poor, with a 2-year survival of only 10%. In contrast, concurrent chemoradiotherapy with cisplatin and fluorouracil regimens is superior to irradiation alone, but this combination is associated with substantial toxicity (Herskovic, 1992). Docetaxel has demonstrated a high radiosensitizing potential in preclinical studies (Mason, 1997). Likewise, weekly docetaxel 20 mg/m2 with concomitant radiotherapy is feasible and active in esophageal cancer (Mauer, 1998). The present study was designed to determine the response and toxicity of weekly docetaxel plus concomitant radiotherapy in pts with unresectable esophageal cancer.

Patients and Methods: Since November 1998, 18 pts with locoregionally advanced esophageal cancer have been treated with weekly docetaxel (20 mg/m2 as 1 hour IV infusion) plus concomitant standard radiotherapy to a total dose of 66 Gy. Patient characteristics: 17 (94%) male; median age, 64 years (range 41-88); median Karnofsky index, 80% (range 70-100%); 14 (77%) squamous cell carcinoma. At diagnosis, pts were considered unresectable due to involvement of tracheobronchial tree in 6 pts (33%), age older than 75 years in 3 pts (16%), distant lymph node metastases in 2 pts (10%) and medically unfit for surgical therapy in 7 pts (39%).

Results: To date, 15 pts have completed therapy. Major responses were seen in 6 pts (40%) including 4 complete responses (27%) and 2 partial responses (13%). No patients progressed during the therapy. Median survival duration is 10 months, and the 1-year is 57%. Hospitalization for toxicity was required in 7 pts (46%), the majority for esophagitis, but significant myelosuppression was not observed. There was one death during the treatment.

Conclusions: This study confirms the feasibility of weekly docetaxel with concurrent radiotherapy in pts with unresectable esophageal cancer. The 1-year survival achieved in this group of patients is promising. Further patient accrual is planned to confirm these results.

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Gemcitabine (GEM) and capecitabine (CAP) for advanced pancreatic cancer. A phase I/II trial

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Purpose: GEM is presently the standard agent for the treatment of advanced pancreatic cancer. Preclinical studies suggest positive interactions between GEM and CAP, an oral 5-fluorouracil prodrug. In this study we in-