Proffered Papers

Gastro-intestinal

496 ORAL

Results of a randomised trial comparing ECF with MCF in advanced oesophago-gastric cancer

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Aims: To compare ECF with a new combination MCF for tumour response, survival, toxicity and quality of life (QL) in patients with previously untreated advanced oesophago-gastric cancer.

Methods: 580 patients were treated with ECF [epirubicin (50 mg/m^2) and cisplatin (60 mg/m^2) every 3 weeks with protracted venous infusion (PVI) 5-FU (200 mg/m^2/day for 24 weeks)] or MCF [mitomycin C C (7 mg/m^{2}6-weekly), cisplatin (50 mg/m^2 3-weeldy) and PVI 5-FU (300 mg/m^2/day for 24 weeks)].

Results: Overall response rate was 41% with both ECF MCF (p = 0.97). Response rates were higher for cancers of the OGJ (48%) than stomach (35%; p = 0.03). Toxicity was tolerable with only 2 toxic deaths. ECF caused more grade 3/4 neutropenia (p = 0.003); grade 3/4 thrombocytopenia was more common with MCF (p = 0.007). Alopecia was more common with ECF (p < 0.0001) whilst plantar-palmar erythema was more frequent with MCF (p = 0.017). Median failure free survival was 7 months with both ECF and MCF. Median survival was 9.4 months with ECF and 8.7 months with MCF (p = 0.89) and 1-year survival was 37% and 33% respectively. For patients with locally advanced disease median survival was 11.3 months with ECF and 11.5 months with MCF (p = 0.203) and 1-year survival was 41% and 48%. QL was superior with ECF compared to MCF after 12 and 24 weeks treatment

Conclusion: ECF and MCF result in equivalent response and survival but QL is superior with ECF. ECF remains one of the reference treatments for advanced oesophago-gastric cancer.

497 ORAL

Efficacy of 5FU + cisplatin (FUP) compared to bolus 5FU (FU) in advanced pancreatic carcinoma (APC)

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Chemotherapy (CT) with 5FU has a marginal efficacy in APC. However, FUP gave us a 27% response rate (RR) and 29% one-year survival (S) in a previous phase II study. We try to confirm the superiority of FUP over FU in this randomized study of the digestive group from the French Anticancer Centers (FNCLCC).

Population: APC histologically proven, measurable or evaluable, metastatic or locally advanced, non pretreated. Chemotherapy regimens were: – arm FU = 5FU: 500 mg/m"/day (d) × 5d every 4 weeks; – arm FUP: continuous infusion of 5FU 1000 mg/md": d × 5d + cisplatin: 100 mg/m" on d1 every 4 weeks

Results: 207 patients (pts) have been randomized by 18 centers, 103 in arm FU and 104 in arm FUP; there was no imbalance between arm FU and arm FUP. Median number of cycles: 2 vs 2 (range 0 to 14). Grade 3–4 toxicity (WHO) was lower in arm FU vs arm FUP: 20% vs 47% (p < 0.001); neutropenia: 6% vs 22%; vomiting: 4% vs 16%; mucositis: 5% vs 13%; toxic deaths: 1 vs 4 early in the trial. Efficacy: 6-month S for arm FU vs arm FUP were 28% vs 38%; one-year S: 8% vs 17% (logrank, p = 0.08), 6-month progression free S (PFS): 5% vs 19% (p = 0.0002). RR (intent to treat analysis) were 0% vs 12% (p < 0.01) (partial response: 0/97 vs 12/94 evaluable patients).

Conclusion: In APC with poor prognostic factors FUP is superior to FU in terms of RR and PFS. The low RR is partly related to the number of patients who received only one cycle. Even if non optimal this FUP regimen give interesting results, better tolerated regimens combining 5FU and P are needed.

498 ORAL

Locally advanced pancreatic carcinoma: Neoadjuvant radiochemotherapy (RCT) with 5-fu and mitomycin c

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Purpose: Rates of curative resection in locally advanced pancreatic carcinoma are low. We investigated if simultaneous RCT can be performed concerning acute toxicity and if operability can be produced.

Methods: 27 patients (pts) have been recruited for RCT between July 1995 and February 1998. Pancreatic carcinoma either was histologically proven or clinically suggested (CT, ERCP, CA 19-9). After exclusion of distant metastases 3d-conformal radiotherapy has been administered with 1.8 Gy daily. Primary tumour, metastatic nodes and high risk nodes were irradiated with a total dose of 50.4 Gy followed by a boost to 55.8 Gy. Simultaneously, we administered 2 courses of 5-FU (1000 mg/m^2 IV as 120 h continuous infusion, d1-5 and 29–33) and Mitomycin C (10 mg/m^2, IV bolus injection, d2 and d 30). Acute toxicity for radiotherapy (RTOG) and chemotherapy (NCI) have been registered. We report upon resectability and survival.

Results: RCT could be fully administered in 25/27 pts. In 2/27 pts it had to be aborted due to distant metastases occurring during treatment. Acute toxicity: upper GI tract 5/27 °III, 0/27 °IV; diarrhea 0/27 °III/IV; leukopenia 6/27 °III/ 1/27 °IV; thrombopenia 1/27 °III, 1/27 °IV; hemoglobine 2/27 stage III, 0/27 stage IV. R0-resection could be performed in 9/25 pts. Median follow-up is 20 mts. 6/25 pts are alive, 3/9 after resection and 3/16 without resection.

Conclusion: Neoadjuvant RCT is a promising therapeutic concept with low toxicity. 36% (9/24) with irresectable/borderline resectable tumours at diagnosis can be completely resected (R0).

499 ORAL

High incidence of K-Ras mutations in the bile fluids of patients with primary sclerosing cholangitis

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Primary sclerosing cholangitis (PSC) is associated in 10%–36% with cholangiocellular carcinoma (CCC). So far no reliable factors have been described which can define high risk PSC-patients for the development of CCC. Since K-Ras mutations occur early during the development of many cancers, we investigated the bile of PSC patients for K-Ras mutations as an possible prognosis factor.

Methods: 50 patients with PSC and 19 patients with other benign cholestatic liver diseases (benign choledochusstenosis after OLT (1I), liver cirrhosis (3), choledocholothiasis (4), Budd chiari syndrome (1)) were included into the study. Bile fluids were obtained by ERC. After extraction of genomic DNA, a mutation "enriched" PCR-RFLP was performed. If K-Ras mutations were detected by a second band in gel electrophoresis, the PCR products were subcloned and DNA sequencing was performed.

Results: None of the 19 patients with benign cholestatic liver diseases

showed any K-Ras mutations in the bile fluid. In contrast 17 (34%) of 50 patients with PSC revealed K-Ras mutations in the bile fluid. The Mayo-score of the PSC patients was not significantly different between the PSC-patients with (n = 15, score = 0.45) and the PSC-patients without (n = 27, score = 0.3) K-Ras mutations. In 6 of the 50 patients with PSC an orthotopic liver transplantation was performed. In 4 of the 6 patients a K-Ras mutation could be observed more than 12 months before OLT. The explanted livers were intensively investigated by a pathologist. The PSC livers without K-Ras mutations revealed only the typically inflammatory bile ducts of PSC. However in the group of the PSC-livers with K-Ras mutations one liver showed high graded dysplasia in the bile ducts and in two livers incidental cholangiocellular carcinomas could be observed. The K-Ras mutations of the bile could be confirmed in the tumors.

Conclusion: Our results suggest that the occurrence of K-Ras mutations is an independent prognostic factor for PSC-patients.

500 ORAL

A randomized trial on hepatic arterial CDDP and i.v. 5-FU in unresectable colorectal liver metastases

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Following a previous phase II study on bolus hepatic arterial CDDP and i.v. 5-FU, this multicentric randomized phase II clinical trial was started to evaluate effectiveness to give hepatic arterial CDDP and i.v. 5-FU. Since the minimum follow-up is 36 months, long-term results are now available.

Material and Methods: One hundred twenty-three pts with colorectal liver metastases staged III and IV A according to the TNM classification modified by Gayowski and Starzl underwent surgical cannulation of gastroduodenal artery and port implantation. Hepatic arterial CDDP 24 mg/m^2/day by bolus (arm A) vs continuous (arm B) infusion and i.v. 5-FU 500 mg/m^2/day were delivered on days 1 to 5 every 28.

Results: Objective responses evaluated by liver sonogram were 52% and complete responders were 17 without significant differences between the two arms. The arm B experienced a lower number of toxic events; overall G3 toxicity was less than 30%. The 5-yr survival was 20.4 and 16.1 in the arm A and B respectively. The responders showed a 5-yr survival significantly higher than the non responders (28.2% vs 16.6%; p = 0.006). The complete responders experienced the highest survival (41.4%) and half of them benefitted by a surgical resection confirming a pathological response in 4 pts. In the arm B, the subgroup whit no change (30%) showed survival rates as high as the responders. All the pts with progression ab initio died within 14 months.

Conclusions: This combined hepatic arterial and systemic therapeutic approach allowed: a) to observe long-term survivors, b) to resect the complete responders, c) to reduce toxicity significantly when CDDP was delivered by continuous infusion.

501 ORAL

Basal level gene expression of thymidylate synthase (TS) in colorectal cancer and normal colon mucosa – No evidence of relation to disease course

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The aim of the present study was to prospectively analyse gene expression of TS as a prognostic factor in colorectal cancer. Biopsies were obtained from both tumour and macroscopically normal colon mucosa in 31 colorectal cancer patients. No patients were previously subjected to chemotherapy. Thirteen patients were classified as having advanced disease, i.e. tumours not amenable to curative resection at diagnosis or developing distant metastases or recurrent disease during the follow up period of 24 to 36 months. Eighteen patients were classified as having a locally controlled disease. The gene expression levels of TS were measured by semi-quantitative reverse transcription-PCR. Gene expression was calculated as the ratio between TS gene cDNA and beta actin cDNA × 10-2, quantitated on an ABI PRISM 7700 sequence detection system. Average TS gene expression was 98.3 ± 87.6 in tumor and 43.9 ± 25.7 in normal mucosa. Gene expression of TS was significantly higher in tumour biopsies than in normal colon mucosa ($p < 0.05$), but there was no significant difference in distribution of tumour TS values between patients with advanced disease and those with surgically controlled disease. Previous reports have suggested that high TS gene expression is associated with lack of response to 5-fluorouracil based chemotherapy and short survival. TS protein has also been proposed as an independent prognostic marker, but there is no evidence in the present study that high tumour TS gene expression predicts a more aggressive course of the disease.

502 ORAL

Value of peptide receptor imaging using indium-111-octreotide (OCT) and iodine-123 vasoactive intestinal peptide (VIP) in patients with carcinoid tumours: Vienna university experience 1993–1998

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Introduction: Radioloabeled peptide analogs (111In-OCT, 123I-VIP) are being used to identify primary and metastatic tumour sites in patients with carcinoid tumours.

Methods: A total of 194 patients with a verified or suspected diagnosis of a carcinoid tumour were referred to our institution between 1993 and 1998. All patients underwent scanning with 111In-OCT, while 131 patients received both 111In-OCT and 123I-VIP in random order. Imaging results were compared to results to conventional staging including CT, sonnographyand endosonography not older than 4 weeks. In case of discrepancies, results of surgical exploration also were taken into account.

Results: In total, 84% primary or recurrent carcinoids could be visualized by means of 123I-VIP, while metastatic sites were indentified in 82% of patients. In patients scanned with 111In-OCT, 91% of primary or recurrent carcinoids could be identified, and metastatic sites could be imaged in 95%. In a direct comparison, 111In-OCT was found to be superior to 123I-VIP, with 93% vs 84% of scans being positive in primary of recurrent tumours, 90% vs 82% in metastatic sites, and 43% vs 25% in patients with carcinoid syndrome. Overall, peptide receptor scanning was more sensitive than conventional imaging, which located malignant lesions in only 71% of patients.

Conclusion: Our results indicate a high sensitivity for both peptide tracers for localizing tumour sites in patients with ascertained or suspected carcinoid tumours, with 111In-OCT scintigraphy being more sensitive than 123I-VIP receptor scanning. Both peptide tracers have a higher diagnostic yield than conventional imaging.

503 ORAL

Health-related quality of life in five-year survivors of endocrine gastrointestinal tumours

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Purpose: Patients with endocrine gastrointestinal (GI) tumours have a relatively long median survival, those with carcinoid tumours, 90 months and those with endocrine pancreatic tumours (EPT), 72 months. In a mailed survey, HRQOL was evaluated in long-term survivors of endocrine GI tumours.

Methods: EORTC QLQ-C30, FACT-G and an importance-satisfaction with HRQOL aspects questionnaire were mailed to a sample of patients (carcinoid tumours n = 64, EPT n = 55) referred to the Dep.E.O., Uppsala University Hospital.

Results: Mean time since diagnosis was 130 months (range 60–360). All patients were still treated at the Dep.E.O. The majority of patients (77/119) had ongoing treatment (interferon, octreotid, chemotherapy, radiotherapy, omeprazol). Both the EORTC QLQ-C30 and the FACT-G ratings suggest that the patients perceive their HRQOL as relatively good. In addition, the ratings of satisfaction with selected HRQOL aspects indicate that quality of life was perceived as satisfactory. There were no major differences in the HRQOL ratings between patients with carcinoid tumours and patients with EPT. Patients who rated that a specific aspect was of a higher importance than their satisfaction with that aspect also rated a low HRQOL on the EORTC QLQ-C30 and/or FACT-G for that aspect.

Conclusion: In spite of a long disease duration and treatment, patients with endocrine GI tumours enjoy a good HRQOL as measured by the EORTC QLQ-C30 and FACT-G. The results suggests that discrepancies in the importance-satisfaction ratings of HRQOL aspects are valid indicators