527

HIGH DOSE INTRA-ARTERIAL PLUS INTRAPERITONEAL CHEMOTHERAPY COMBINED WITH HEMOFILTRATION IN LIVER METASTASES FROM COLORECTAL CANCER. Dazzi C.[1] Fiorentini G.[2], Daviffi R.[3], Canosi V.[3], Marangolo M.[2] and Casciani G.[1] Oncology, City Hospital, Lugo RA [1] and the Departments of Oncology[2], Surgery II [3], Ospedale S. Maria delle Croci, Ravenna, Italy.

Twenty three patients with liver metastases from colorectal cancer were entered into a prospective, phase II pilot study to evaluate the efficacy and feasibility of high dose hepatic intra-arterial chemotherapy (IAHC) plus intraperitoneal chemotherapy (IPC) combined with hemofiltration. All patients had abdominal laparotomy to position a hepatic artery infusion port and in some cases an implantable system for IPC. A double lumen filtration catheter was placed in the vena cava via the saphenous or femoral vein and connected to a modified hemofiltration unit. The treatment schedule consisted of mitomycin 30-50 mg/sqm and epirubicin 60-90 mg/sqm as IAHC combined with cisplatin 60 mg/sqm given in 2000 ml saline solution by IPC. The high dose IAHC-IPC was followed by four cycles of intra-arterial standard dose chemotherapy (mitomycin 6 mg/sqm and epirubicin 20 mg/sqm) and if possible by another cycle of high dose IAHC-IPC. We obtained 2 CRs (8.7%) and 11 PRs(47.8%); moreover 4 out of 7 pre-treated patients obtained response to treatment. As a result, an objective tumor response was observed in 56.5% of patients (13/23). Therefore a dose response behaviour has been demonstrated also in tumor with low chemosensitivity. The median duration of response and survival was 10 and 14 months respectively. Toxicity was usually mild but we reported one toxic death due to treatment complications. Further prospective randomised study are needed to confirm the results of our study.

528

FLUOROURACIL(5-FU)AND FOLLINIC ACID(FA)WITH OR WITHOUT a2b-INTERFERON(IFN) IN ADVANCED COLORECTAL CANCER(ACC).A PROSPECTIVE RANDOMIZED TRIAL.

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Purpose of our study was to investigate if IFN can potentiate the efficacy of the combination 5-FU and FA in ACC From 2/1990 to 2/1992, 95 ACC untreated patients(pts)51 men, 44 women were randomized in 2 groups.Group A 45 pts received FA 200mg/m^2 IV 2h infusion, 5-FU 450mg/m^2 IV mid-infusion of FA weekly for 6 wks and 2 wks rest period Group B, 50 pts received in addition IFN 5x10^6 U thrice in a week. Pts characteristics were well balanced in both groups for age (median 64 vs 59) p.s., DFI(12.7 vs 13.5 months), site of disease (liver 31 vs 32) and grade. Response rates:Group A:CR 2 (4.8%),PR 7(14.3%) SD 17(38,1%) P.D. 18(40.5%) 1 non-evaluable. Group B:CR 1,(2.0%), P.R. 2 (4.0%) S.D. 19 (38%) P.D. 24 (48%), 4 non-evaluable.Median time to progression was 5.8 months in Group A vs 4.0 in Group B. Median survival for Group A was 10 months vs 7 in Group B. Prognostic factors which influenced significantly survival were site (colon rectal), sex (m f), grade (3 1), DFI (0-12m 12-48m). Toxicity was significantly more pronounced in Group B.

529

HLA EXPRESSION ON TUMOR CELLS AND SERUM LEVELS OF SOLUBLE IL-2 RECEPTOR IN COLORECTAL CANCER

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In 20 colorectal cancer patients, HLA expression on tumor cells and serum levels of sIL-2R were examined.Using flow cytometry and in comparison with normal mucosa, 45% of tumor samples showed an increase of HLA class II expression, 35% a reduced expression and 20% no variation. sIL-2R was increased in serum of patients (507.3±297 U/ml), respect to control group (360.3±226 U/ml, p=0.047).We found that of 13 patients with sIL-2R levels above the mean value of control group (>360U/ml),8 showed an increased expression of class II antigens (62%), while 5 patients of 7 with sIL-2R <360.3U/ml had a reduced expression of class II (71%) and only 1 patient of 7 had an increased expression of class II(14%).The preliminary results suggest that these parameters may derive from the same physiopathologic alterations; further study are in course in order to verify if an association there exists. Supported by: M.L. n.541; C.N.R. Special Project "Oncologia" and "Biotecnologie".

530

p53 AND Ki-RAS ALTERATIONS IN COLORECTAL ADENOCARCINOMAS

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We examined 20 colorectal adenocarcinomas (13 distal colon and rectum, 7 proximal colon) compared to adjacent normal mucosa by PCR and a hybridization using ^{32}P-SSOs to c-Ki-ras codd.12,13,61. In a preliminary study, 11 out of 20 adenocarcinomas were also analyzed for the loss of heterozygosity of the human p53 tumor suppressor gene using RFLP detected by MvnI restriction enzyme. This enzyme identifies a two-allele polymorphism within exon 4 (base 733, C or G) of the p53 gene: A1 allele = 259 bp, A2 allele = 160, 99 bp. We observed Ki-ras point mutations in 5 of 20 adenocarcinomas (25%) and a total localization of the mutations in distal colon and rectum. As concerns p53 gene, 4 of 11 tumor samples (36.4%) showed the loss of one allele (A2) when compared with normal colorectal samples of the same patient. These data suggest: 1) Ki-ras mutations are an important but not obligatory event in the development of colorectal cancer; 2) a probable association between Ki-ras alterations and tumor site; 3) the importance of the p53 as a target of chromosome 17 deletions involved in the colon malignant tranformation. **Supported by: M.L.n.541; CNR Special Project "Oncologia" and "Ingegneria Genetica".**

531

STRATIFYING FOR VENOUS INVASION ENHANCES THE PROGNOSTIC VALUE OF THE DUKES' AND ASTLER-COLLER CLASSIFICATIONS.

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The numerous modifications of the Dukes' classification of colorectal Ca lack sufficient power to predict prognosis for the individual patient. Personal,familial, clinical and histologic data of 247 consecutive pts., following curative resection of colorectal Ca (Minimal follow-up: 5y; average f-u: 12.6y) were retrospectively analyzed by univariate and multivariate (Cox) analysis with respect to their impact on prognosis.

Tumor recurred in 28.9%.

VENOUS INVASION emerged as the objective pathologic variable with the strongest independent impact on prognosis, and was therefore used for stratifying pts. within each Dukes' and Astler-Coller class.

The resulting sub-groups differed significantly with regard to overall and disease-free surgival, and could clearly be classified as high or low risk for recurrence.

This modification of the traditional staging systems may aid in the selection of pts. for adjuvant tx.

532

NAVELBINE PLUS 5-FU AND FOLINIC ACID (FA) IN PRETREATED COLO-RECTAL CANCER PATIENTS. PRELIMINARY DATA

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Introduction: The percentage of objective responses obtained with the standard first line therapy in advanced colo-rectal cancer pts (5-FU + FA) is approximately 33 % and poor is the non responders prognosis. From February to December 1992, 32 patients (pts) with advanced colo-rectal carcinoma, all pretreated with schedules containing 5-FU and FA, received a new antineoplastic combination treatment including 5-FU (375 mg/m^2 days 1-5)+ FA (200 mg/m^2 days 1-5)+ Vinorelbine (30 mg/m^2 e.v. days 1-8).

Patients: median age was 57 years (36-70), male 21 and female 11. Metastatic sites were lymphatic nodes 18/32, peritoneum 6/32, lung 3/32, liver 15/32 and pelvic 2/32.

Toxicity: overall 81 courses have been administered up to now. Grade III-IV neutropenia occurred in 29/81 (35.8 %) courses. Nausea, vomiting and paresthesia were well tolerated. The most important side effect was vascular toxicity in the site of injection (54/81 courses, 66.6 %).

Results: 26 pts are evaluable for clinical response. 8/26 (30.7 %) objective responses were obtained : 6 PR (5 LN, 1 liver, 2 ascites) and 2 MR (LN, liver, lung, ascitis).

Conclusions: navelbine shows in this new combination a good efficacy with moderate toxicity and preliminary data seem encourage a larger phase III trial.