this disease and the combination with CPT 11 is therefore a priority. Adding these two non-cross-resistant drugs without overlaping toxicities was the rationale of this alternating schedule. **Treatment Schedule:** CPT11· 350 mg/m^2 iv, 90 mn (day 1) and 5 FU. 425 mg/m^2 iv 15 mn, immediately after FA 20 mg/m^2 iv push, daily times 5 (d22 to d26) every 6 weeks.

Population: Pts with metastatic CRC and bidimensionally measurable lesions, no prior CT or only adjuvant regimen ended more than 6 months before study entry. Age. 18–70 years, PS ≤ 2; adequate hematological, renal and hepatic functions Tumor assessment is performed every 2 single cycles.

Results: 33 pts have been treated· 18 men (55%), 15 women (45%), 17 colon (52%), 13 rectum (39%), 3 rectosigmoid (9%), 15 PS = 0 (45%), 18 PS = 1 (55%). Preliminary efficacy results (after at least 2 single cycles completed) reviewed by External Response Review Committee among 29 evaluable patients show: 9 PR, 4 MR, 13 SD and 3 PD. Out of 133 performed single cycles, 22 (16%) have been delayed (14 CPT11 cycles and 8 5 FU cycles) and 11 cycles (8.3%) have been performed with those reduced (8 CPT11 cycles and 3 5 FU cycles). **Toxicity:** (>WHO grade 2): preliminary results on 30 evaluable patients are neutropenia (6 pts – 20%), febrile neutropenia (4 pts – 13%), vomiting (2 pts – 70%), diarrhea (6 pts – 20%), mucositis (3 pts – 10%) and cholinergic syndrome (1 pt – 3.3%).

Conclusion: These preliminary results indicate that an alternating schedule of CPT11 and 5 FU/FA is feasible and that the antitumor activity is promising in metastatic CRC.

759 POSTER

Phase II study of 24 hours-infusion of 5-fluorouracil and high dose folinic acid in patients with progressive or recurrent colorectal cancer (CRC)

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Purpose: To evaluate the therapeutic activity of 24 h continuously infused 5-FU modulated by HD-folinic acid (FA) in pts with metastatic CRC who had recurred or progressed following bolus 5-FU based chemotherapy (CTX).

Patients and Methods: 42 pts, 27 men and 15 women with a median age of 59 years (45–76), were enrolled. Karnofsky status: 90% (80–100); previous CTX regimens. bolus 5-FU/FA acid n = 31 (74%), c.i. 5-FU ± IFN-α2 n = 9 (21%), other n = 2 (4%). Treatment schedule: 500 mg/m^2 FA given as 2-h infusion followed by a 24 h infusion of 2 6 g/m^2 5-FU once weekly × 6 (i.v.).

Results: All pts were assessable for toxicity and for response evaluation having completed at least 1 full course of ctx. No CR but 6 PR were observed [ORR, 14% ($CI_{95\%}$: 3.5–25.1%)]. The median response duration was 7.3 mon (1.4–10.6), median survival 11.6 mon [2–27 ($CI_{95\%}$: 9.4–13.8)] and the 1-year-survival rate 46%. SD/MR were achieved in another 25 pts (61%). Median treatment duration was 19 weeks (range, 6–48). WHO °III/IV diarrhea occurred in 26%, mucositis, nausea/vomiting and hand-foot-syndrome in 5% each of patients. No severe infection/fever or evidence of hematological toxicity was observed, except WHO °III anemia and leukocytopenia (each 5%). Dose reductions in 11 pts and subsequent stop of treatment in 2 pts had to be performed because of unacceptable diarrhea. PD while receiving previous ctx was associated with lower response rate (p = 0.02), shorter PFI (p = 0.02) and survival (p = 0.01) as compared to the subset of pts who achieved temporary SD.

Conclusion: C.i. infusion of 5-FU/FA displays activity in advanced CRC with toxicity being acceptable. Pts who had achieved at least SD during previous bolus 5-FU based CTX appear to benefit from second-line continuously infused 5-FU/FA. Questions remaining to be addressed in order to optimize the approach include (1) the optimal start dose of 5-FU (2) whether FA can be reduced or eliminated to achieve a better toxicity profile and lower costs.

760 POSTER

Quality of life (QL) is a prognostic factor (PF) for survival in patients with advanced colorectal cancer (CRC)

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Recent years have seen a discussion on which group of patients should be offered chemotherapy for advanced CRC regarding the limited efficacy and high costs of treatment and its' possible side effects on patients' QL. In a randomized phase III trial, 142 patients with advanced CRC were treated with 5-fluorouracil and either interferon α-2b or folinic acid. For the QL self-assessment before and during chemotherapy, a major end point of the study, patients used the validated EORTC QLQ-C30 questionnaire, which consists of 5 functional scales (physical state, ability to work, and cognitive, emotional and social state), 9 symptom scales (pain, nausea, vomiting, fatigue, dyspnea, loss of appetite, sleep disturbances, diarrhea, and constipation), and one global QL scale. Next to the above 15 QL scales we tested 20 covariates for their relevance as PF and survival. In univariate analysis, response to therapy, performance status (PS), appetite loss, physical, emotional, and role function as well as AP, SGOT, SGPT, and WBC had a significant impact on survival. However verifying the influence of these variables on survival in a multivariate setting reduced the number of significant prognostic factors to only three: a Karnofsky PS > 70% (p = 0.003), little or no loss of appetite (p = 0.003), and a WBC < 10.000 (p < 0.001). A classification including these three PF was able to distinguish between low-risk patients, who survived a median of 12 months, and high-risk patients, who had a median survival time of only 3 months. Therefore, this prognostic classification can facilitate the decision whether patients with advanced CRC should be considered for systemic chemotherapy

761 POSTER

Orthotopic transplantation of intact human colorectal and pancreatic tumor tissue in nude mice

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Purpose: A relevant model of human gastrointestinal cancer in nude mice will improve our understanding of carcinogenesis and cancer metastasis.

Methods: We have established an orthotopic transplantation model in nude mice with intact tissues of human colorectal and pancreatic cancers. The biological characteristics of the original and the corresponding transplanted tumors were investigated by HE staining, PAS staining and immunostaining.

Results: (1). There were totally 9 of 16 surgical specimens growing in nude mice subcutaneously and/or orthotopically (4/6 colon and 5/10 pancreatic cancer). Freezing of tissue specimens and tumor cell content of the specimens influenced the take rate of transplanted tumor. In the group of fresh tumor tissues with greater than 50% tumor cell content, the take rate was 100% (3/3 pancreatic and 3/3 colon). (2). The transplanted tumor closely resemble the original tumor morphologically and biologically, including TAA expression such as CEA by immunostaining, and CEA level in the serum of mice. (3). The detection of dissemination of cancer cells can be achieved by immunostaining. (4). Antigen expression of Ki-67, K-ras, 17-1A and RA-96 were associated with the potential of tumor growth in nude mice.

Conclusion: An orthotopic transplantation model and a sensitive detection method for human colon and pancreatic cancer in nude mice were established. This study will be helpful for monitoring therapeutic intervention strategies for micrometastatic disease.

762 POSTER

MRI and endoluminal ultrasound result in different staging in 5 out of 17 patients with anal cancer

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Purpose: In cancer of the analcanal endoluminal ultrasound (US) is the staging modality of choice. Treatment of choice is chemoradiotherapy. Accurate staging is extremely important as many clinicians treat patients with T1/2 tumors with a lower dose of RT and CT than in T3/4 tumors. Because there are no data available in the literature we investigated the role of MRI in the staging of analcanal cancer and compared it with endoluminal US.

Methods: 17 patients underwent both, MRI with a body coil and US. Tumor stage by US was the following: uT1 (<2 cm): 3; uT2 (2–5 cm): 9; uT3 (>5 cm): 3 and uT4: 2. Positive lymph nodes were seen in 4 patients.

Results: In 5 out of 17 patients (30%) a higher stage was seen using MRI. In three cases the stage was changed from T1/2 up to T3 and therefore

these patients were treated more aggressive. Moreover, suspicious lymph nodes only in MRI were seen in two additional patients.

Conclusions: Our results indicate that US possible understages anal-canal cancer in various cases. An important fact is that these differences could result in different treatment for selected patients. However, no pathological staging was done and it is possible, that MRI overestimates the tumor extension. As the treatment is curative, further studies are necessary for definite conclusions. in future using endorectal coils for MRI.

763 POSTER

Preoperative thermoradiotherapy in combined treatment of rectal cancer patients

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Purpose: To improve results of surgical method of treatment, using preoperative thermoradiotherapy in the combined treatment of patients with rectal cancer.

Methods: 202 patients, divided into 3 groups: 70 patients (group I) that received surgical treatment only, 68 (group II) that received preoperative radiotherapy only and 64 (group III) that received local UHF hyperthermia combined with preoperative radiotherapy were enrolled in the randomized prospective study. Preoperative gamma-therapy was performed using a single dose of 5Gr up to 25Gr of summed lesion dose, followed by an operation in 3 days. UHF hyperthermia was carried out during 3–5 days starting from the second day of radiotherapy.

Results: True reduction of cancer recurrences frequency from 23.3% (group I), to 13.4% (group II) and to 3.3% (group III) was observed. In group III decrease of distant metastases-4.3% was noted, compared with group II-9.2% and in group I-12 3%. As the result improvement of 5-year treatment outcome from 57.3% (group I), to 72.7% (group II) and 82.3% (group III) was achieved. The best results were obtained in cases of metastatatic involvement of regional lymph nodes in which 5-year results constituted 25.0% (group I), 48.6% (group II) and 86.7% (group III).

Conclusion: Local UHF hyperthermia combined with preoperative radiation is a strong radiomodifying agent of radiotherapy, increasing tumor sensitivity to ionizing radiation, thus improving distant results of the combined method of treatment.

764 POSTER

Thymidylate synthase (TS) and P53 as prognostic factors for patients (PTS) with colorectal cancer (CA) treated with adjuvant 5-fluorouracil (5FU) and levamisol (LEV)

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TS has been reported to be predictive in pts with advanced gastric and colorectal ca and prognostic in adjuvant treatment of rectal cancer. P53 expression can be regulated by TS protein. We evaluated the expression of TS and p53 by immunostaining in 175 paraffin-embedded samples of pts entered in the Dutch adjuvant trial comparing 5FU/lev with surgery alone. The male/female ratio was 94/81 pts; Dukes B/C ratio was 91/84; 127 of the pts had colon ca; 106 of the pts were >61 yrs; 150 pts had WHO performance status 0. TS was scored as 1+, 2+, 3+, p53 as + and −.

	TS1+	TS2+	TS3+	Total
p53−	19	37	24	80
p53+	35	33	27	95
Total	54	70	51	175

Median time for survival was too short, precluding evaluation according to DFS or OS. So far trend analysis showed a positive relationship between TS and p53 level. Subgroup immunostaining (79 pts) for Ki67, a proliferation marker, and bcl-2 showed that high proliferation was equally divided between all three TS groups and bcl-2 was positive in ±50% of the pts in all three TS groups. In conclusion; in combination, TS and p53 are probably useful markers for prediction of prognosis in colorectal cancer patients.

765 PUBLICATION

Preliminary study of GSH L-Cysteine Anthocyane (Recancostat Compositum™) in metastatic colorectal carcinoma with relative denutrition

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Reduced glutathione (GSH) is a sulphur-containing nucleophile natural metabolic molecule able to maintain cellular integrity and protect healthy cell against toxic and radicalic compounds at physiological doses. Administrated orally at high doses GSH associated with both L-Cysteine Glutathione precursor and Anthocyane (Recancostat Compositum™). The drug had been reported concerning a chemoprotection against tissue toxicity of cytotoxic agents and multidrug resistance. Also the drug may induced inhibition of tumor growth in vitro and tumor regression with recovered nutrition and weight in vivo (on rats). A clinical trial had conducted in 11 metastatic colorectal carcinoma chemoresistant patients with various denutrition phase and loss of weight. We report first clinical date of this study. Treatment consisted in oral administration of 800 mg GSH twice a day for a minimum of 90 days or until progression or toxicity (total dose: 144 g GSH, 28.8 g L-Cysteine, 23 g Anthocyane). No drug related toxicities were observed. 8 patients were evaluated (3 early deaded). All patients (8) are living (3 to 10 months) and the median duration of treatment was 21 weeks (11–33). 4 patients are recovered normal diet, high karnofsky and increased weight (3 patients were able to back home), 4 patients have negative response.

Conclusion: In addition of active therapeutic effect in cancer and chemoprotection, Recancostat Compositum™ maintains karnofsky, nutrition and weight of multi treated patients. Because no toxicity with Recancostat Compositum™ at high dose, we will select patients with cancer cachexia in second step of extended trial.

766 PUBLICATION

Colorectal liver metastases (CLM): Surgical or transcatheter treatment?

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Aim: To evaluate effectiveness of hepatic artery infusion (HAI), hepatic arterial chemoembolization (HACE), combined hepatic arterial and portal vein chemoembolization (HA&PVCE), and hepatic resection for liver CLM.

Methods: Our prospective study included 99 pts with Gennan's stage II and III of CLM. HAI with 5-FU was performed in 23 pts. HACE with 30–100 mg Doxorubicin-in-iodized oil plus gelatin sponge was carried out in 28 pts. Combined treatment in 23 pts included HACE and 10 to 15 days later PVCE. Every therapy was performed 2 to 4 times yearly. Curative hepatic resection was made in 25 remaining pts.

Results: Partial tumor response was seen in 2 (9%), 8 (29%), and 19 (83%) pts after HAI, HACE, HA&PVCE, respectively. Mean survival rates were 7.8 ± 3.3 mo for HAI, 20.5 ± 7.5 mo for HACE, and 22.9 ± 7.5 for HA&PVCE ($p < 0.001$ if compared with HAI and $p < 0.05$ with HACE). After hepatic resection, the survival was 22.6 ± 11.4 (NS in comparison with HA&PVCE).

Conclusion: In our series, both the HA&PVCE and hepatic resection were effective for CLM. However, there was no significant difference between these treatments in survival of pts.

767 PUBLICATION

Increased serum deoxycholic acid levels in acromegalic patients with colorectal neoplasia

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Acromegaly is associated with an increased prevalence of both colorectal carcinoma and tubulovillous adenomas. As the bile acid deoxycholic acid (DCA) has been implicated in the pathogenesis of non-acromegalic colorectal cancer, we measured its levels in acromegalic patients with and without colorectal adenomas.

Methods: Fasting serum DCA was measured, using gas chromatography mass spectrometry, in 10 acromegalic patients (6M; mean age 59 yrs, range 39–73) known to have colorectal adenoma and 29 acromegalic patients (15