

and 88% for FA. Overall response on 68 evaluable pts: 7 CR (10%), 19 PR (28%), 15 MR (22%), 16 SD (24%) and 11 PD (16%) have been reported. Median time to progression: 6.6 months and median duration of response: 11.1 months. The combination is well tolerated with G 3/4 diarrhea (pt/cy) of 15%/1% and G 3/4 neutropenia (pt/cy) 68%/20%. Febrile neutropenia was reported in 2 pts and G3/4 infection with neutropenia in 7 pts. Only 5% of the cycles were administered with a reduced dose. This combination appears to be very promising with a good benefit risk/ratio. A phase III is ongoing to compare this regimen to the reference CPT-11 combined with 5FU/FA de Gramont schedule.

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POSTER

CPT-11 and 5 fluorouracil/folinic acid (5-FU/FA) mayo clinic regimen in advanced colorectal cancer (CRC) as front line therapy: a phase III study

T. Kuehr¹, P. Ruff², B. Rapoport³, C. Jacob⁴, N. Davidson⁵, F. Daniel⁶, S. Falk⁷, B. Boussard⁸, D. Oulid-Aissa⁹, J. Carmichael⁹. ¹University Clinic for Internal Medicine, Innsbruck, Austria; ²University of Witwatersrand, Johannesburg, South Africa; ³Rosebank Oncology Centre, Johannesburg, South Africa; ⁴East Cape Oncology centre, Port Elizabeth, South Africa; ⁵Broomfield hospital, Chelmsford, UK; ⁶Derriford Hospital - Plymouth, UK; ⁷Bristol Oncology Centre - Bristol, UK; ⁸Aventis Pharma - Antony, France; ⁹City Hospital - Nottingham, UK

CPT-11 combined with 5-FU either infusional or bolus is the new reference regimen in front line treatment of CRC. Mayo clinic bolus (b) regimen is also widely used in this setting. The combination of CPT-11 combined with Mayo clinic regimen has been assessed in a phase I/II. CPT-11 was administered as 30-90 min IV infusion, day 1 immediately followed by FA 20mg/m² 15 minutes followed by 5-FU at a fixed dose of 425mg/m² IV, 15 min, from day 1 to day 5 every 4 weeks. Two dose of CPT-11 were tested in phase I: level 1: 250 mg/m², level 2: 300 mg/m². Major inclusion criteria: measurable lesion, no previous chemotherapy for advanced disease, WHO performance status less or equal to 2. Twenty-three patients have been treated in phase I, 14 males/9 females. Median age is 58 (30-69), median organ involved 2 (1-4). 43 cycles (cy) and 63 cy were administered at level 1 (10 patients, pts) and 2 (13 pts) respectively. RDI of CPT11/5-FU/FA was 94.0% for each compound and for both levels. At first cycle, dose limiting toxicities at level 2 were: diarrhea grade 4 (4 pts). Overall, main grade 3-4 toxicities were diarrhea (4pt/5cy) at level 1 and 6pt/9cy at level 2, neutropenia (5pt/6cy) at level 1 and (7pt/15cy) at level 2. Three partial responses were observed at each dose level. The recommended dose was defined as CPT-11 250 mg/m². Efficacy is promising and safety is manageable. The combination was assessed in phase II: 50 patients have been treated at RD. Preliminary results will be presented at the meeting.

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POSTER

Radiotherapy of inoperable recurrent rectal carcinoma

L. Radosevic-Jelic, M. Durbaba, D. Scepanovic, S. Stojanovic, S. Isakovic. Institute for Oncology and Radiology of Serbia, Radiotherapy, Belgrade, Yugoslavia

Purpose: Radiotherapy (RT) is the treatment of choice for inoperable locoregional recurrent rectal carcinoma (ILRCR). The aim of this work was to present that radical doses of RT as well as different RT techniques influence overall response rate (ORR) and overall survival (OS) in this group of patients (pts).

Methods: From 1995 till 2000, at the Institute of Oncology and Radiology of Serbia, Belgrade, 60 pts had been treated for ILRCR, median age 60 years (37-76), male:female ratio 1:1.4. There were 26 pts with Dukes B stage, 30 pts with Dukes C stage while 4 pts had unknown primary stage. Abdominoperineal resection was the most common initial therapy (in 65% of pts) with median disease free survival (DFS) of 24 months (12-60). The sites of recurrent disease were: presacral (21 pts), presacral and vaginal (18 pts), presacral and perineal (11 pts), vaginal (7 pts), at anastomosis (2 pts) and 1 perineal. Each pt was treated with radical RT doses. External beam RT (EBRT) was solely applied in 35 pts, 3 and 4 fields technique and doses of 50-62 Gy. Combined EBRT and brachytherapy (BHTh) was applied in 25 pts. EBRT doses were 30-65Gy and BHTh doses 12-40Gy. Acute skin RT complications were notified in 29 pts (48%) of GI and GII.

Results: The ORR was registered in 40/60 pts (66%) (CR-33%, PR-33%) and was estimated 2 months following RT. The median follow-up time was 19 months (8-60) and 27 pts (46%) had disease free, 7 pts (12%) residual disease, 4 pts stable disease, 15 pts local progression (25%), 6 pts distant progression and 1 pt was lost. There was 38 pts (63%) alive and 22 pts had

died (37%). In the group of complete responders (20 pts), 3 yrs DFS was 63,92% and 3 yrs OS 84,85%. Among treated pts (60) there was 3 yrs DFS of 41,14% and 3 yrs OS of 55,11%.

Conclusion: The radical doses of RT improved the local control and OS. We find that there was not statistically significant difference between different RT techniques (EBRT and EBRT+BHTh) regarding DFS and OS.

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POSTER

Serum levels and tumor expression of HER-2 in colorectal cancer (CRC) - a prospective analysis

M. Behnecke¹, A. Fruehauf¹, H.J. Holzhausen², A. Grothey¹. ¹University of Halle, Hematology/Oncology, Halle, Germany; ²University of Halle, Pathology, Halle, Germany

Rationale: The oncogene HER-2 is overexpressed in 20-25% of breast and ovarian cancers and is the target for novel therapeutic strategies with monoclonal antibodies or small molecules. Reports on the expression levels of HER-2 in CRC have been inconsistent, potentially due to differing methods of detection. Recently, soluble HER-2 has been characterized in the serum of patients with various carcinomas, however the correlation between tumor expression of HER-2 and respective HER-2 serum levels is still unknown. Therefore, we prospectively analyzed sera and tumor samples of patients with metastatic CRC for the expression of HER-2 using standard ELISA and immunohistochemistry (IHC) techniques and tried to correlate it with the clinical course of the disease.

Patients and Methods: Serum levels of HER-2 were determined in 88 pts (52 m, 36 f) with metastatic CRC and 20 healthy controls using a commercially available ELISA system (Dako). In 46 pts, tumor expression of HER-2 was analyzed by IHC (Hercept-Test*, Dako). Routine lab parameters and tumor markers CEA and CA19-9 were recorded in all patients.

Results: HER-2 serum levels were significantly higher in pts with CRC compared with the control group (mean 2511 vs. 2184 U/ml; p=0.038). 21 of 88 pts (23.9%) showed elevated serum levels (>3000 U/ml), but in only 6 of 46 pts (13%) weak expression of HER-2 could be detected in tumor samples (2x 1+, 4x 2+, 0x 3+ Dako-score). However, a positive correlation could be found between serum levels and tissue expression of HER-2 (p=0.035). HER-2 serum levels were further significantly correlated with CEA (p=0.031), bilirubin (0.04) and with ongoing anti-tumor therapy (p=0.0083), but not with CA19-9, CRP, LDH, creatinine, hematological parameters (Hb, leukocytes, platelets) and age. Patients with liver metastases were more likely to demonstrate elevated serum levels of HER-2 (p=0.0033), but did not show HER-2 overexpression in the respective primary tumors. In preliminary analysis, HER-2 serum levels did not correlate with overall survival.

Conclusions: Very few colorectal cancers overexpress HER-2 when assessed by standard IHC. Therefore, molecular approaches targeting this oncogene in CRC are not necessarily warranted. The pathophysiological role of elevated levels of soluble HER-2 in the serum of a substantial number of patients with CRC has yet to be determined. Supported by a research grant from Hoffmann-La Roche.

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POSTER

Preoperative 5FU and mitomycin-c with concomitant radiotherapy for locally advanced rectal cancer

M.C. Liu¹, S.Y. Leu², S.H. Cheng³, W.J. Fang¹, S.Y. Tsai¹, J.J. Jian³, J.M. Cheng³, M.H. Tsou³, A.T. Huang¹. ¹SYSCC, medical oncology, Taipei, Taiwan; ²SYSCC, colorectal surgery, Taipei, Taiwan; ³SYSCC, radiation oncology, Taipei, Taiwan; ⁴SYSCC, pathology, Taipei, Taiwan

Purpose: Investigate the effectiveness and toxicity of pre-operative chemoradiation for adenocarcinoma of the rectum.

Methods: Eight-six patients were assessed. Pre-Operative pelvic radiotherapy was delivered in three or four fields. 50~50.4Gy in 25~28 fractions over 5 weeks. Concurrent chemotherapy with mitomycin C at 10 mg/m² on day 1 and continuous infusion of 5-fluorouracil (5-FU) at 1000mg/m²/day on days 1~4 and days 29~33 was delivered to the patient during radiotherapy. Total mesorectal excision of the rectal tumor either by anterior or abdomino-perineal resection was planned at 6~8 weeks from completion of pre-operative radiotherapy. Response to therapy was assessed by microscopic measurement of the surgical specimen.

Results: All 86 patients undergoing chemotherapy and radiotherapy completed therapies as planned, with no treatment-related interruptions. Nine patients refused to have surgery. Grade 3 or more diarrhea was observed in 36(42%) patients, leukopenia 17(20%), and infection 4(5%) patients. Anal preservation rate in patients whose tumor located within 5 cm to anal verge was 86%. Complete pathologic remission was observed in

11(13%) patients and more than 90% necrosis was observed in additional 14 patients (18%). After a median follow-up of 36 months, survival and overall survival rates of the resected patients were 95%, 69% and 86% respectively.

Conclusion: The pre-operative chemo radiation regimen employed had a tolerable acute toxicity profile. It is a reasonable option in patients who have locally advanced or lower 1/3 rectal cancer and with low locoregional recurrence.

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POSTER

COX-2 expression in rectal cancer: immunohistochemical pattern and prognostic value

S. Petersen¹, G. Haroske², G. Hellmich¹, C. Petersen³, W. Eicheler³, M. Baumann³, K. Ludwig¹. ¹General Hospital Dresden-Friedrichstadt, Dpt. of General & Abdominal Surgery, Dresden, Germany; ²General Hospital Dresden-Friedrichstadt, Dpt. of Pathology, Dresden, Germany; ³Medical Faculty Carl Gustav Carus, Dpt. of Radiation Oncology, Dresden, Germany

Purpose: It is controversial whether COX-2 expression is a prognostic factor for rectal cancer with respect to other established prognostic parameters for local recurrence and/or survival in this disease.

Methods: To evaluate the impact of COX-2 on outcome of rectal cancer we reviewed data of 62 patients with adenocarcinoma of the rectum treated between 1995 and 1996, all patients in stage I-III were resected curatively. The samples were stained for COX-2 expression using a polyclonal antibody for human COX-2. According to the intensity and extend of positive reaction of tumor cells the labeling index of stained cells was calculated.

Results: The median labeling index was 0.58. The chi-square-test revealed no correlation between COX-2 and the established prognostic factors. In the univariate analysis COX-2 overexpression did not show a significance according to the endpoints local recurrence ($p=0.41$) or disease specific survival ($p=0.28$). In contrast COX-2 was a significant prognostic factor for pulmonary metastasis ($p=0.04$).

Conclusion: The majority of specimens showed a mild or moderate immunoreactivity for COX-2 but there is a lack of significance for COX-2 expression as a prognostic factor for local control and survival. However, there is evidence that COX-2 overexpression might be linked to an increased risk for hematogenous metastatic spread.

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POSTER

Irinotecan (CPT-11) plus oxaliplatin (LOHP) plus infusional 5-fluorouracil (5-FU) and leukovorin (LV) as first line treatment for metastatic colorectal cancer (MCC): A phase II trial

J. Souglakos, S. Kakolyris, A. Athanasiadis, Ch. Kouroussis, D. Mavroudis, N. Xenidis, A. Pallis, H. Adamtziki, V. Georgoulas. Hellenic Organisation for Cancer Research (HOCCR), Department of Medical Oncology, University General Hospital of Heraklion, Crete, Greece

Background: A phase II study was conducted in order to evaluate the toxicity and efficacy of the combination of CPT-11 plus LOHP plus infusional 5-FU/LV in MCC.

Patients and Methods: Thirty-five chemotherapy-naïve patients were enrolled. The median age was 60 y; male/female: 21/14; PS (WHO) 0/1/2: 16/14/5; prior surgery 24 pts; adjuvant chemotherapy: 18 pts; adjuvant RT: 3 pts; Number of metastatic sites 1/2/≥3: 13/12/10. CPT-11 was administered on d₁ at the dose of 150 mg/m² over a 90 min infusion, LOHP on d₂ at the dose of 65 mg/m² over a 2 h infusion, simultaneously but in different lines with LV (200 mg/m² on days 2 and 3) followed by 5-FU administration as bolus iv infusion at dose of 400 mg/m²/d and as 22 h continuous infusion at the dose of 600 mg/m²/d on days 2 and 3. The regimen was repeated every 2 weeks.

Results: All patients were evaluable for toxicity and 28 (5 too early, 2 not evaluable) for response. CR was achieved in 2 pts (7.1%) and PR in 14 pts (50%) (ORR: 57.10%; 95 ci: 39.12%–82.64%); 9 pts (32.1%) had SD and 3 (10.7%) PD. The median duration of response was 4.5 m; the median TTP and OS have not yet been reached; after a median follow up period of 11 months. Grade 3 and 4 neutropenia occurred in 12 pts (34.29%), febrile neutropenia in 2 pts (5.7%), anemia grade 2 in 5 pts (19%), while thrombocytopenia didn't exceed grade 1. Diarrhea grade 3/4 was observed in 10 pts (28.5%), neurotoxicity grade 3/4 in 3 pts (8.5%), asthenia grade 3 in 2 pts (8.5%). No treatment related death occurred.

Conclusions: The combination of 5-FU/LV + CPT-11 + LOHP is an active and well-tolerated regimen as front-line treatment in MCC and merits further evaluation in prospective randomized trials.

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POSTER

Joint United States of America (USA)/Japan study of UFT (uracil and tegafur) plus leucovorin (LV) in patients (pts) with metastatic colorectal cancer (CRC)

P.M. Hoff¹, P. Loehrer², J.L. Abbruzzese¹, A. Ohtsu³, I. Hyodo⁴, K. Shirao⁵. ¹The University of Texas M. D. Anderson Cancer Center, Gastrointestinal Medical Oncology, Houston, USA; ²Indiana University Cancer Center, Indianapolis, USA; ³National Cancer Center Hospital East, Kashiwa, Japan; ⁴National Shikoku Cancer Center, Matsuyama, Japan; ⁵National Cancer Center Hospital, Tokyo, Japan

Introduction: UFT is a 5-FU prodrug developed as a single agent against various solid tumors in Japan. Based on the extensive use of LV with 5-FU in the West, UFT was combined with LV for the treatment of CRC in the USA and European countries. Two large phase III study demonstrated equivalency between intravenous 5-FU/LV and UFT/LV among Western patients with CRC (Pazdur R., and Carmichael J., ASCO 1999). Although different doses and schedules of UFT in CRC have been tried in Japan, there is no study with the combination of UFT plus leucovorin in that Country.

Methods: To evaluate the applicability of the results of the large Western trials to the Japanese population we decided to compare the response rates, the PK, and the type, frequency, and severity of side effects in American and Japanese pts with metastatic CRC.

Results: A total of 99 pts (45 in USA; 44 in Japan) has been enrolled; all are evaluable for toxicity and 98 pts are evaluable for response. Both groups were well matched for gender, age, performance, and prior adjuvant treatment. As of now, results show a comparable response rate of 36% and 34% in Japan and the USA, respectively. Diarrhea was the main toxicity in both groups and severe diarrhea was seen significantly less often among Japanese pts (9% versus 22% in the USA). Hematological toxicity was very mild and not significantly different in both groups. There were no other significant differences in toxicity. This indicates that UFT/LV is equally active in both ethnic groups but potentially more toxic among Western pts. Although AUC and Cmax of FT, 5-FU and Uracil were slight higher in Japanese pts than in the USA, when the results are adjusted for BSA, the parameters are similar.

Conclusion: The present study indicated that UFT/LV therapy is an equally efficient and reasonably well-tolerated treatment for American and Japanese pts with metastatic CRC. This data indicates that an extrapolation of clinical data from the West to the East is reasonable.

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POSTER

Serum concentration of soluble adhesion molecules and cytokines in patients with colorectal cancer

F. Guadagni¹, M. Roselli², F. Martini³, M.R. Abbolito¹, A. Spila¹, S. Mariotti², S. Basili³, P.P. Gazzaniga³, M. Cosimelli¹, P. Ferroni³. ¹Regina Elena Cancer Institute, Rome, Italy; ²University of Rome Tor Vergata, Rome, Italy; ³University of Rome La Sapienza, Rome, Italy

Purpose: Human colorectal cancer cells express sialyl Lewis (a)(CA 19-9), which acts as a ligand for E-selectin, an adhesion molecule involved in the binding of colorectal cancer cells to endothelial cells. Circulating levels of inflammatory cytokines have been associated with the disease status of cancer patients. Moreover, IL-6 has been associated with CA 19-9 levels in patients with colorectal cancer. Therefore, this study was aimed to verify whether tumor marker levels correlate with blood concentrations of cytokines and adhesion molecules involved in the haematogenous spread of colorectal cancer cells.

Methods: Serum tumor markers (CEA, CA 19-9, CA 72-4), cytokines (TNF-alpha, IL-6, IL-1beta) and soluble adhesion molecules (sP- and sE-selectins, sVCAM) levels were measured in serum samples from 76 patients with primary (Stages: A=6, B=34, C=19, D=2) or recurrent (local=3, distant=12) colorectal cancer.

Results: Median cytokine levels were higher in cancer patients (TNF: 13.8 pg/ml; IL-1: 0.5 pg/ml; IL-6: 2.4 pg/ml) compared to controls (TNF: 0.3 pg/ml; IL-1: 0.1 pg/ml; IL-6: 0.2 pg/ml) (all $p<0.001$). Moreover, mean (SD) sE-selectin and sVCAM levels were higher in cancer patients [sE-selectin: 56.2 (32.5) ng/ml; sVCAM: 985 (509) ng/ml] compared to controls [sE-selectin: 39.3 (14.8) ng/ml, $p<0.01$; sVCAM: 478 (239) ng/ml, $p<0.001$]. Plasma sP-selectin levels did not show any significant difference. IL-6 levels directly correlated with sE-selectin ($r=0.40$, $p<0.01$) and sVCAM ($r=0.48$, $p<0.002$), and sE-selectin directly correlated with sVCAM ($r=0.43$, $p<0.006$). Patients with sE-selectin >70 ng/ml [mean (2SD) of controls] also had higher levels of CA 19-9 ($p<0.0005$), CEA ($p<0.002$) or CA 72-4 ($p<0.02$). IL-6 and sE-selectin levels were higher in patients with metastasis (median IL-6=5.5 pg/ml; median sE-selectin=71.5 ng/ml) than