acute toxicity and patterns of failure in patients that receive chemoradiation (CRT) for inoperable cancer of the pancreas, after non-progression on C. Conformal RT is delivered, but elective nodal irradiation is omitted.
Material and Methods: All patients received neo-adjuvant C, if tolerated at least 6 months were delivered. CRT followed this if no evidence of progressive disease was found. A dose of 45−54 Gy in 1.8 Gy/fraction was delivered with 3D conformal planning. The planning target volume (PTV) was limited to visible tumour with 1.5 cm circumferential and 2 cm cranio-caudal margin. Elective nodes were not included. Toxicities were recorded prospectively during treatment. Local progression was defined as failure within PTV and local nodes, systemic as visceral disease present. Time to progression (TTP) and overall survival (OS) are reported from the date C was started.
Results: 45 patients, M/F = 23/22; median age 61 years (range 41−83) treated between 01/1997 and 12/2006. Stage IIb = 6, III = 39; ECOG PS 0−1/2/NA = 34/6/5; CA19.9 < 100 = 24, >100 = 21. C consisted of protracted infusion 5FU modulated with other agents (PVI5FU) = 14, Capecitabine (X) = 3, Gemcitabine (G) = 13, G+X = 15. A median of 6.6 months (range 1−16.8) of C were delivered. Median dose of RT 50.4 Gy, range (23.4−54). 27 patients received C with RT (19 X, 7 PVI5FU, 1 G). RT stopped due to toxicity in 2 patients (23.4 Gy, 46.8 Gy). 6 patients had breaks in RT: 2 non-compliance (4 days), 4 due to toxicity (2−28 days). During CRT 13 (28.8%) patients had grade 3 toxicities, 9 (20%) patients GI toxicity: (nausea = 6, vomiting = 2, diarrhoea = 1); fatigue = 2, abdominal pain due to tumour = 3, sepsis = 4, skin = 2, other = 3. One patient had grade 4 vomiting and 1 patient died shortly after RT due to perforated duodenal ulcer in RT field. 5 had C stopped or dose reduction during RT. The first site of failure was local in 8 patients, local and systemic in 6 and systemic in 22 patients. Median TTP was 13.5 mo; median survival 19.7 mo, 1-year OS = 79%, 2-yr OS = 28%.
Conclusion: Sequential C then CRT shows promising efficacy in the treatment of LAPC in a highly selected group of patients. The low proportion of local failures indicates that prophylactic nodal irradiation could be omitted to facilitate delivery of CRT.

3532 POSTER

Histopathological response to preoperative chemoradiation for resectable pancreatic adenocarcinoma: the French phase II FFCD 9704-SFRO trial

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Background: To define and evaluate histopathological response rates with preoperative chemoradiation (RT-CT) for resectable pancreatic adenocarcinoma.
Materials and Methods: Forty-one patients (pts) with localized, potentially resectable pancreatic adenocarcinoma were treated with 50 Gy combined with 5-Fluorouracil (300 mg/m^2 /d; d1-d5; week 1−5) and Cisplatin (20 mg/m^2/d; d1-d5 and d29-d33). Radiographic restaging was performed 4 to 6 weeks later and pts presenting with resectable disease underwent surgical resection.
Results: Twenty-six (63%) of 41 pts underwent curative surgery. Standardized histologic response was measured and graded by a single pathologist. The effectiveness of the preoperative chemoradiation was defined by the proportion of severly degenerative cancer cells (SDCC), their density and histological distribution and the proportion of necrotic tumoral tissue. Eleven of 24 (46%) specimens presented more than 80% of SDCC, and 8/11 (72%) specimens were associated with large necrosis areas. The histologic distribution was characterized by the low density of nonaffected cancer cells, and an important fibrous and amorphous connective tissue associated with cancer-cells' defects (type A of the Ishikawa's classification). Histologic complete response was observed in one specimen, and 9/24 (37%) specimens were characterized by 50 to 80% of SDCC. Finally, 4/24 specimens presented with a low rate of SDCC, few necrosis area and several non affected cancer cells (Ishikawa C).
Conclusion: Preoperative 5-Fluorouracil-Cisplatin-based concurrent RT-CT for resectable pancreatic adenocarcinoma provides antitumoral effect. With regard to the feasibility of this therapeutic schedule and the rate of major histologic response, this approach could offer a clinical benefit. Further gemcitabine-based chemoradiation regimens, will determine the predictive factors of the treatment response, and the improvement in survival. This study is the first in Europe to present histopathological data on a prospective approach.

3533 POSTER

Cetuximab plus Gemcitabine/Oxaliplatin (GEMOXCET) in 1st line metastatic pancreatic cancer – a multicenter phase II study

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Background: Targeting the epidermal growth factor receptor (EGFR) pathway in pancreatic cancer seems to be an attractive therapeutic approach. The present study assessed for the first time the efficacy of cetuximab plus the combination of gemcitabine/oxaliplatin in metastatic pancreatic cancer.
Methods: Eligible subjects had histological or cytological diagnosis of metastatic pancreatic adenocarcinoma. The primary endpoint was response according to RECIST. Patients (pts) received cetuximab 400 mg/m^2 at first infusion followed by weekly 250 mg/m^2 combined with gemcitabine 1000 mg/m^2 as a 100-minute infusion on day 1 and oxaliplatin 100 mg/m^2 as a 2-hour infusion on day 2 every 2 weeks.
Results: Between January 2005 and August 2006 a total of 64 pts [22 women (34%), 42 men (66%); median age 64 years (range 31−78)] were enrolled at 7 study centers. At April 2007 a total of 37 pts are still alive. 58 pts are evaluable for baseline and toxicity analysis. 6 pts had no treatment or an incomplete drug combination within the first cycle of the treatment plan (n = 3 hypersensitivity reactions to the first cetuximab infusion, n = 1 rapid tumor progression, n = 2 lost of follow-up). Reported grade 3/4 toxicities (% pts) were: leucopenia 12%, anemia 16%, thrombocytopenia 11%, diarrhea 7%, nausea 14%, infection 19%, allergy 4%. Cetuximab-attributable skin reactions occurred as follows: grade 0: 28%, grade 1: 43%, grade 2: 22%, grade 3: 7%. The intention-to-treat analysis of 50 evaluable pts shows an overall response rate of 32% including 1 (2%) complete and 15 (30%) partial remissions. There were 30% pts with stable and 38% pts with progressive diseases or interruption of the therapy. Median time to progression is 123 days with a preliminary overall survival estimation of 8 month. A clinical benefit response was noted in 23 of evaluable 54 pts (43%).
Conclusion: The addition of cetuximab to the combination of gemcitabine and oxaliplatin is well tolerated and exhibits a high response rate. Further evaluation in a phase III trial is warranted.

3534 POSTER

Patients with ERCC1-negative tumors may benefit from preoperative CRT in resectable esophageal cancer

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Background: We reported that preoperative chemoradiotherapy (CRT) did not show survival advantage to surgery alone in general patients with resectable esophageal cancer (Lee JL et al., Ann Oncol 2004;15:947−54). We investigated the effects of preoperative CRT on survival according to ERCC1 status in resectable esophageal cancer.
Materials and Methods: Paraffin-embedded pretreatment tumor specimens, collected by endoscopic biopsy from patients treated either with surgery alone or with preoperative CRT (5-FU/cisplatin or capecitabine/cisplatin with 46.5−48 Gy of radiation) followed by surgery, were analyzed by immunohistochemical assay for ERCC1. Staining intensity and proportion of ERCC1 were graded on a scale of 0 to 3, and the resulting scores were multiplied to obtain a semiquantitative score (0−9).
Results: Between March 1993 and June 2005, 175 patients were treated with preoperative CRT followed by surgery or surgery alone as part of prospective clinical trials. Of those, 152 biopsy specimens (111 in the

preoperative CRT [CRT-S] group and 41 in the surgery alone [S] group) were available for immunohistochemical analysis. ERCC1 expression were classified into positive (score >4) and negative (score⩽4) based on median value of ERCC1 expression. Patients and disease characteristics were comparable between 2 groups. ERCC1 expression was positive in 71 patients (47%). With a median follow-up of 44 months, median overall survival (OS) of surviving patients was 45.6 months in the S group and 47.8 months in the CRT-S group, and median event free survival (EFS) was 36.7 months in the S group and 38.4 months in the CRT-S group. Neither EFS nor OS differed between groups (p = 0.763 and 0.462, respectively). However, among patients with ERCC1-negative tumors, those who received preoperative CRT had longer OS and EFS compared with those treated with esophagectomy alone (median OS; 59.2 months vs 29.4 months, p = 0.0568, median EFS; 50.7 months vs 19.7 months, p = 0.0415) but not among patients with ERCC1-positive tumors (p = 0.304 and 0.516, respectively). Among patients who received esophagectomy alone, those with ERCC1-positive tumors had a tendency toward longer OS and EFS compared to those with ERCC1-negative tumors (p = 0.085 and 0.094, respectively).
Conclusions: Patients with ERCC1-negative tumors may benefit from preoperative CRT compared with surgery alone in resectable esophageal cancer.

3535 POSTER

Phase II trial investigating the efficacy and safety of sunitinib in patients with unresectable hepatocellular carcinoma (HCC)

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Background: The oral multitargeted tyrosine kinase inhibitor, sunitinib malate (SUTENT®; SU), has demonstrable antitumour activity and is approved for the treatment of advanced RCC and imatinib-resistant or intolerant GIST. The tyrosine kinases VEGFR and PDGFR, which play key roles in HCC proliferation and tumour angiogenesis, are targets for SU. In this phase II, open-label, single-agent study, we investigate the efficacy and safety of SU in European/Asian patients (pts) with unresectable HCC.
Patients and Methods: Pt eligibility criteria included histologically confirmed HCC, ECOG PS ⩽ 1, CP score −A/−B, adequate organ function and no brain metastases, clinically relevant ascites or prior liver transplant. Pts received SU 50 mg/day for 4 wks, every 6 wks (4/2 schedule). The primary endpoint was ORR measured by RECIST. Other endpoints included time-to-event rates, safety (NCI CTCAE v3.0), PK and other measures of antitumour activity (tumour density, volumetric measurement of percent tumour necrosis [VMTN] and intra-tumour blood perfusion by CT scan).
Results: Baseline pt characteristics were: n = 37; median age=61 yrs, range 29–82; male=92%; PS 0:1, 51%:49%; CP −A/-B, 84%/16%; 40.5% with prior local treatments. Pts received a median of 2 SU cycles (range 1–8). RECIST assessment indicated one partial response and 35% with stable disease. Median overall survival was estimated to be 45 wks (range 22.0–not reached). Grade 1/2 skin toxicity was common. Grade 3/4 toxicities included thrombocytopenia (35%), neutropenia (24%), CNS symptoms (22%), asthenia (22%) and haemorrhage (22%). Grade 5 events included bleeding, drowsiness, hepatic encephalopathy and renal failure (n = 4). 43% of pts required at least one SU dose reduction. There were no differences in drug exposure between CP-A and −B groups. Tumour density decreased in 68% of pts. Major (>50%) and minor (<50%) post-treatment tumour necrosis, measured by VMTN, occurred in 46% and 25% of pts, respectively. A 39% decrease (range 13–72%) in post-treatment tumour blood perfusion parameters (blood volume and flow) occurred.
Conclusions: Major tumour necrosis was observed in almost half of pts in this study following SU treatment, suggesting potent antitumour activity of SU in unresectable HCC. Change in tumour size may not be the most appropriate endpoint for assessing SU efficacy in HCC pts. These findings, which are consistent across European and Asian pts, warrant further investigation of SU in this pt population.

3536 POSTER

A phase II study of induction chemotherapy with gemcitabine plus S-1 (GS) followed by chemoradiation for locally advanced pancreatic cancer (LAPC)

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Background: Most patients (pts) with LAPC treated by chemoradiation (CRT) eventually develop metastasis progression. Thus, effective systemic chemotherapy is required, even for pts with LAPC. Gemcitabine plus S-1 (GS) chemotherapy has been shown to yield a high tumor response rate in cases of advanced pancreatic cancer. Here, we conducted an early phase II study to examine the efficacy of GS therapy followed by CRT in pts with LAPC.
Methods: The eligibility criteria for enrolment in the trial were: histologically proven LAPC, age >20 years, performance status (PS) of 0 or 1, and no history of prior therapy. The pts received 4 cycles of induction GS chemotherapy (gemcitabine, 1000 mg/m^2, days 1, 8; S-1, 40 mg/m^2 bid, days 1−14; every 21 days). Subsequently, pts who did not show progression received CRT (30 Gy, 10 fractions, 2 weeks; gemcitabine, 250 mg/m^2, days 1, 8). After the CRT, at least 2 cycles of standard gemcitabine (1000 mg/m^2, days 1, 8, 15; every 28 days) were administered. The primary endpoint of the study was the progression-free survival (PFS) rate at 6 months. A PFS of 50% at 6 months was expected in this trial.
Results: Between February 2005 and October 2006, 20 pts (median age: 63.5 years [33−75 years], PS 0/1: 15/5, male/female: 10/10) were enrolled. The induction GS chemotherapy was completed in 18 pts. Two pts showed disease progression (general deterioration) during the induction GS chemotherapy. Grade 3/4 hematological toxicities were observed in 13 pts (65%), and grade 3 febrile neutropenia was observed in 1 patient. Grade 3 non-hematological toxicities were observed in 5 pts (nausea and anorexia were the most common). Dose reduction was necessitated in 5 pts (25%). Two pts showed disease progression after completion of the induction GS chemotherapy. Subsequently, 16 pts received CRT, which was completed without delay in all. Grade 3 hematological toxicities were observed in 2 of these 16 pts. Five (25%) partial response were observed among all evaluable pts. Laparotomy with curative intent was undertaken in 4 pts, and R0 resection could be accomplished in 3. A pathological complete response was observed in 1 of these patients. The PFS rate at 6 months was 70% (14/20, 95% CI: 45.7−88.1%). The median overall survival period was 11.0 months (95% CI: 5.4−16.5 months).
Conclusions: Induction GS chemotherapy followed by CRT is a feasible and promising strategy for the treatment of LAPC. A multicenter trial on a larger sample size is warranted to confirm the efficacy and survival benefit of this treatment observed in this study in patients with LAPC.

3537 POSTER

Variations in KIT and PDGFRA mutations in gastrointestinal stromal tumours

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Gastrointestinal stromal tumors (GISTs) are characterized with oncogenic mutations, leading to constitutive, ligand independent activation of KIT tyrosine kinase. KIT (CD117) appeared to be an extremely helpful marker in discriminating GISTs from other mesenchymal tumors. In GISTs with wild-type KIT protein the mutations in PDGFRA gene were shown. To determine the KIT and PDGRFA mutations in GISTs and estimate their prognostic value, we analyzed 68 genomic DNA extracted from paraffin sections. DNA was amplified with primers to exons 11, 9, 13, 17 of KIT and exon 18 of PDGRFA followed with direct sequencing. Seventy three percents of GISTs harbor KIT mutations in exon 11, namely, 74% of gastric tumors, 63% of intestinal tumors and 100% of GISTs of rectum. The most frequent mutations were in-frame deletions in the region of 550–563aa at the 5′-end of KIT exon 11. The point mutations were localized in 557, 559 and 560 codons. GISTs with KIT mutations that targeted to 557, 558