754 POSTER

5-FU/FA IV BOLUS THERAPY VS WEEKLY HIGH-DOSE 5-FU/FA 24-HOUR INFUSION IN METASTATIC COLORECTAL CARCINOMA: PRELIMINARY RESULTS OF AN ONGOING RANDOMIZED PHASE III STUDY

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Since January 1993 we are conducting a randomized phase III study in pts with metastatic colorectal carcinoma comparing 5-FU (425 mg/m^2)/FA (20 mg/m^2) days 1–5 as iv bolus therapy given every 4 weeks (arm A) with weekly high-dose 5-FU (2600 mg/m^2) 24-hour infusion (arm B).

So far, 37 pts in each arm are evaluable for response and toxicity. Pts in both arms are comparable with regard to sex, age, performance status, localization of metastates and number of metastatic sites. Preliminary response rates are: PR 22% (A) and 27% (B), SD 32% (A) and 51% (B), PD 46% (A) and 22% (B). Probability of median survival is 12 (A) and 15 (B) months, respectively. Moderate mucositis, diarrhea and nausea are the most frequent toxicities in both arms. Hematotoxicity is absent in arm B, but about one third of the pts develop reversible hand foot syndrome.

Conclusion: Although no statistically significant differences between the two treatment arms are seen so far, we believe that these preliminary results justify the continuation of the study.

755 POSTER

RADIOIMMUNOTHERAPY OF METASTATIC COLON CANCER: PHASE I STUDY WITH ANTI-CEA F(AB)'$_2$ FRAGMENTS LABELED WITH ESCALATING DOSE OD IODINE 131

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Experimental studies demonstrated efficiency of F(ab)'$_2$ antibody fragments to CEA labeled with Iodine 131 (131-I-F(ab)'$_2$). A phase I study was designed to determine the maximum tolerated dose (MTD) of 131-I-F(ab)'$_2$. Ten patients with liver metastases (LM) from colorectal cancer were treated with 131-I-F(ab)'$_2$ ranging from 87 mCi to 300 mCi. No adverse event was observed during and just after infusion. The only toxicity was hematologic and no aplasia was observed up to 300 mCi infused. At this dose, the five patients presented grade 3 or 4 hematologic toxicity, the nadir for neutrophils and thrombocytes ranged from 25 to 35 days after infusion and bone marrow rescue was infused. In conclusion, this study demonstrated that MTD of 131-I-F(ab)'$_2$ is 300 mCi with bone marrow rescue.

756 POSTER

RECTAL BALLOON FOR CT OF RECTAL CANCER CLINICAL APPLICATIONS AND METHODS

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CT plays an important role for the pre-surgical evaluation of rectal cancer, both for staging versus RT and for planning the operation. Pelvic scans provide the surgeon with a complete, readable map of the anatomy. The aim of the study is to optimise the protocol for CT of rectal cancer.

The luminal distension of visceral wall has been obtained in a clean, well tolerable way by using a balloon catheter filled with water. The catheter is positioned in the rectum at the level of the neoplastic lesion. It consists of a 20 cm long latex balloon 6 cm in diameter, assembled over 12F double-way polyethylene catheter: one to inflate the balloon, the second for a guidewire, both for giving stiffness to the system, to advance it and to make the catheter radiopaque to evaluate the correct positioning by CT Fluoroscopy or Scout View. The balloon in gently injected with water, monitoring the degree of distension on minimal discomfort complained by the patient. Optimal distension is usually obtained by injecting 100–200 ml of water. The patient decubit is determined by the position of the lesion leaving it sloping.

The scans are performed by a General Electric Pro Speed. After the exam without contrast, 80 ml bolus of lopamidol 370 is injected in 60'.

CT with the rectal balloon allows a precise evaluation of a series of parameters important for the pre-surgical staging: the distance between anal sphincters and tumor, extension of the tumor and the invasion of perirectal fat and surrounding structures, lymphnodes metastases.

The execution of this exam is simple and clean. Rectal distension is well tolerated by patients, without complaints as when entire colon is involved. Avoiding the injection of contrast material in the colon, the CT doesn't interfere with other exams that can be executed on the same day.

The quality of images allows a high diagnostic accuracy.

757 PUBLICATION

ANALYSIS OF PROGNOSTIC FACTORS AFTER CURATIVE RESECTION OF RECTAL CARCINOMA

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The prognostic factors in 100 cases of rectal adenocarcinoma curatively treated at Ankara Oncology Hospital between 1986 and 1993 were retrospectively reviewed using multivariate analysis. Age, sex, symptoms of obstruction and perforation, duration of symptoms, hemoglobin and serum albumin levels, anatomic localization, diameter and macroscopic appearance of the tumor, the type of curative surgical procedures, radical pelvic lymph node dissection, perioperative whole blood transfusion, postoperative complications, adjuvant therapy, multiple colorectal tumors, lymphatic, venous and perineural invasion, grade, lymph node metastases and stage of the disease were used as prognostic parameters. According to Kaplan Meier method five-year survival rate was 62.2%. Cox regression analysis revealed that symptoms of obstruction and perforation, annular tumors, localization, grade, perineural invasion, perirectal lymph node metastases and perioperative transfusion were dominant prognostic factors in patients with rectal carcinoma.

758 PUBLICATION

THE VALUE OF CITOSTATIC CHEMOTHERAPY IN COLORECTAL CANCER

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Between 1980–1992, we studied 104 patients with advanced colorectal cancer (ACRC): 64 cases in Duke's C and 40 in Duke's D stage. There were 2 groups: (A) 42 inoperable cases reconverted for surgery after 3–4 neoadjuvant chemotherapy schedules (CTS); (B) 62 patients with radical or cytoreductive surgery followed by 6–10 adjuvant CTS every 21 days. CTS were: FU-Fol-C (florouracil 750 mg. + folinic acid 200 mg./day) × 4days + Cisplatinum 80 mg./m^2 and Fu-Fol-L. Fu-Fol + Lomustine 60–70 mg./m^2. Mild mucositis occurred in 2% of cases (nausea was prevented by Zofran). *Results:* (A) 90% overall response rate with surgical reconversion and 2 years free disease survival (fds.); (B) overall 61% partial remission lasting 2–12 months, 15% no change, 23% failures. Fu-Fol schedules in ACRC realise: the rise of fda., the possibility of safe less extensive surgery, the improvement of the quality of life.

759 PUBLICATION

A PHASE II STUDY OF CPT 11 (IRINOTECAN) IN REFRACTORY TO 5 FU COLORECTAL CANCER WITH CURATIVE TREATMENT OF DELAYED DIARRHEA BY ACETORPHAN

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Due to its secretory type, CPT 11-induced diarrhea might be controlled by loperamide (L) and Acetorphan (A) combination, two-drugs with complementary antisecretory mechanisms of action: inhibition of Ca^{++}/Calmodulins complex and inhibition of enkephalinase, respectively. Preliminary results as an ongoing pilot study aimed to determine the precise etiology of diarrhea, support this hypothesis.

In order to optimize the curative intent anti-diarrheal treatment, we performed an open label phase II randomized study comparing high dose Acetorphan versus combined Acerorphan + Loperamide: (A) 200 mg ×

3 per day versus (A) 100 mg × 3 + (L) 4 mg × 3 per day. Sixty-two patients with advanced colorectal cancer refractory to 5 FU received CPT 11 at the dose of 350 mg/m^2 every 3 weeks. Only 27 are so far evaluable. However is too early to draw any conclusion. Final result will be presented.

760 PUBLICATION

METHOTREXATE (MTX) AND 5-FLUOROURACIL (5-FU) IN ADVANCED COLORECTAL CANCER PATIENTS PREVIOUSLY TREATED WITH ADJUVANT 5-FU

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5-FU cytotoxicity may be increased through biochemical modulation with MTX. This can be important in patients who have already received 5-FU in the adjuvant setting. We have employed a combination regimen of MTX followed by 5-FU, with leucovorin (LV) rescue, in a series of patients with advanced disease. Pts were required to have symptomatic, measurable, inoperable lesions from colorectal cancer, recurring after adequate radical surgery of the primary tumor and adjuvant 5-FU + LV, concluded at least 3 months before recurrence. Pts received MTX, 250 mg/m^2 as a 2-hours i.v. infusion, followed by two doses of 5-FU, 500 mg/m^2 as i.v. bolus 1 hour and 21 hours after the end of methotrexate infusion. LV rescue, 15 mg orally every six hours for 7 times, was started 1 hour after the second 5-FU dose. The cycle was repeated every 2 weeks.

Results: Twenty-two pts entered the trial, and 21 were evaluable. An objective response was observed in one pt (4.8%), 7 pts (33.3%) obtained tumor regression < 50% or disease stabilization. Thirteen pts (61.9%) progressed. Median survival in the whole group was 11 months. Toxicity was mild.

Conclusions: biochemical modulation with MTX does not seem a satisfactory mean to increase 5-FU activity, when the patient has been previously exposed to 5-FU plus LV.

761 PUBLICATION

CURATIVE SURGERY IN METASTATIC OR RECURRENT COLON CANCER

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Twenty-eight pts with recurrent or metastatic colon cancer underwent radical resection of disease with curative intent. 16 were male and 12 female. The mean age was 65 years (median 68, 38–84). 4 pts had stage B1, 8 had B2, 2 had stage C1, 4 C2 and 10 had stage D at presentation according to Astler-Coller staging system. In 8 pts local recurrence was resected, in 15 surgery was performed for liver metastases (8 at diagnosis and 7 for recurrences), in 3 lung secondaries were resected and in 2 pts Krukenberg tumors of the ovaries were removed at first operation. The median time interval from diagnosis to surgery was 13 months (mean 16, 0–85). 11/28 pts (40%) are alive with no evidence of disease, 7–66 months from surgery (2 local recurrence, 6 liver metastases and 3 lung secondaries).

Conclusion: Curative radical resection in recurrent or metastatic colon carcinoma can produce long term disease free survival in a selective group of patients.

762 PUBLICATION

MORPHOLOGIC FEATURES AND ASSESSMENT OF CARCINOMAS RISK DEVELOPMENT IN PATIENTS WITH COLORECTAL ADENOMAS

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The clinical significance of colorectal polyps emerges from the adenoma-carcinoma sequence theory. This theory includes size-dependent risk of malignancy in adenomas and a failure to find minute, "de novo" carcinomas surrounded only by normal mucosa. The retrospective study was carried out on 141 colorectal adenomas diagnosed in 94 patients; male to female ratio 2.35:1. Polyps were obtained by endoscopic polypectomy performed during the total colonoscopy. Most adenomas were located in the sigmoid colon and the rectum, and the percentage decreased proximally to the right colon. Histological examination revealed that, among 141 adenomatous polyps, there were 122 (86.52%) tubular, 12 (8.51%) tubulovillous and 7 (4.96%) villous adenomas. The epithelial dysplasia was graded as mild in 57 (40.42%) adenomas, moderate in 44 (31.20%) and severe in 6 (4.25%). Invasive carcinoma was observed in 11 (7.80%), while 23 (16.31%) adenomas were without dysplasia. The percentage of severe dysplasia was greater in villous than in tubular adenomas ($P < 0.01$) and correlated with the increasing size of the adenomas ($P < 0.01$). There were no complications during endoscopic polypectomy. Follow-up over 6–24 months revealed no recurrences in any case.

763 PUBLICATION

CONTINUOUS LOW DOSE, ORAL DOXIFLURIDINE (DFURD, 5'-DEOXY-5-FLUOROURIDINE) FOR THE GENERATION OF NON-TOXIC 5FU LEVELS IN COLORECTAL CANCER

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Fluoropyrimidines are one of the few treatment options for colerectal cancer. We describe the use of oral dFUrd (a 5FU prodrug) administration in order to generate low, stable 5FU concentrations and to avoid toxic side-effects. dFUrd (D = 600–1000 mg/m^2) was given to 6 colerectal patients. Daily doses resulted in continuous systemic levels between 1–5 μg/ml which could be maintained during several weeks without any side-effects at all. The biovailability was 32–45%. Renal excretion (3.2–46%) was dose dependent and related with changes of 5FU metabolism. One patient had a partial remission and one a stable disease at 1000 mg/m^2, illustrating the known activity of fluoropyrimidines in the treatment of colerectal cancers. It is concluded that continuous, low dose oral dFUrd results in continuous, non-toxic levels of dFUrd up to 5 μg/ml for several days. These findings are supplementary to the sensitizing influence of ras (frequently mutated in colerectal cancer) for dFUrd activity.[1] But also the possible drag carrier function of dFUrd (enhanced anthracycline uptake in cell lines after dFUrd exposure, non-related to multidrug resistance) makes the further study of continuous, low dose oral dFUrd administration warranted as non-toxic (adjuvant) treatment for colerectal cancer.[2]

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