1256 POSTER

Surgical therapy of the squamous cell carcinoma of the thoracal esophagus

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Purpose: These carcinomas mostly are detected in an advanced disease. Thus there is a poor prognosis in survival for the patients.

Methods: Between 1986 and 1995 we treated 512 consecutive patients (450 men (88%) median age 59 years) with squamous cell carcinoma of the thoracal esophagus (upper:middle:lower third Δ 81 (15%): 167 (32.6%): 147 (28.7%) patients, other Δ 117 (22.9%) patients).

Results: 106 patients (20.7%) were resected curatively (R0 resection), 23 (4.5%) patients underwent noncurative resection and 383 patients (74.8%) had palliative therapy. At the time of the initial diagnosis in 48 patients (45.3%) of the 106 R0 resected regionary lymph node metastases were evident (the border lymph node in 16 patients (15.1%)). The category pT0/T1 was shown in 32 patients (30.2%), pT2 in 16 patients (15.1%) and pT3 in 52 patients (49.1%).

The overall 5-year-survival rate was the best for the lower third, followed by the middle and the upper third: 18 ± 10% vs. 12 ± 6% vs. 10 ± 8%. This one for the nonresected differed with 3 ± 3% significantly. It also differed significantly from this one of the R0 resected patients, who survived in 28 ± 8%. Within the group last named there still is a significant difference according to the pT category: pT1 Δ 68 ± 19 years, pT2 Δ 29 ± 35 years and pT3 Δ 24 ± 15 years.

Conclusion: The sole therapeutic option for an acceptable survival is R0 resection of the tumor in the category pT0/T1. Thus the main problem seems to be the early detection of this kind of cancer. Another important approach might be the (neo)adjuvant therapies, but our absolute number of patients treated in this way still is too small for a final assessment.

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Continuous 120 hours-infusion of mitomycin C (MMC) as salvage treatment in progressive or rapidly recurrent gastric cancer

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Purpose: To evaluate the safety and therapeutic activity of continuously infused MMC in metastatic gastric cancer patients with disease recurrence or progression following first-line chemotherapy (ctx).

Patients and Methods: Pts were treated with MMC 20 mg/m² i.v. over a time period of 120 h followed by a 3-weeks rest under prophylacticlly applied prednisone 50 mg p.o. for 5d. 13 pts were enrolled and all were assessable for toxicity and 11 for response (2 pts evaluable but not measurable). Pts characteristics: Median age: 53 years (32–68); Sex (m/f): 10/3; Karnofsky status: 65% (50–90); Previous ctx: Bolus 5-FU/FA n = 5 (38%), ELF n = 4 (31%), EAP n = 3 (23%), c.i. 5-FU/FA/DDP n = 1 (8%); Resection of primary tumor n = 5 (38%); Site of metastases: hepar n = 12 (92%), locally advanced n = 7 (54%), peritoneum n = 7 (54%), pulmo n = 4 (31%), bone n = 1 (8%).

Results: In 11 evaluable pts 1 CR and 4 PRs were observed (ORR: 45% [$CI_{95\%}$: 15.4–75.4%). The median response duration was 3.5 mon (2–6), the median survival 4.8 mon (2.7–8.6). Median number of treatment cycles was 2 (1–6). WHO °III/IV mucositis, diarrhea and fever/infection occurred each in 1 pts. Cumulative thrombo- and leukocytopenia (WHO °III/IV) were observed in 3 and 1 pts and treatment had to be stopped early in 1 case. No severe renal dysfunction, pulmonary toxicity or evidence of hemolytic uremic syndrome was observed. Fatigue during the 120 h-infusion of MMC was common (5/13 pts).

Conclusion: The incidence of severe and cumulative thrombocytopenia was 15% in 13 pretreated pts receiving 120 h c.i. of MMC as salvage ctx. Other side-effects were rare. No renal side effects or hemolytic uremic syndrome occurred Based on a small number of pts c.i. infusion of MMC has favourable single-agent activity in advanced gastric cancer progressing during or shortly after 5-FU- (ELF, 5-FU/FA) or anthracycline-(EAP) based ctx.

1258 POSTER

Liver resection and liver transplantation for primary hepatocellular carcinoma

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Purpose: In case of still circumscribed hepatocellular carcinomas (HCC), the sole curative therapeutic option providing a reliable prolongation of live, is surgical removal. We compared different surgical approaches.

Methods: Between 1980 and 1994 we treated 181 consecutive patients with HCC, 93 patients between 1980 and 1989 (first group), and 88 patients between 1990 and 1994 (second group). There were 34 (19%) women and 147 (81%) men ranging in age from 22 to 81 years (median: 61 years). The median follow up time was 75 months.

Results: The resection rate for the first group was 37% (34/93) and for the second group 59% (52/88) (p = 0.02) whereas the postoperative mortality was reduced from 35% to 19% (n.s.). Two of 13 (13%) patients of the second group died after liver transplantation. The 5-year-survival rate of the total 181 patients (without postoperative mortality) for the second group (n = 77) was significantly better than for the first one (n = 78) (32 ± 31% versus 12 ± 7%).

This result was significantly influenced by the kind of therapy and the possibility for curative resection. For the curative resected a significant correlation was shown for pT classification, pathological stage and grade of malignancy. A cirrhotic liver and multiple tumours in one lobe were of no significant influence.

Conclusion: The results after liver resection or liver transplantation for HCC nearly approach the survival rates for other gastrointestinal carcinomas. Thus, only if curative treatment is not possible because of concomitant factors, palliative therapies may be employed.

1259 POSTER

A phase II study of chronomodulated (CHR) 5-fluorouracil (5-FU) and leucovorin (LV) in combination with epirubicin (EPIDX) and Cis-Platin (CDDP) in the treatment of metastatic gastric carcinoma (MGC)

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PELF is an active regimen in MGC although is associated with moderate to severe toxicities. Some studies have demonstrated that a circadian infusion pattern of 5-FU and LV can improve antitumor activity while reducing toxicity. In preclinical studies we have demonstrated that the administration of CDDP after 5-FU improves the synergism of the two drugs. Based on these studies we have treated 23 patients affected by MGC with a modified schedule of PELF. Patients characteristics were as follows: M/F: 19/4, median age 60 years (range 34–71), single metastatic sites in 16 pts and multiple in 7. The initial treatment was Epidx 75 mg/m² day 1 i.v. bolus, Cis-Platin 75 mg/mq day 8 i.v. bolus and 5-Fu 200 mg/m²/day +LV 5 mg/m²/day as a i.v. continuous CHR infusion (g.1- > 14), with 68% of 5-FU and LV dose administered between 4 pm and midnight. Cycles were repeated every 28 days. After the initial 10 pts 5-FU dose was reduced to 150 mg/mq/day, Epidx and CDDP dose to 60 mg/mq because of severe mucositis in 40% of pts and 2 toxic deaths (both because of grade 4 mucositis and sepsis). Total cycles administered were 69 (range 1–6) and all the patients are evaluable for toxicity. In the initial schedule (10 pts) toxicity gr. 3–4 was the following: stomatitis in 4 pts (40%), diarrhoea in 2 pts (20%), vomiting in 1 pts (10%), leucopenia in 3 pts (30%) and thrombocitopenia in 1 pts (10%). In the reduced schedule (13 pts) the only grade 3–4 toxicity observed was stomatitis in 2 pts (15%). 13/23 pts are evaluable for response: 5 CR, 2 PR, 1 MR and 5 PD were observed (RR 53% and 95% confidence limit interval 25–91). Median time to progression was 4.5 months. Although the study is ongoing, preliminary results seem to support that CHR PELF we used has elevated activity in MGC and the reduced schedule is well tolerated.

1260 POSTER

Surgical therapy of gastric carcinoma in the elderly

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Purpose: Due to increased life expectancy, the number of elderly patients suffering from gastric carcinoma is continuously rising. We analysed our

series of resectable gastric carcinoma (n = 616, April 1986–July 1995) to look for the results of surgical therapy in elderly patients.

Methods: One hundred twenty six patients older than 75 years (20.5% male, n = 69, female n = 57, mean age 77.8 ± 3.5 years) were operated. All patient data were retrospectively studied with special regard to perioperative morbidity, mortality and survival (Kaplan-Meier, log-rank-test, $p < 0.05$).

Results: The majority of patients had at least two risk factors (69.8%, n = 88) in particular cardiovascular and lung disease. 26 patients had no risk-factors. Of all resections, 62.7% (n = 88) were classified as curative resection (R0). Postoperative morbidity and mortality rates were 26.2% and 4.1% respectively. Median survival after resection was 45 ± 4.4 months with statistically significant differences ($p < 0.05$) for R-classification and tumor stage.

Conclusion: Due to improved perioperative management, resection of gastric carcinoma in elderly patients is the treatment of choice. Although these patients often have age-related cardiovascular and pulmonary risk factors, postoperative morbidity and mortality even after extensive resection is low. Survival rates are comparable to younger patients and the prognosis is best after R0 resection, which therefore should be the goal of surgery for gastric carcinoma in elderly patients.

1261 POSTER

Double biochemical modulation of cisplatin, leucovorin and 5-fluorouracil in advanced gastric cancer

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Purpose: This phase II study was designed to evaluate the activity, safety and tolerability of weekly cisplatin (CDDP), leucovorin (Lv) and 5-fluorouracil (5-FU) in patients (pts) with advanced gastric cancer (AGC).

Methods: Between 9/93 and 8/96 28 patients (pts) with AGC were treated with CDDP 33 mg/m^2 as a 1-hour infusion, Lv 300 mg/m^2 in bolus and 5-FU 500 mg/m^2 in bolus, days 1.8 and 15 every 28 days, in an outpatient clinic. All but one had measurable disease by CT scan. Median age was 58 years (range 44–79). Nine were female and 19 male. Six pts were performance status (PS) 0, 18 pts PS 1 and 4 pts PS 2. Thirteen pts had primary metastatic disease. 17 pts had liver metastasis. All were evaluable by WHO criteria for toxicity and 24 for response (4 pts died of intercurrent disease). A median of 4 cycles were given (−9).

Results: Intent to treat analysis (N:28): Three pts (11%) had CR, 12 (43%) had PR, for an overall response rate of 54% (95% CI: 36%–72%), and 5 (18%) pts had stable disease. Median survival was 45 weeks for all the group (range 2–170+). Severe toxicity included neutropenia grade 3 in 8 pts and grade 4 in 2 pts, thrombocytopenia grade 3 in one and diarrhea grade 3 in 2 patients. Minor toxicity was grade 1 neuropathy in 11 and grade 2 in 2; grade 2 stomatitis in 2; grade 2 diarrhea in 5; grade 1 asthenia in 3; grade 2 nausea and vomiting in 12. Eight pts required blood transfusion.

Conclusion: This outpatient regimen has showed remarkable responses with excellent tolerability in AGC, survival ranks equally with more toxic regimens.

1262 POSTER

Treatment of hiliar cholangiocarcinoma (Klatskin's tumour). Our experience

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Between 3/89 until 1/97, 50 patients (pts) (30 males and 20 females) with hiliar cholangiocarcinoma (HCC) have been treated in our Hospital. In 33 pts (66%) the treatment were a palliative cutaneus transhepatic biliary drainage tube (group 1). In 17 pts (34%), radical surgical resection were performed (group 2): 7, all of them with Bismuth IV, liver transplantation (LT) and the rest, biliary resection +/− partial hepatectomy. Combined chemotherapy (5Fluorouracil+ Mytomicin C) and radiotherapy was performed in 13 pts: 2 of group 1 and 11 of group 2 after surgical resection.

Results: Secondary complications to the treatment were: Group 1: 21 pts (64%) (15 cholangitis, 4 septic shock, 4 biliary blockage, 4 gastrointestinal hemorrhage, 4 pancreatitis). Group 2: 12 (70%) (4 abdominal abscess, 3 biliary fistulae, 2 septic shock, 3 others) without postoperative mortality. Median survival was: Group 1, 5 +/− 5 months (range 0–15); group 2, 17 +/− 14 months (range 0–51) ($p \approx 0.015$). Patients with LT had a median survival of 27 +/− 12 m (range 18–51) whereas pts with biliary resection 11 +/− 11 m (range 0–33) (non statistically significance).

Conclusions: Surgical resection is the treatment of choice for HCC, with a significance increase of survival without a high morbimortality. Although the number of pts is low, LT is an effective new approach to the treatment of Bismuth IV HCC.

1263 POSTER

Proposal for an international multi center study: E-cadherin mutationspecific antibody to detect exon deletion in diffuse type gastric cancer

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Background: E-cadherin, a membrane bound homophilic adhesion molecule, was shown to be mutated in diffuse type gastric cancer. Due to splice site mutations, Exon 8- and Exon 9-deletions were detected in 39% of the patients using RT-PCR and direct sequencing of the E-cadherin gene in malignant tissue. Monoclonal antibodies were subsequently generated against the fusion site of exon 8 and exon 10, that recognize only cells with exon 9 deleted E-cadherin, whereas wildtype E-cadherin is not recognized. On this basis a mutationspecific detection of malignant cells is possible. Due to the location of the mutated protein (transmembrane protein with presentation of the mutated part extra cellular) it might be a target for antibody based therapy. Additionally there are possibilities to prime the immune system to mutated protein by peptide vaccination.

Aim: Due to the small number of patients carrying the mutation we propose an international multi center study to evaluate:

1. Epidemiology of E-cadherin exon 9 deletion in high risk countries for gastric carcinoma 2. Prognostic impact of E-cadherin exon 9-deletions and possible correlation to clinical data 3. Planning of future trials concerning a) toxicological background of the underlying reason for the mutation and b) therapeutic approach using monoclonal antibodies, immunotoxins and peptide based vaccination.

1264 POSTER

Phase II study with 5-fluorouracil and Ginkgo Biloba extract in patients with pancreas CA

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Purpose: To evaluate the efficacy, tolerability and quality of life (QL) of 5-FU combined with Ginkgo Biloba extrakt (GBE 761 ONC).

Methods: 46 pts with pancreas ca were treated in a prospective phase II study. The treatment (day 1–6) was repeated every 3 weeks until PD. Response to therapy was evaluated after 2 and 4 treatment courses.

Results: At present 46 pts were included, 25 pts were evaluable for response up to now. All pts were assessed for tolerability and QL. We observed a complete response (CR) in 1 patient, a partial response (PR) in 1 patient, an no change (NC) in 12 patients and a progressive disease (PD) in 11 patients. 7 patients are still on study. 5-FU + GBE was well tolerated. The toxicity consisted mainly of myelosuppression and gastrointestinal symptoms judged as 5-FU related.

Conclusions: The combination 5-FU and GBE is well tolerated, the objective response rate is in the range already known from 5-FU alone therapy. Overall survival data presentation are in progress.

1265 POSTER

Teniposide, mitomicin C and cisplatin combination in treatment of advanced gastric cancer

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A pilot study was performed to assess the efficacy and toxicity of the combination – teniposide (Vm-26), mitomycin C (MMC) and cisplatin (DDP) in patients with advanced gastric cancer.

Patients and Methods: Twenty-four patients (Sex: M-14, F-10. Mean age 50.1.) with measurable advanced gastric cancer received MMC 5 mg/m2 i.v. 1 and 7 ds.; DDP 40 mg/m2 i.v. 2 and 8 ds.; Vm-26 60 mg/m2 i.v. 4, 5, 6 ds.. Interval 28 ds.. A mean number of cycles were four.

Results: 21 pts. are evaluated for response and toxicity. The overall response rate was 42.7% (CR-5/21 (14.2%); PR 6/21 (28.5%)). 6 out of