Gastric and Colorectal Cancer

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ORAL ADJUVANT CHEMOTHERAPY IN STAGE II (B2-3) AND III (C) COLON CANCER. A. Abad*,MP López,E. Batiste-Alentorn,A.Arcusa,I. Moreno, M.Gallen,L. Jolis, A. Font, RM Franquesa, R. Blanco, R. Rosell. Colon Adjuvant Treatment Group. *Hosp Germans Trias Pujol.08916 Badalona.Spain.

From March 89 to March 92, 164 patients (p) with stage II and III colon cancer were included in a adjuvant trial using an oral schedule of UFT (tegafur+uracil) 400 mg/24 h continuous plus Levamisole 150 mg/24 h x 3 days/ 15 days. The purpose was to demonstrate the benefit in the disease free interval and survival of a non-toxic and comfortable treatment. Patients aged from18 to 75 years undergoing curative surgery were included after the informed consent was obtained. For stage II we compared 12 months (m) of chemotherapy vs control. For stage III, as the benefit of adjuvant chemotherapy was proved by preliminary results of MOF and FU+levamisole, we compared 6 vs 12 m treatment without control group. The study was stopped prematurely due to several reasons. We present the results of 164 p with a median follow-up of 52 m (minimum 42, maximum 78). For stage II 96 p were included, 42 control (C) and 54 treatment (CT). No differences in prognostic factors were observed between the groups. The results show no statistical difference in disease free survival (DFS)(19% C relapses vs 18.5% CT relapses) and 78 months survival (S), but S was 10.5% superior for CT group (78.5% C vs 89% CT). For stage III 68 p were included. 35 in 6 m treatment (6CT) and 33 in 12 m treatment (12CT) without differences in prognostic factors. No differences in DFS (34% 6CT relapses vs 33% 12CT relapses) and S (74.2% 6CT vs 69.7% 12CT). The toxicity was mild. 4% grade 3-4 gastrointestinal toxicity and 0 grade 3-4 hematologic toxicity.The small number of cases do not permit to achieve statistical conclusions but our results reproduce with an oral and non-toxic treatment those obtained by Mayo Clinic and intergroup (ECOG; NCCTG;SWOG) using a intravenous schedule (N Engl J Med 1990). It is also remarkable that in stage III the survival is 69-74% at 6 1/2 years without difference between 6 and 12 months of CT. These results suggest the UFT plus Levamisole oral combination is a schedule to have in mind in future trials in adjuvant colon cancer treatment.

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PROGNOSTIC SIGNIFICANCE OF THE nm23-H1 PROTEIN EXPRESSION IN COLORECTAL CANCER.

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The gene nm23-H1 (Steeg, JNCI,80, 1988) has been considered as a tumour suppresor gene implicated in metastatic spread. In some murine and human tumours, as breast cancer, its expression is linked to a low metastatic potential and a better prognostic. We have studied the nm23-H1 protein expression and the clinical agresivity of 62 cases of colorectal cancer that had been treated with radical surgery. Expression of nm23-H1 was determined by inmunohistochemical methods, using the monoclonal antibody NCL-nm23-2. Of the 62 cases studied, 25 (40%) expressed the protein (nm23 +) and 37 (60%) did not (nm23 -). We analized the correlation between the presence or the absence of nm23 and some known clinical and hystological prognostic factors and the relapse probability, the disease free survival (DFS), and the overall survival (OS). No statistical differences were observed between the two groups in relation to lymph nodes afectation, hystological grade and CEA serum level. With a follow-up between 6 and 10 years, there were no differences in relapse appearance. DFS and OS were significantly better for nm23 - patients. 31% of the nm23 + patients and 70% of nm23 - patients were free of disease at 5 years with 26% and 52% at 10 years ($p<0.04$). OS was 29% for nm23 - patients and 75% for nm23 + patients at 5 years and 24% and 54% at 10 years ($p<0.01$). These results shows worse prognosis for those patients with nm23-H1 protein expression, against what was expected because of the suppression function that has been described for such gene. This study is being continued in order to confirm these results.

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THE S.M.A.C. STUDY: LARGE SCALE COLLABORATIVE TRIAL OF ADJUVANT THERAPY IN COLON CANCER.

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The efficacy of adjuvant therapy in stage B2 - C colon cancer patients has been proven for 5FU-Levamisol and 5FU-Folinic acid combinations. A pooled analysis of intraportal 5FU demonstrated a significant reduction in mortality. Therefore, the combination of intraportal and systemic therapy might reduce mortality achieved with each single regimen.

On April 1992 a multicentric randomized trial of adjuvant chemotherapy in completely resected colon cancer patients was launched in Italy, comparing the efficacy of: 1) systemic 5FU (370 mg/m^2 on days 1,2,3,4,5) + Folinic acid (100 mg/m^2 on days 1,2,3,4,5) (FUFA); cycles were repeated every 28 days for 6 months; 2) continuous intraportal vein infusion of 5FU (500mg/m2/day) + heparine (5000 UI/day/c 7 days) (IP); 3) combination of the two. Treatment is allocated by central randomization during surgery. As at October 1995, a total of 1001 patients have been enrolled by 62 general hospitals, with an average accrual of 300 patients/year. Post surgical complications were 9%, equally distributed among the three arms. Complications at anasthomosis affected 19 (2.1%) patients and 2 patients experienced liver toxicity. Overall, 7 patients died for surgical complications. Systemic therapy has been completed in 74% of patients, while 82% of patients completed IP. Intraportal therapy was interrupted for surgical complications (5,4%), problem related to catheter inserction/dislocation (12,5%) and toxicity (3,3%). Treatments were well tolerated. Diarrhoea was the most important problem, occurring in 3.1% of patients. At a median follow-up time of 23 months 69 relapses (30 of the liver) and 49 deaths (28 correlated to disease progression) have been reported. No deaths related to toxicity were reported.

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PHASE I/II TRIAL OF EPIRUBICIN (EPI) AND HIGH DOSE TAMOXIFEN (TAM) AS A POTENTIAL MODULATOR OF MULTIDRUG RESISTANCE IN ADVANCED HEPATOCELLULAR CARCINOMA (HCC)

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30 patients (pts) with unresectable HCC were treated with oral TAM 160 mg/day for 9 days, and EPI administered as a continuous infusion over 24 hous on day 8 with an initial dose of 70 mg/m2. Subsequent EPI dose escalation levels were 80, 90, 100, and 110 mg/m2. Consecutive cohorts of 3 to 6 pts were planned at each dose level. Treatment cycles were repeated every 4 weeks. Myelosuppression was the dose-limiting toxicity with an MTD of 100/mg/m2 for epirubicin. 0/3 pts at the first 3 dose levels experienced any severe toxicity, though 3/6 and 4/6 had grade 4 granulocytopenia during their first two treatment courses at levels 100 and 110 mg/m2, respectively. Apart from alopecia and local reactions in patients without a central venous access, nonhematologic toxicity was uncommon, generally modest, and did not correlate clearly with the anthracycline dose. None of the 21 pts, who were treated in the escalating-dose phase I stage of the study, and only 1/9, who were subsequently treated at the MTD achieved objective remission to this therapy. Stable disease was noted in a total of 14 pts, and tumour progress occurred in 15. The MTD of EPI for this regimen with TAM was 100 mg/m2 every 4 weeks. The disappointing antitumour activity observed in this study seems to support that reversal of MDR remains an experimental approach without established clinical relevance in most solid tumours.