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NEO-ADJUVANT CHEMOTHERAPY IN OPERABLE ESOPHAGEAL SQUAMOUS CELL CANCER; AN INTERIM REPORT OF A RANDOMIZED CONTROLLED TRIAL.

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METHODS: A multicentre prospective randomized controlled trial was initiated for patients(pts) with operable esophageal squamous cell cancer between neo-adjuvant chemotherapy(chemo) followed by surgery (blunt esophageal-cardiac resection with stomach tube reconstruction) versus surgery alone. Endpoint: survival.

TREATMENT: Pts with a Karnofsky Index >70%, normal kidney function, and a garanteed calorie intake were randomized after stratification (sex, age, weight loss, and tumor size) to up-front chemo with Cisplatin (CDDP:80mg/m$^2$ day 1) and Etoposide (E:100 mg iv day 1+2; 200 mg/m$^2$ orally day 3+5), q 3 wks, followed by surgery (group A), or surgery alone (group B). After 2 cycles of chemo, a clinical response evaluation was done (ct-scan, endoscopy with biopsies, endoscopic ultrasound); pts with a major tumor response received another 2 cycles followed by surgery, whereas non-responding pts underwent surgery following up the 2$^{nd}$ cycle. No post-operative therapy was considered in this protocol. RESULTS: Until January '93, 66 consecutive pts entered the study: 49 male, 17 female, med.age 64, weight loss 8%, med. tumor size 6 cm. Group A(n=32): 2 pts inevaluable for response (refusal chemo after randomisation). Response rate 11/30=37% (cCR 2/30). No serious haematological toxicity, no toxic death; 11 pts 4 cycles, 19 pts 2 cycles, 2 pts 1 cycle (early progression). No resection in 6 pts; local irresectable 4, metastases during chemo 2. Med. follow-up 14 months, med. survival 14 months. A major response after chemo predicts survival benefit: 9/11 responding pts are still alive at med.18 months(9-44). Group B(n=34): no resection in 5 pts; local irresectable 2; distant metastases 3. Med. follow-up 8 months, med. survival 10 months.

CONCLUSIONS: Neo-adjuvant chemo with CDDP and E is feasible. This interim analysis shows median survival benefit and more longterm survivors in the combined modality treatment group. A further analysis of this ongoing study will be done after 90 entered pts.

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CHEMOTHERAPY(CT)WITH CISPLATIN(DDP)+CONTINOUS 5FLUORURACIL(5FUc)IN THE TREATMENT OF ADVANCED ANAL SQUAMOUS CELL CARCINOMA(SCCa)

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The role and type of systemic CT in the treatment of advanced anal SCCa is still controversial.From October 88 to December 92 we treated 18patients(pts),13 5 ,median age 59(range 44-78),3with PS(ECOG)3/4.All had histological proven advanced anal SCCa.4pts had locoregional disease,9had metastases(met)and 5had both.All but one received previous treatment,6with CT(MMC±5FU)+radiotherapy.14pts were evaluable;all were treated with DDP 100mg/m2dl+5FUc 1g/m2dl-5.Efficacy:Complete responses(CR)-6pts(43%), parcial responses-2pts(14%)(OMScriteria).Median duration of response-6months(m);median survival-7.5m,with 2met pts still in CR at 15and 21m.6pts(43%)had treatment limiting toxicities -lacral erythema,1mucositis,2neurological,2renal,2cardiac and 3ototoxicities,none of them lethal.Although toxic,DDP+5FUc allows for long term control of disease in some patients.

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HIGH RESPONSE RATE OF A CHEMOTHERAPY USING CARBOPLATIN (CARBO) + CISPLATIN (CDDP) + 5-FLUOROURACIL (5-FU) FOR ADVANCED OESOPHAGEAL CANCER.

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The aim of this study was to evaluate the efficacy of a regimen using the dose-intensity of platinum compounds combined with 5-FU in continuous infusion (c.i.) for advanced oesophageal cancer. From 02/90 to 08/92, 27 patients (pts), all with W.H.O. PS < 2 and creatinine clearance (Cr.Cl) > 60 ml/mn, received a combination of CARBO (300 mg/sq.m./day (d), d1) + CDDP (25 mg/sq.m./d, d2-d5) + 5-FU (c.i.) (750 mg.sq.m./d, d1-d4). Q4W, for 3 cycles (cy). At inclusion a 25 % reduction dose of CARBO and CDDP was applied when Cr.Cl. was between 60 and 80 ml/mn. Group 1 with an initially inoperable local advanced disease (LAD) = 15 pts, mean age 64 years (45-74) ; localizations : upper third 3, middle third 10, lower third 2 ; histologic types : epidermoid 10, adenocarcinoma 5. EFFICACY : 100 % of disappearance of dysphagia after 1 cy ; CT-scan response : 14 pts evaluable (1 toxic early death) with 4 CR, 4 PR > 75 %, 4 PR < 75 % and > 50 % and 2 MR. TOXICITY (mainly hematological) : for 43 evaluable cy, neutropenia G3-4 = 10 cy (23 %) in 6 pts, thrombopenia G3-4 = 13 cy (30 %) in 9 pts ; anemia G3 = 3 cy (7 %) in 3 pts. After chemotherapy 8 pts received surgery (100 % resecability, 1p CR), 6 pts refused surgery and were treated with a concomitant chemoradiotherapy. Group 2 definitively inoperable (5 metastasis, 2 recurrence, 5 LAD) = 12 pts, mean age 61 years (43-72) ; localizations : upper third 2, middle third 7, lower third 3 ; histologic types : epidermoid 11, adenocarcinoma 1. EFFICACY : clinical response on dysphagia in 9/12 pts : mediastinal CT-scan response : 2 CR, 1 PR > 75 %, 3 PR < 75 % and > 50 %, 2 PR < 50 %, 2 SD, 1 progression : metastasis response : 2 CR and 3 progression in 5 pts. TOXICITY (mainly hematological) : on 36 evaluable cy, neutropenia G3-4 = 7 cy (19 %) in 5 pts, thrombopenia G3-4 = 7 cy (19 %) in 7 pts, anemia G3 = 3 cy (8 %) in 3 pts. After this inductive chemotherapy pts were treated either with the same regimen but at a low dose or with a concomitant chemoradiotherapy. CONCLUSION : this inductive regimen seems interesting in neoadjuvant and palliative circumstances (objective OR of 85 % and 70 % respectively).

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GASTRIC CARCINOMA: CONTINUOUS INFUSION 5-FLUOROURACIL PLUS CISPLATINUM: DOSE INTENSIFICATION STUDY

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Between 3/88 and 12/92, 40 consecutive patients with advanced gastric carcinoma were entered into a prospective chemotherapy protocol of continuous infusion 5-FU 1000mg/m$^2$ for 5 days plus 70-100 mg/m$^2$ cisplatinum on day 2 given every 3 weeks. 15 were women with a median age of 66 years (range 45-75) and 25 were men with a median age of 67 years (range 32-82). 37 were Stage 3 inoperable disease or Stage 4. Metastases were found in: Liver -22; lung-6; omentum-3; RP lymph nodes-8; bone-2; ovary, colon, pancreas-1 each. 16 underwent previous subtotal gastrectomy; 7 received prior chemotherapy and 5 radiotherapy. Median number of courses was 3 (1-10). Overall response rate was 38% (8% CR and 30% PR). 2 of the complete responders received additional radiotherapy to the tumor bed. 15% had clinical response judged by improvement in symptoms, with stable disease. Median survival of all the patients from the beginning of the treatment was 7 months (range 1-19 months). Toxicity included: Nausea & vomiting Gr 2-3: 95%; weakness:90%; mucositis Gr 2-3:40%; nephrotoxicity (CCT < 50 ml/min):12%; peripheral neuropathy: 12%; Grade 1 neutropenia: 23%. We conclude that our dose intensification regimen, given every 3 weeks, added toxicity without improving response.

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FUNCTIONAL HEPATIC RESERVE AFTER ARTERIAL LIPIODOL-CARBOPLATINUM THERAPY IN CIRRHOTIC PATIENTS WITH HEPATOMA

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Planning the therapy of the unresectable Hepatocellular carcinoma (HCC) is essential to achieve a clear antitumor activity and few side effects upon the cirrhotic liver. Today the so called "targeted chemotherapy" by using ethiozide oil ultrafluid (Lipiodol) as a carrier of intrarterial anticancer drugs seems to achieve these goals. In this study we observed the influence of the Lipiodol-Carboplatinum intrarterial administration upon antipyrine metabolism in 21 pts with liver cirrhosis and unresectable HCC. These were 16 males and 6 females (average age 65 y, range 49-76); all were assigned to Child-Pugh cirrhotic class A. None of them received prior therapy. In each patient the Antipyrine metabolism test (18 mg/Kg/os) and the standard liver function tests were assessed just before and 72 hours after the Lipiodol-Carboplatinum administration. All the patients received Lipiodol 10-15 ml mixed with Carboplatinum 150 mg/m2 into the common hepatic artery. Seventytwo hours later we observed a transient impairment of Antipyrine metabolism (AP clearance before 0.299±0.12 ml/min/Kg, half-life 30.3±3.9 h, AUC 0-24 h 550±85, 72 h after 0.26±0.11, Half-life 17.6±3.6 h, AUC 0-24 h 538±70, p=0.5), no change on Volume of distribution (VD before 42.4 L, VD after 39.5 L) and a transient rise of serum aminotransferases (AST 85±56 UI/l, ALT 67±36 UI/l, after 275±156 UI/l, ALT 193±147/l, p<0.001). No change was observed on serum albumin, bilirubin and prothrombin activity level. In pts bearing unresectable HCC, even in presence of Child A cirrhosis, the arterial chemoembolization with Lipiodol and Carboplatinum mixture does not influence the functional heaptic reserve.

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DIAGNOSTIC WORK-UP (DW) IN STAGING AND EVALUATION OF RESPONSE IN HEPATOCELLULAR CARCINOMA (HCC) TREATED WITH CHEMOEMBOLIZATION (CE)

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The following is a multidisciplinary protocol integrating informations of DW in staging and evaluation of the response to CE in HCC is presented. The protocol includes US, Doppler-US, CT, angiography (AG) with Lipiodol (+/-anti-cancer drug), esofagogastroscopy as well as routine laboratory investigation, alfa-Fetprotein level and residual liver function with Antipyrine clearance; Lipiodol-CT (L-CT) is performed after one month or more after CE to differentiate L accumulation in the tumor and in non-neoplastic liver parenchyma. The protocol started in 01/92 and included 27 pts (22 males, 5 females; average age 64 y). In 16 pts (59%) US-CT-AG findings and L-CT findings showed concordant results regarding number and site of lesions, while in 11 pts (41%) discordant results were recorded. In this latter group the total number of lesions identified by US was 20, CT 18, AG 35 and L-CT 23. Thus the most sensitive procedure in identifying HCC nodules was AG. The advantage of AG was particularly evident in detecting smaller lesions (<1 cm). 7 nodules were depicted with AG otherwise not shown with US and CT. This preliminary report suggests how integrated interpretation of diagnostic findings leads to a more accurate definition of the extent of the disease, fundamental for therapeutic oriented decisions.