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Oral uracil/tegafur (UFT) plus leucovorin (LV) in patients with metastatic colorectal cancer (CRC)

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Purpose: In this phase-II trial, the efficacy and toxicity of the oral "UFT + leucovorin" combination was investigated in 51 chemotherapy-naive patients (pts) (31 male, 20 female) diagnosed hystologically with metastatic CRC.

Methods: Median age of the enrolled pts was 59 (22–84) and metastatic sites were liver (30), lung (15), periton (14), adrenal glands (2) and soft tissue (1). In the therapy protocol, oral UFT 300 mg/m^2/day and oral d,l leucovorin 90 mg/day were given daily three divided doses for 28 days every 5 weeks.

Results: Median number of cycles is 3 (1–8) and objective response rates are 1 CR (5%), 6 PR (28%), 9 SD (43%). Five pts (24%) had progression. In 35 of 51 pts included in clinical evaluation, 77% (27/35) improvement was noted in the clinical symptoms and signs. Improvement in pain was 18/25 (72%), weight gain was 14/26 (54%). Analgesic consumption reduced in 11/21 pts (52%). Fifty pts are evaluated for toxicity; no grade IV toxicity was observed. Grade III toxicity was only diarrhea (10%). Grade I–II toxicities were diarrhea (24%), fatigue (10%), emesis (8%) and anemia (2%). No mucositis or hand-foot syndrome observed. Treatment delay was median 7 days (4–14) in 8 cycles due to diarrhea. No dose reduction required.

Conclusion: Oral UFT + LV is a well tolerated and active regimen in pts of all ages CRC without the common toxicities of intravenous 5-FU such as mucositis and hand-foot syndrome. Forty six pts are continuing treatment without any dose reduction. Enrollment will be completed at 54 pts.

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Assessment of biomarkers in paired primary and recurrent colorectal adenocarcinomas

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Purpose: To better understand the biological characteristics of the recurrent colorectal tumor, we investigated various biomarkers regulating cell proliferation and cell loss in paired primary and recurrent colorectal tumor specimens within each individual.

Materials and Methods: From a total of 11 colorectal adenocarcinoma patients, 22 specimens of paired primary and recurrent tumors were obtained for analysis. Apoptosis was evaluated by TUNEL labeling of apoptotic DNA fragmentation. Other biomarkers including PCNA, p53, WAF1, p34cdc2, and cyclins B1 and D1 were analyzed by immunohistochemical stains.

Results: PCNA index (PCNAI) showed an increase in 6 and a decrease in 5 recurrent tumors compared to primary tumors. Mean PCNAI in primary and recurrent tumors were 38.7 ± 20.7 and 49.6 ± 18.1, respectively ($p = 0.16$). In contrast, the apoptotic index (AI) decreased in 9 of 11 recurrent tumors compared to primary tumors. Mean AI decreased from 3.83 ± 3.43 in primary tumors to 1.6 ± 1.4 in recurrent tumors ($p = 0.04$). The p53 expression increased in more than half of recurrent tumors compared to primary tumors. Mean staining score increased from 0.7 ± 1.0 in primary tumors to 1.2 ± 0.9 in recurrent tumors ($p = 0.059$). WAF1 and cyclin B1 did not show significant change. In contrast, both cyclin D1 and p34cdc2 increased significantly in recurrent tumors. These two biomarkers showed increased expression in 8 (cyclin D1) and 7 (p34cdc2) recurrent tumors, respectively, compared to their primary counterparts. Mean staining scores of both biomarkers in recurrent tumors increased by more than 2-fold compared to those in primary tumors and these differences were statistically significant (cyclin D1, $p = 0.007$; p34cdc2, $p = 0.008$).

Conclusion: This study showed significantly decreased apoptosis in recurrent colorectal tumors compared to their primary counterparts. The underlying regulatory mechanisms included increased expression of p53 and altered cell cycle regulators such as increased cyclin D1 and p34cdc2.

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Adjuvant 5-FU based therapy for colorectal cancer

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Objective: To analyse survival and disease free interval in colorectal cancer with adjuvant therapy, and toxicity of treatment.

Material and Methods: From January 94 to December 96, 124 patients were treated. 36 females, 88 males. Mean age 61 y (range 32–77). 65 colon: B, 33 C, 29 and D (R0) 3.59 rectum: B, 25 C, 30 and D (R0) 4. Treatment protocol: Rectum: 5FU 425 mg/m^2 iv d 1–5 + folinic acid 30 mg/8 h po d 1–5 every 28 days, six cycles, with radiotherapy (45 Gy) in 3rd–4th cycles. Colon: 5FU 450 mg/m^2 iv d 1–5 followed by 5FU 450 mg/m^2/week × 48 weeks + levamisole 50 mg/8 h po for 3 days every 15 d × 52 weeks.

Results: 60 colon cancer patients, treated with 5FU and levamisol. In 14, treatment was stopped: 5 due to hepatic progression, 3 due to thrombocytopenia, 2 digestive intolerance, 1 local recurrence, 1 hepatic toxicity, 1 anemia and 1 second tumour. 59 rectum and 5 colon patients received 367 cycles of 5FU and folinic acid, mean 5:73 per patient (range 2–6). Toxicity grade (g) III–IV: Diarrhea gIII 15 episodes (ep), gIV 1 ep, mucositis gIII 13 ep, neutropenia gIII 9 ep, gIV 2 ep. No toxic deaths. Follow up minimum 26 months, maximum 62 months. Overall survival rate (Kaplan-Meier) is 73% at 5 years: Colon: 64% and Rectum 82%. Mean disease free interval 35.40 months (range 5–59 m): Colon, 33.24 m (8–59) and Rectum, 37.78 m (5–57). 36 recurrences (29%); Colon 24 (36%: 11 B, 11 C and 2 D): 12 deaths, 11 alive without disease and 1 with disease; Rectum 12 (20%: 2 B, 6 C and 4 D): 8 deaths, 1 alive without disease, 2 with disease and 1 lost in follow-up.. Initial stage D(R0) (7 patients): 1 alive free of disease, 1 in treatment, 5 have died.

Conclusions: Adjuvant therapy of colo-rectal cancer improves surgical results. Toxicity was low and, although, higher during concomitant chemo-radiotherapy, was manageable. Surgical rescue of metastasis and recurrences allows an increase in the survival of this group of patients.

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Fas-APO1 (CD95+) expression on peripheral blood T lymphocytes (Ly) before and after surgery in colorectal cancer (CRC) patients

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Purpose: Antigen stimulation enhances expression of Fas receptors on Ly and tumor cells can evade immune attack by killing Ly through expression of Fas-ligands. In the study, expression of Fas receptors on peripheral blood T Ly before and after surgery in 62 CRC patients was evaluated.

Methods: CD95+, CD3+, CD4+, CD8+ and CD38+ cells were determined by laser flow cytofluorimeter of 38 men and 24 women with histologically conformed CRC before and on the 10th day after curative or palliative surgery. 28 healthy individuals served as a control.

Results: The number of CD95+ cells before surgery was elevated in CRC patients to compare with control: 623 ± 216 and 394 ± 164 cells/mm^3 respectively ($p < 0.05$). Absolute count of CD95+ cells increased with the cancer spread and decreased after curative surgery. There was positive correlation between CD95+ and CD4+ cells ($r = 0.6$) and between CD95+ and CD38+ cells ($r = 0.58$) in CRC group.

Conclusion: The elevated number of CD95+ cells in CRC patients allows us to suggest that T Ly apoptosis would be increased by Fas-mediated pathway and tumor extirpation would related to decrease this process. Increasing of peripheral blood T Ly apoptosis may contribute CRC escape from immunological control.

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A bi-modality treatment of hepatic arterial therapy (HAT) of unresectable isolated colorectal liver metastases (CLM). Our experience

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Purpose: At our Division of Oncology, hepatic arterial infusion ports were