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Gemcitabine (GEM) as salvage treatment in patients (pts) with advanced colorectal cancer (CRC) progressing after treatment with 5-fluorouracil (FU), irinotecan (Iri) and oxaliplatin (oxa)

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Sequential combinations of FU and either IRI or OXA are currently used as standard first and second line treatment for advanced CRC. Multiple studies are also investigating the concomitant use of the three agents up-front. Progressing patients often have an acceptable PS and continue to require treatment. GEM has shown clinical activity in adenocarcinomas of multiple sites and has a favorable toxicity profile. Since September 2000, 35 pts with progressive advanced CRC (males/females: 24/11; median age 65, range 46-79 yrs; ECOG PS 0/1/2: 7/23/5; median CEA 97, range 1-5780 ng/ml) previously treated with FU, IRI and OXA, were thus accrued in a phase II study of GEM (1000 mg/m2 weekly for 7 consecutive courses and then weekly x 3 q 4 weeks) with abrogation of progression as the main end-point. 20 pts had been treated with a triple combination including FU, IRI and OXA as first line therapy and thus received GEM as second line treatment, while for 15 pts GEM was given as salvage treatment after a median of 2 previous CT lines (range 2-4, median administered FU:25,600 mg, median administered IRI:2,430 mg, median administered OXA:1,300 mg). Metastatic disease was at multiple sites, in the liver only and in the lung only in 26, 6 and 3 cases, respectively. Overall, 56 cycles were delivered (87.7% of the planned weekly administrations). The median number of cycles administered to each patient was 2 (range 1-4) and the median number of weeks of CT was 8 (range 3-22). Only 20 of 322 (6.2%) weeks of GEM were delayed because of toxicity while 24 of 322 (7.4%) weeks were delivered at a reduced dose. Toxicity was mild with only 1 and less than 20% of the pts experiencing grade IV (neutropenia) and grade III (nausea and vomiting, neutropenia and thrombocytopenia) events, respectively. Flu-like syndrome was observed in 8 pts but did not exceed grade I. 4 pts are still completing the first cycle. Response was analysed on all the other registered pts according to the intention-to-treat principle (n=31) and 1 PR, 2 MR, 15 SD and 13 PD were observed. Overall, disease progression was abrogated in 18 of 31 cases, equally distributed in the two subsets of pts (57.8% in the cohort receiving GEM as second line treatment and 58.3% in the group receiving GEM as salvage therapy after two or more previous CT lines).

These data suggest that GEM is well tolerated and may abrogate disease-progression in approximately half of the pts refractory to FU, IRI and OXA. A larger confirmatory trial is planned.

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A phase II trial of oxaliplatin (L-OHP) and UFT/leucovorin (LV) for advanced colorectal cancer (ACC) in elderly patients

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Background: Colorectal cancer is usually diagnosed in elderly patients. Since the increase of life expectancy makes chemotherapy more appealing in this setting, we test the activity and toxicity of L-OHP and UFT/LV in patients with ACC aged 70 or older. Patients and methods: A two-stage trial was planned with an accrual goal of 44 patients. The treatment included L-OHP 65mg/m2 on day 1 and 8 plus UFT 300mg/m2 and LV 90mg in three divided doses given on days 1-14 of each three-week cycle. Patients were followed by a geriatric and a quality of life assessment with specific scales and EORTC-QLQ-C30 questionnaire.

Results: The first 23 patients were evaluable for toxicity and 17 for response, M/F 14/9, age 70 to 89, PS 0/1/2 10/12/1, colon 15 and rectum 8. Metastases locations: liver 17, lung 11, peritoneal carcinomatosis 5. 5/23 had had prior adjuvant chemotherapy and 2 radiotherapy outside on target lesions. Myelosuppression was mild with 5 grade 2 thrombocytopenia and 2 grade 2 anemia. Non-hematological toxicities were grade 3 diarrhea in 3 cases and grade 1-2 nausea/vomiting in 6 patients. Intermittent grade 1-2 neurotoxicity was observed in 4. Only one case of unacceptable cardiotoxicity was registered. Eight (47%) patients had an objective response, complete in 1 and partial in 7 cases.

Conclusions: These preliminay results confirmed that this tested chemotherapy combination is active and tolerated in elderly patients with ACC.

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The potential role of TGF-beta-1, TGF-beta -2 and TGF-beta-3 proteins expression in colorectal carcinomas, and their possible correlation with classic histopathologic factors and patients survival.

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Background: This study investigates TGFbeta1, TGFbeta2 and TGFbeta3 proteins expression in patients with colorectal carcinoma and evaluates their correlation with classic prognostic markers and patients' survival.

Materials and Methods: The study comprised 124 patients with colorectal carcinoma. According to Astler-Coller system, 42 tumors were of stage A, 42-B, 48-C and 20-D, whereas 106 tumors were low-grade and 18 high-grade of malignancy. On paraffin sections the streptavidin-biotin technique, using antibodies to TGFbeta 1, TGFbeta 2 and TGFbeta 3 (SantaCruz, USA) was employed. Staining results followed morphometric analysis and were correlated with clinicopathologic parameters.

Results: TGF beta1 protein was expressed in 88/124 (71%) carcinomas whereas TGFbeta 2 and TGFbeta 3 proteins were detected in all tumors examined. Normal colonic mucosal epithelial cells expressed less TGFbeta 2 ($p<0.01$ compared to neoplastic cells) and less TGFbeta 3 ($p>0.05$ compared to neoplastic cells), but not at all TGFbeta 1. Statistical analysis revealed higher expression of TGFbeta1 in low grade carcinomas ($p=0.009$) and higher TGFbeta 2 presence in advanced stage tumors ($p=0.008$). TGF-beta1 expression was related with higher disease free survival and higher total survival ($p<0.05$ respectively). TGFbeta2 presence was correlated with worse prognosis ($p<0.05$). Cox analysis revealed that besides tumor grade and stage, TGFbeta 1 expression constituted independent prognostic factor.

Conclusions: This study shows that in cases of colon adenocarcinoma there is different expression of TGFbeta 1, TGFbeta 2 and TGF beta3. TGFbeta 1 may be implicated in the pathogenesis of these tumors since it is expressed only within neoplastic and not normal cells. TGFbeta 1 is related with higher disease free survival, higher total survival and constitutes an independent prognostic factor. In the late stages, TGFbeta 2 seems to be involved in tumor progression and it is related with worse prognosis.

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Phase II study of bi-weekly oxaliplatin,UFT and leucovorin (OXA-UFT-LV) in pretreated metastatic colorectal cancer(MCRC).

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Introduction: OXA has previously demonstrated high efficacy combined with 5FU-LV.The combination of UFT and LV is effective and is associated with limited toxicity in the treatment of MCRC. This phase II clinical study was designed to evaluate the efficacy and toxicity of the combination of OXA-UFT-LV for more than 1ª line treatment of MCRC.

Patients and methods: Between 01/00 and 12/01, 23 patients have been included. Mean age is 57 years(39-69), ECOG 0/1/2 ratio 8/3/2. Every patient has received at least one line of previous chemotherapy with 5FU and/or CPT11. This regimen consisted on: OXA 85 mg/m2 D1 and 14+LV 500 mg/m2 2h infusion D1. Oral administration of UFT 300 mg/m2/d (in 2 doses) D1 to 14 and LV 15 mg q 12h D2 to 14.Cycles are repeated every 28 days until progression or toxicity.

Results:. 20 patients are evaluable for response and 23 for toxicity. Up to the current analysis was observed: G1 neurotoxicity in 6/23 (28%) patients;G2 in 3/23(15%) patients; G3 in 1 (7%) patients. Gastrointestinal toxicity:G3-4 diarrhea1 (7%) patients,G3-4 nausea and vomiting 1 (7%) patients. No dose reductions have been necessary. Efficacy results: 5/20(25%) partial response,7/20(35%) stable disease and 8 progression(40%).

Conclusion: Although preliminary, these results show that this combination is associated with an acceptable toxicity and clinical benefit was observed in 12/20(60%).

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Phase I study of Irinotecan (I), Raltitrexed (R), and 5-fluorouracil (5FU) in the treatment of metastatic colorectal cancer (MCRC) refractory to thymidylate synthase inhibitors (TSI)

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Background: TSI are a standard component of treatment for all patients with MCRC. There is evidence of synergetic activity between I, R and 5FU in MCRC. Objectives are to establish the dose limiting toxicity (DLT), maximum tolerated dose (MTD) and recommended doses (RD) of all 3 agents combined in patients with previously treated MCRC.

Methods: This is a prospective phase I, dose escalating study. Patients (pts) were eligible if they had received a single TSI regimen in monotherapy for metastatic disease. For cohorts (coh) 1-4, pts received fixed doses of I (300 mg/m^2) with atropine on day (D) 1 and R (2.5 mg/m^2) D2. 5FU (mg/m^2) was started at 600 IV 90 min D3, and escalated by 300 until MTD was reached. Then 5FU dose was decreased to MTD-1, and R escalated to 2.75mg/m^2.

Results: 22 pts were enrolled (5, 6, 6, 2 and 3 pts in coh 1, 2, 3, 4 and 5, respectively). 77% were males. PS was 0, 1, 2, 3 in 41%, 41%, 14% and 4%. Pts received an average of 8 cycles (range: 1-16). 20 pts are evaluable for toxicity and response (2 pts in coh 5 too early). DLTs were: febrile neutropenia (coh 3), grade (gr) 3 lethargy with gr 4 neutropenia (coh 4) and febrile neutropenia with gr 3 vomiting and nausea (coh 4). MTD for escalating 5-FU was reached in coh 4 (1500 mg/m^2). Coh 5 (R 2.75 & 5FU 1200 mg/m^2) is currently ongoing. Severity of granulocytopenia appears related to 5FU dose. Gr 3-4 was seen in 20%, 67%, 83%, and 100% in coh 1 to 4. Cholinergic symptoms were rare and mild (1 gr 3). Gastro-intestinal toxicity was not dose related. Diarrhea was frequent (90%) but usually mild to moderate (2 gr 3, coh 1&4). Nausea and vomiting (N&V) were common (80%) but usually mild to moderate and controlled with anti-emetic therapy. N or V was gr 3-4 in 3 pts (2 in coh 3, 1 in coh 4). Lethargy (gr 1-3) and anemia (gr 1-2) were also common (95% each). Gr 2-4 rises in hepatic transaminase levels were infrequent (15%) and reversible. Responses were seen in all cohorts. Objective response rate: partial response 5 (25%), stable disease 14 (70%). Median progression free and overall survival were 31 and 56 weeks, respectively.

Conclusions: Further dose escalations are not planned. If coh 5 is deemed tolerable, these doses will be recommended for further studies. Combination of R, I and 5FU is well tolerated at near maximum doses of single agents and has a promising activity level in pts previously treated with a TSI. Further evaluation of this regimen in first-line for MCRC is warranted.

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Preoperative chemotherapy plus concomitant radiotherapy in rectal cancer patients (pts): updated results of a phase II study

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Background: Preoperative chemo-radiotherapy proved to be an effective approach for resectable rectal cancer patients. Our study aimed to evaluate the efficacy [tumour downstaging, disease free (DFS) and overall survival (OS)] and toxicity of chemo-radiotherapy in patients with locally advanced rectal cancer.

Patients and Methods: Eligibility criteria were: stage T2-4, N0-2, M0 histologically confirmed, rectal adenocarcinoma, ECOG < 2, age > 18 yrs, adequate haematological, renal and liver function. Chemotherapy consisted of cis-platinum 60 mg/m2 (day 1 and 29) and 5-FU 1000 mg/m2/day PVI for 96 hours (day 1 to 4 and day 29 to 32). Concomitant radiotherapy was administered at a total dose of 5040 cGy with 3-4 fields box-technique (28f, 180 Cgy/day). Surgery was performed 6-8 weeks following chemoradiation. Adjuvant chemotherapy (5-FU 370 mg/ m2 bolus and folinic acid, 10 mg/m2, day 1-5, every 28 days) was administered within 60 days from surgery.

Results: Forty-one pts entered the study (M/F=32/9, median age at diagnosis 59 yrs, range 37-75). Preoperative tumour stage was: T2N0M0 in 7 (17%) pts, stage T3-4 N0M0 in 16 (38%), 16 (38%) pts were N+. In 2 further pts tumour stage could not be assessed (TxN0M0). In 25 (61%) pts tumour was located within 6 cm from the anal verge. To date all pts completed neoadjuvant therapy and 40 underwent surgery (34 pts had a low anterior resection and 6 pts had an abdominoperineal resection) and 22 (54%) pts completed adjuvant chemotherapy. We observed a pathologically confirmed tumour downstaging in 21 (51%) pts with a complete response in 8 (19,5%) cases. At a median follow-up of 24 months, 10 (24%) pts relapsed (1 pts showed local recurrence and 9 pts metastatic disease), with a DFS of 18 months and OS of 25 months. Chemo-radiotherapy related toxicity was modest (NCI grade III diarrhea in 3 pts), 1 patient died for post-surgical complications.

Conclusions: Although a longer follow-up is required for more definitive conclusions, in our experience neoadjuvant chemo-radiotherapy for rectal adenocarcinoma seemed well tolerated and effective with a high response rate (22% complete response) and satisfactory local control

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The conservative treatment of anal canal carcinoma

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Background: In anal canal carcinoma optimal radiotherapy doses and chemotherapy schedules are not well established.

Combined chemo-radiotherapy has better survival rates than surgery, achiving preservation of anal sphincter function in the majority of patients.

Materials and methods: Between 1989 and 2002, 60 patients with basaloid or squamous cell carcinoma of the anal canal were treated at the Department of Radiology of the University La Sapienza, Rome. Patients underwent pretreatment evaluation with clinical examination, complete blood cell count, chest radiography, transrectal sonography, anorectoscopy and anal biopsy, anorectal manometry and abdominopelvic CT or MR.

Patient population consisted of 43 females and 17 males, with a median age of 65 years. Stage was: 27 cases T1-T2 N0 (45%), 8 T3 N0 (13%), 6 T4 N0 (10%), 2 T2 N+ (5%), 10 T3 N+ (16%) and 7 T4 N+ (11%).

Thirty-nine patients (65%) received concurrent chemo-radiotherapy and 21 (35%) exclusive radiotherapy because clinical contraindications to chemotherapy.

Concurrent chemotherapy included 2 cycles of infusional 5-Fluorouracil at 1000 mg/m^2/day for 4 days in the first and last week of radiation, in addition to Mitomycin C 10 mg/m^{2}or CDDP 50-75 mg/m^{2}or CBDCA 150-200 mg/m^{2}on the first day of treatment. Combined radiotherapy consisted of external-beam pelvic irradiation to a dose of 45 and a boost of 10-15 Gy or two cycles of 23.4 Gy and a boost of 15-20 Gy. Radiotherapy alone regimen consisted of 50-60 Gy and a boost of 10-15 Gy.

Results: Complete response was observed in 12/21 (57%) patients treated with exclusive radiotherapy and in 30/39 (77%) patients treated with concurrent chemo-radiotherapy. Abdominoperineal resection was performed in 5/21 (24%) patients treated with exclusive radiotherapy and in 6/39 (15%) patients of chemo-radiotherapy group. There was a small difference in the incidence of acute toxicity (evaluated with WHO scale) in the two groups. Radiotherapy exclusive regimen caused grade II proctitis 9% of patients, grade III acute haematologic toxicity in 4% and compromising sphincter function in 4%. Combined treatment caused grade II proctitis 25% of patients, grade III acute haematologic toxicity in 10% and compromising sphincter function in 13%. Median follow up was 40 months, the 5-year overall survival was 79% in the chemo-radiotherapy group vs 62% in the exclusive radiotherapy. The 10-year overall survival for the exclusive radiotherapy and chemo-radiotherapy groups was 47.6% and 69.2% respectively.

Conclusion: Combined therapy using radiation and concurrent chemotherapy with preserving anorectal function, has replaced surgery as definitive treatment for cancer of the anal canal. Variation in radiation technique have been proposed to reduce acute and late tissue toxicity observed when high radiation doses are combined with chemotherapy.