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Preoperative staging and tumor resectability assessment in pancreatic cancer. Prospective study comparing endoscopic ultrasonography (EUS), computed tomography (CT), magnetic resonance imaging (MRI) and angiography

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Background/Aim: So far, there is no consensus about the best strategy for staging and tumor resectability assessment in pancreatic cancer. In this prospective study, efficacy of EUS, helical CT, MRI and angiography were compared.

Method: All patients with pancreatic or periampullar cancer judged fit for laparatomy were studied by EUS, CT, MRI and angiography. Analyses included: extension of primary tumor, loco-regional, lymph-node, vascular and metastatic invasion, TNM stage, and tumor irresectability. Imaging results were correlated with surgical findings.

Results: Sixty-two patients were included, 51 (82%) with pancreatic and 11(18%) with periampullar cancer. Of them, 44 (71%) patients had loco-regional invasion, 26 (42%) lymph-node involvement, 25 (40%) vascular invasion, and 12 (19%) distance metastases. In addition, tumor was irresectable in 25 (40%) patients. CT had the highest accuracy in assessing extension of primary tumor (73%), loco-regional invasion (74%), vascular invasion (83%), distance metastases (88%),and TNM stage (41%). By contrast, EUS had the highest accuracy for lymph-node involvement (65%). CT was the most effective individual technique for establishing tumor irresectability (table).

	Se	Sp	PPV	NPV	A
EUS	23	100	100	64	67
CT	67	97	95	77	83
MRI	57	90	81	73	75
ANG	37	100	100	65	71

Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; A, accuracy. ANG, angiography. All values in %.

When imaging techniques were evaluated altogether, combination of CT and EUS had the highest sensitivity (74%) for tumor irresectability. If both tests were in agreement, specificity was maximum (100%). In discordant cases, angiography contributed to reestablish 100% specificity.

Conclusions: Helical CT is the most useful individual imaging technique for tumor staging in pancreatic cancer. Combination with EUS may represent the most effective strategy for establishing tumor irresectability, being angiography only needed in discordant cases.

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Prospective assessment of functional results and quality of life in patients treated for locally advanced anal canal carcinoma by high dose radio-chemotherapy:

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Objectives: Functional results of conservative treatments must be evaluated, especially in locally advanced tumors, when the sphinter can be destroyed by the tumour or late treatment effects. Quality of life(QOL)is an end point of a four arms prospective phase III study of treatment intensification by induction chemotherapy (CT) and a higher dose of irradiation (RT). The prime objective of this trial is to improve the colostomy-free survival. We studied the functionnal results of the first 60 patients included in the study.

Patients and Methods: There were 48F/12M (mean age = 65, range 31-79). The T-stages were 3 T1, 37 T2, 13 T3, 7 T4, 30 N0, 15 N1, 15 N2-3, 60 M0. They received a pelvic RT(45Gy in 25 fractions over 5 weeks) combined with concomitant 5-FU-CDDP CT in weeks 1 and 5, followed by a RT boost(15Gy). Two cycles of induction CT were delivered in two arms, and a higher dose (20-25Gy)in two arms. QOL was assesed by two validated questionnaries: the EORTC QLQ-C30, and the Anal Sphincter Conservative Treatments Questionnaire. The forms are filled at inclusion, at 2 and 6 months after the end of the treatment and annually.

Results: The first two questionnaires where analised in 56/60 patients. Diarrhea was present in 17% and 9.4% of the cases respectively and an adjunctive treatment prescribed in 12% and 16.6% of the cases respectively. Constipation was present in 23% and 3.1% of the cases respectively, and an adjuntive treatment was prescribed in 22.4% and 9.4% of the cases respectively. Incontinence for gaz, stools,and mucous was not modified (77.6% and 81.8%, 96% and 100%, 91.7% and 96.9% respectively). The need of a protective pad,and imperious bowel movements were not modified. Diet was modified in 28.5% and 48.5% of the cases respectively. The patients were unsatisfied for their bowel work in 20.8% and 9.7% of the cases respectively and moderately satisfied in 33.3% and 42% respectively. The health status perception was qualified of median in 45.6% and 40.6%, and very good in 42.5% and 47% of the cases respectively.

Conclusion: This prospective evaluation of the digestive function and QOL shows the improvements partially linked to the adjunctive treatments. The proper role of the specific cancer treatment will be analized from the different treatment modalities. The high rate of responses depicts the high interest of the QOL in patients and physicians considering the conservative treatment of anal canal carcinoma.

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Pemetrexed disodium (Alimta™) with folic acid (FA) in advanced or metastatic gastric cancer

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Purpose: A clinical trial was undertaken in order to evaluate the efficacy of the new antifolate Alimta in chemonaive patients (pts) with locally advanced or metastatic gastric cancer. After the first few pts, an oral supplementation with FA was also given due to major drug-related toxicity observed. In fact an early clinical study and preclinical studies with Alimta suggested that FA should reduce antifolate toxicity, especially in pts likely to have folate deficiency, and have little or no impact on efficacy.

Methods: In this ongoing study Alimta is administered at a dose of 500 mg/m^2 as a 10-minute infusion every 21 days (d). In addition, an oral supplementation with 5 mg FA/d for 5d starting 2d before Alimta is given.

Results: Each of the first 6 pts had at least one episode of Grade (Gr) 3/4 toxicity; Gr 3/4 neutropenia occurred in 10 of 15 cycles completed. One pt discontinued, and three died, all due to toxicity related to study drug. As a result, subsequent pts were given oral supplementation with FA. Twenty-five pts with measurable disease have since enrolled receiving 97 cycles (median 2, range 1–8). Median age was 60 years (range 44–76); all but one pt had a ECOG PS of 0–1. Main metastatic sites were liver (15/25), abdominal lymph nodes (12/25) and lung (6/25). Thus far, 6 of these 25 pts have had confirmed objective responses (2 CRs + 4 PRs) with an overall response rate of 24%; an additional pt had an unconfirmed complete remission. Gr 3/4 treatment-related toxicities have been neutropenia (24%), leucopenia (4%), thrombocytopenia (8%) and raised transaminases (4%).

Conclusion: Although the trial is still in progress, the early clinical findings show that Alimta has a very promising activity in gastric cancer, while supplementation with low-dose FA orally is able to dramatically improve safety profile of the antifolate.

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Final results of a phase 1 and PK study of capecitabine (XEL) in combination with epirubicin (E) and cisplatin (C) [ECC] in patients with advanced oesophagogastric (OG) adenocarcinoma

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The standard treatment of advanced OG adenocarcinoma in the UK is with EC and continuous infusional 5-FU by an indwelling central venous catheter [ECF] which has a significant complication and morbidity rate. Capecitabine is an orally-available tumour-selective fluoropyrimidine carbamate which is bio-activated by a 3-enzyme process to provide prolonged high levels of the active moiety, 5-FU, within tumour cells, and is active in breast and colorectal cancers. To reduce the morbidity of ECF associated with Hickman line insertion we have conducted a dose-finding and PK study of capecitabine in combination with EC.

32 patients (28M/4F) median age 63 (range 32-76) years, ECOG performance status 0-2, with histologically proven unresectable (10) or metastatic

(22) oesophageal (1) gastric (9) or OG junction (22) adenocarcinoma received up to 6 courses of E (50 mg/m2) C (60 mg/m2) and XEL at 3-weekly intervals. XEL was administered orally in an intermittent schedule (14 days treatment, 7 days rest period) at doses of 500 mg/m2 bd, 825 mg/m2 bd, 1000 mg/m2 bd, and 1250 mg/m2 bd in successive cohorts. Up to 6 evaluable patients were recruited into each dose cohort with no intra-patient dose escalation. Dose escalation occurred after 6 patients had completed at least 1 cycle of chemotherapy at the previous dose level. DLT was assessed on the first-cycle toxicity only. The MAD was 1250 mg/m2 bd with 2 of 5 patients experiencing DLT (grade 2 stomatitis [1], grade 3 diarrhoea with febrile neutropenia [1]). Cumulative toxicity for all cycles (n=140) (worst NCI-CTC grade per patient) included grade 4 oesophagitis (1 patient) grade 3 diarrhoea (5) grade 4 neutropenia with infection (7) grade 2 stomatitis (4) and grade 4 thrombocytopenia (1). Of 29 patients with evaluable disease there was 1 documented CR and 11 PR (41%). PK analyses (first cycle only) confirm absorption of capecitabine in patients with active OG cancer or previous OG resection with peak concentration of 291-9499 ng/ml, of DFCR from 701-9586 ng/ml, and of DFUR of 611-8948 ng/ml. A dose of 1000 mg/m2 bd capecitabine is recommended in combination with EC. This is tolerable and active and a randomised comparison with ECF is justified.

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Multicenter phase II trial of first-line irinotecan (CPT-11) and gemcitabine (GMB) in patients with unresectable pancreatic cancer

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Objectives: GMB is considered as standard treatment of pancreatic cancer conferring a significant clinical benefit to the patients. CPT-11 is active in gastrointestinal malignancies. Based on preclinical data suggesting synergism between the two drugs and their different mechanism of action a multicenter phase II study was conducted in order to evaluate the tolerance and the efficacy of their combination.

Patients and Methods: Fifty-seven chemotherapy-naïve patients with advanced pancreatic cancer [median age: 65 years, F/M: 33%/67%, PS 0/1/2: 5/36/16, median involved sites/pt: 2] were enrolled. Patients received GMB (900 mg/m^2 over a 30-min infusion) on days 1 and 8 and CPT-11 (300 mg/m^2 over 1 h infusion) on day 8 every 3 weeks.

Results: All pts were evaluable for toxicity, 52 for response (intention-to-treat). Two (4%) CRs, 10 (19%) (ORR 23%; 95% C.I. 11.63%–34.53%) PRs, 18 (35%) SD and 22 (42%) PD were documented (intention-to-treat-analysis). The median duration of response is 3.25 months, the median TTP is 6.3 months and the median survival 8 months. Grade 3–4 neutropenia occurred in 24 (42%) pts and 9 (16%) of them developed febrile neutropenia; 3 pts died because of sepsis. Grade 3 anemia was observed in 2 (4%) pts and grade 3–4 thrombocytopenia in 7 (12%). Non hematologic toxicity included grade 3 diarrhea in 4 (7%) pts, grade 3 vomiting in 2 (4%), grade 3 fatigue in 8 (14%). The other toxicities were mild.

Conclusion: The combination of GMB/CPT-11 is a relatively active regimen for patients suffering from pancreatic cancer with acceptable toxicity.

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Treatment of pancreatic endocrine tumours with adriamycin-streptozotocin association: evaluation of efficacy and prognostic factors of response and survival

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Introduction: Adriamycin-streptozotocin association has been considered as the chemotherapy of choice in the treatment of advanced pancreatic endocrine tumour (PET) until recently when a trial failed to confirm the efficacy of this chemotherapeutic regimen. Because of these conflicting results, we decided to present our experience of this specific therapeutic regimen in the treatment of advanced PET. The aim of our study was to assess retrospectively the objective response rate and survival of patients suffering from PET and treated by this association. Furthermore, we tried to determine prognostic factors of response and survival. Finally, we analysed the toxicity of this regimen.

Material and methods: between January 1995 and December 1999, we investigated retrospectively 45 consecutive patients suffering from advanced PET and receiving adriamycin-streptozotocin association. The chemotherapeutic protocol was adriamycin 50 mg/m2 day 1 and 21 and streptozotocin 500 mg/m2 day 1 to 5. This treatment was administered every 6 weeks(day 1= day 43). The patients were assessed every two months by radiological examination.

Results: there were 18 women and 27 men, median age 54 years. Fourty two of the 45 patients had metastases (liver 39/42, lymph nodes 18/42, peritoneum 3/42, others 12/42). Performance status was 0 in 34, 1 in 7, 2 in 3 and 3 in 1 of the patients. Sixteen patients have been previously treated by surgery, 11 by systemic chemotherapy, 4 by radiotherapy, 4 by chemoembolization, and 11 by somatostatin analogues. Sixteen of the 45 patients had partial response and seven had a minor response. The objective reponse rate was 35.6%[IC95%:0.22-0.49]. Several prognostic factors of response to chemotherapy have been isolated, especially previous chemotherapy (p=0.0033)or hepatomegaly (p=0.0156) which worsened the response to chemotherapy. Furthermore, previous chemotherapy (p=0.00835)or chemoembolization (p=0.00546) and hepatomegaly (p=0.05) were associated with a poor overall survival. Finally, the association was well-tolerated with 7 grade 3-4 digestive side effects (OMS classification)and 3 febrile neutropenia.

Conclusions: adriamycin-streptozotocin combination was well tolerated and associated with up to 35% of objective response rate, which confirm the results of the Mayo Clinic trial. Moreover, prognostic factors of response and survival isolated in our study could be interested to select patients who received this chemotherapeutic treatment.

1159 POSTER

Survival in the surgery of pancreatic tumours with vascular involvement

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The aim of the study is to evaluate survival time, with a retrospective analysis of a database of patients with pancreatic adenocarcinoma who underwent pancreatic and portal or mesenteric resection. In the period between January 1994 and December 1999 were admitted 74 patients affected by solid pancreatic adenocarcinoma (men 59%, women 41%). The diagnosis of vascular involvement was done with the angioscan, angiography or surgical exploration. Survival data were evaluated according to Kaplan Mayer, Wilcoxon Test was used to assess statistical differences between groups. The software was Statistical for Windows, version 4.0 Stadfot Inc., 1993. In this group, 59 patients were submitted to resection or palliative surgery, 5 had a diagnostic laparatomy and 10 medical therapy only. Of 59,in 33 cases pancreas underwent resection and, among these, 10 vascular resections were performed: 5 resection of the portomesenteric axis and direct end-to-end reconstruction and 5 marginal resections and direct suture. In 26 patients was performed a palliative operation. Histologic evidence of tumour cell infiltration of vessel walls was present in the majority of the resected specimens. Thirty-day mortality was 6.6% in the pancreatic resection without vascular involvement, 8.3% in vascular resection and 11.5% in the palliation. All patients were submitted to chemotherapy (5Fu and/or Gemcitabine) when required. Significant results were shown for the mean survival of 6,5 months for the vascular resections and 18.3 months for the pancreatic resections without vascular involvement (Wilcoxon P=0.02703, Cox P=0.042).The mean survival was also of 7 months for the surgical palliation and 6.8 months for the diagnostic laparatomy. Finally there was no significant survival time difference between palliation versus vascular resection, 7 and 6.6 month respectively, with the Wilcoxon test P =0.462 and the Cox test non significant.

Conclusion: Patients undergoing vascular resection have an uniformy poor outcome despite resection. The prognosis of these patients is dismal and corresponds to the prognosis with palliative nonresectional surgery. We believe that vascular resections can be safely performed and seems to improve the quality of life but needs further study in these high-risk patients.