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

E. Goker[1], N.F. Aykan[2], S. Serdengecti[2], N. Gunel[3], M. Alakavuklar[1], F. Icli[3], I. Yucel[4], N. Uskent[2], F. Arpaci[3], D. Firat[3]. [1]*Turkish Oncology Group, Medical Oncology, Izmir;* [2]*Turkish Oncology Group, Medical Oncology, Istanbul;* [3]*Turkish Oncology Group, Medical Oncology, Ankara;* [4]*Turkish Oncology Group, Medical Oncology, Samsun, Turkey*

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.

248 PUBLICATION

Assessment of biomarkers in paired primary and recurrent colorectal adenocarcinomas

J. Seong[1], E. Chung[1], H. Kim[2], G. Kim[1], N. Kim[3], S. Sohn[3], J. Min[3], C. Suh[1]. [1]*Yonsei University Medical College, Radiation Oncology, Seoul;* [2]*Yonsei University Medical College, Pathology, Seoul;* [3]*Yonsei University Medical College, General Surgery, Seoul, South Korea*

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.

249 PUBLICATION

Adjuvant 5-FU based therapy for colorectal cancer

A. Muñoz[1], I. Rubio[1], J.M. Mañé[1], J.R. Barceló[1], R. Fernández[1], G. Abón[1], N. Fuente[1], G. López-Vivanco[1]. *Oncología Médica, H. Cruces, Osakidetza/SVS, Barakaldo, Spain*

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.

250 PUBLICATION

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

S. Donina[1], L. Engele[1], I. Jaunalksne[2], G. Zakenfelds[1], M. Citovica[1], I. Klestrupe[1]. [1]*Latvian Cancer Center, Riga;* [2]*P. Stradina Clinical Hospital, Riga, Latvia*

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.

251 PUBLICATION

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

G. Jafelice, C. Pittureri, A. Mazziotti[1], E. Jovine[1], G.L. Grazi[1], R. Golfieri[2], M. Giampalma[2], E. Piccinini[3], A. Di Stefano, E. Piana, A. Martoni, F. Pannuti[4]. *Div. Oncologia Medica;* [1]*Ist. di Clin. Chir. II;* [2]*Serv. di Radiodiagn. III;* [3]*Ist. di Clin. Chir. III, Policlinico S. Orsola-Malpighi Bologna;* [4]*ANTBologna, Italy*

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

placed in 54 Patients (Pts) with isolated colorectal liver metastases (CLM).

The first group (30 Pts) received intra-arterial therapy with 5-FU 600 mg/sm plus Folinic Acid (FA) 100 mg/sm at a dose previously calculated to achieve both high-dose regional therapy and adequate systemic levels; the second group (24 Pts) was treated with a regimen combining intrahepatic 5-FU 750 mg plus EPI 40 mg by 1/2-hour infusion every two weeks alternately, and bolus systemic infusion consisted of 5-FU 600 mg/sm plus FA 100 mg/sm.

Methods: (Group A) 30 Pts (21 male, 9 female; median age 62 yrs "range 46–84"; median Karnofsky-Index 80 "range 60–100"; 24 pts previously untreated with chemoteraphy) received bolus hepatic arterial infusion consisted of 5-FU and FA for once a week; there were 986 administrations. (Group B) 24 pts (16 male, 8 female; median age 54 yrs "range 31–69"; median Karnofsky-Index 80% "range 60–100"; 19 pts previously untreated with chemotherapy) received intraarterially 5-FU plus EPI every two weeks alternately, and bolus systemic infusion consisted of 5-FU and FA, there were 897 administrations. Efficacy and toxicity were regularly evaluated by clinical investigation, CT scan, X-ray, and tomografy according to WHO criteria. Survival analysis (Kaplan-Meier) was used to predict median survival and time to progression. The treatment was administered on an outpatient basis until progression (PD) or complete response (CR).

Results: (Group A): median survival time 19.6 months (range 4–63; 95% CI 17–28 months); response rate 13.3% (CR + PR), 13% PD, 74% stable disease (SD). The median time to progression was 11 months (range 2–59+; 95% CI 7–16 months). The extrahepatic progression was 45% (13/29 Pts: only extrahepatic 11%, intra-extrahepatic 34%).

(Group B): median survival time 23.3 months (range 5–41; 95% CI 13–33 months); overall response rate 46% (11/24) with 21% (5/24) of CR and 41% (10/24) of SD. The median time to progression was 11.6 months (range 2–31; 95% CI 9–16 months). The extrahepatic progression was 58% (11/19 Pts: only extrahepatic 37%, intra-extrahepatic 21%). In both groups toxicity was absent or mild and no patient stopped treatment because of side effects.

Conclusions: HAT is an effective treatment for CLM with a moderate toxicity. More studies of combined use with systemic chemotherapy are needed to finally determine the position of this therapy in the treatment system for CLM; therefore it is necessary to conduct comparative trials versus systemic chemotherapy, using the survival time as the end-point.

252 PUBLICATION

Phase I of CPT-11 (CAMPTO®) combined with 5-FU/folinic acid (FA) nordic schedule in first line metastatic colorectal cancer (CRC)

R. Ristamäki[1], B. Glimelius[2], T. Linné[2], B. Boussard, D. Oulid-Aïssa, S. Pyrhonen[1]. [1], *Finland;* [2], *Sweden*

For 40 years, 5-FU was a standard in the treatment of CRC. Multiple schedules of administration of 5-FU have been tested Combination of 5-FU with new drugs such as CPT-11 has shown promising results in 1st line treatment. A phase I/II was conducted to determine the MTD of CPT-11 150–240 mg/m^2) day 1 combined with a fixed dose of bolus 5-FU 500 mg/m^2) followed by FA (60 mg/m^2), day 1 and 2, q 2 wk as the Nordic schedule (Glimelius, Ann Oncol 4, 1993). DLT is defined as neutropenia G 4, thrombocytopenia G 4, febrile neutropenia, G 3–4 infection and any grade 3–4 non hematological toxicity that occurred at cycle 1. Preliminary results are:

CPT-11	Nb pts	Nb cycles	DLT	Responses
150	3	23	0	2 PR
180	3	25	0	1 PR, 2 NC
210	6	22	1*	1 PR, 1 NC
240	3	3	0	too early

* *G4 Neutropenia*

At 210 mg/m^2, one DLT was reported at first cycle out of 6 patients treated. The other toxicities are mild to moderate being mainly cholinergic syndrome and diarrhea. The MTD is not reached so far. Updated results will be presented at the meeting.

253 PUBLICATION

CAMPTO® (CPT-11) combined with different schedules of bolus 5-FU in 1st line treatment of metastatic colorectal cancer

U. Graeven[1], K. Ridwelski[1], M.P. Manns[1], P. Espana[2], G. Carlsson[3], M. Borner[4], B. Boussard, D. Oulid-Aïssa, H. Hemmers, W.H. Schmiegel[1]. [1], *Germany;* [2], *Spain;* [3], *Sweden;* [4], *Switzerland*

CPT-11 as single agent has shown a significant benefit on survival compared to 5-FU, in 2nd line CRC. Moreover, CPT-11 alternating with the Mayo Clinic regimen (Van Cutsem, Ann Oncol 98) has shown very promising results in first line setting. Taking into account the wide use of 5-FU in clinical practice, either as a bolus or infusional administration, it was worthwile to assess the different combination options with CPT-11 in 1st line CRC. This trial was designed to randomly assign patients (pts) in different arms as follows: A: CPT-11 + bolus 5-FU/FA weekly (4 wk–2 wk rest, CPT-11: 125 mg/m^2; FA: 20 mg/m^2; 5-FU: 500 mg/m^2); B: CPT-11 alternating with 5-FU/FA (q 6 wks, CPT-11: 350 mg/m^2; FA: 20 mg/m^2; 5-FU: 425 mg/m^2), C: 5-FU/FA (Mayo regimen FA 20 mg/m^2, 5-FU 425 mg/m^2 bolus). Efficacy is assessed every 2 cycles (cy) and safety every cy. Quality of life is evaluated by the EORTC questionnaire (QLQ-C30). The study is ongoing and 80 patients have been treated so far with 217 cy administered. Preliminary response assessment on 34 pts showed promising results with 1 CR, 3 PR, 1 MR, 1 SD and 4 PD in Arm B. Out of 58 pts evaluable for safety so far, the tolerance is good. Updated results will be presented at the meeting.

254 PUBLICATION

Advanced colorectal cancer (ACC): Impact of chronotherapy (chrono) on patients' (pts) quality of life (QoL)

P. Pugliese, C. Garufi[1], M. Perrone[2], A.M. Aschelter[1], A. Zappalà[1], D. Giannarelli[1], M. Cosimelli[1], E. Terzoli[1]. [1]*Regina Elena, Oncologia Medica Complementare, Roma;* [2]*Regina Elena, Servizio di Psicologia, Roma, Italy*

Introduction: Chrono consist of delivering chemotherapy according to different drug timing. Differences in tissues susceptibility, drugs metabolism and pharmachocynetics have been observed for 5-fluorouracil and platinum compounds resulting in a reduction of toxicity and improvment in efficacy in ACC pts.

Purpose: To evaluate the impact of Chrono on ACC patients' QoL and relationship between toxic events, PS, response and QoL.

Methods: QoL was assessed with EORTC QLQ C30 + 3 questionnaire, administered at baseline, To, after the 3rd, T1, the 6th, T2, and the 9th, T3 course (c). Pts were treated with Chronomudulated infusion of 5-fluorouracil, folinic acid ± oxaliplatin for 5 d q 3 wks by ambulatory pumps.

Results: Patient data: 84 pts were included; mean age was 62 (25–78); M/F: 52/32; PS: 0 (44 pts); 1 (25 pts); 2–3 (15 pts); 20 patients experienced WHO Grade 0–1 has maximal toxicity vs 51 with Grade 2–3; 28 obtained a PR, 43 had SD + PD. Functionig scales mean scores (phisical, role, cognitive, emotional, social function and global physical, global health, global QoL) where high during the whole period of treatment with an improvment prevalently at T2. Global physical functioning was better at T2 vs T0 ($p < 0.05$). A constant improvement of symptom scales was observed at T2 vs T0 but not at T3. Patients in the G2–3 toxicity group at 3rd and 9th c showed QoL emotional, global physical, blobal health, global QoL functioning scales scores lower than the G0–1 group ($p < 0.05$). PS 0–1 pts showed better QLQ mean scores than PS 2–3 pts for all functioning scales at T0, at the 3rd and the 6th c of therapy ($p < 0.05$). Pts who responded to therapy had higher mean scores of global QoL then patients who were resistent to therapy at the 3rd and 9th c ($p < 0.05$).

Conclusions: QoL during chrono remained high during a 6 month period of therapy. A better QoL was observed in those pts with better prognostic factors as PS and tumor responsiveness and in those who displayed a good treatment tolerance. This seams to indicate that infusional chronotherapy has a positive impact on pts QoL.