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INTRA-ARTERIAL CHEMOTHERAPY FOR LOCALLY ADVANCED CARCINOMA OF THE PANCREAS (LAPC)

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Background: the very limited efficacy of current chemotherapeutic strategies in LAPC, the pattern of metastatic spread largely confined to the upper abdominal organs within the arterial supply of celiac axis induced us to design this phase II study of locoregional intra-arterial chemotherapy. *Purpose:* the aim of the present study was to evaluate the feasibility, the toxicity, the response rate and the real impact on survival of a new combination of drugs administered intra-arterially in the treatment of LAPC. *Patients and methods:* from January 1994 to March 1995, twenty-five consecutive patients with LAPC were given 2 intra-arterial cycles of chemotherapy through a catheter in celiac axis introduced via the femoral artery, on days 1 and 22. The schedule was FLEC: 5 fluoruracil (5FU) 1000 mg/sqm; leucoverin (LV) 100 mg/sqm, epirubicin (EPI) 60 mg/sqm and carboplatin (CP) 300 mg/sqm: each drug was infused over a period of 10 minutes and only one day of hospitalization was necessary for each cycle. After 2 cycles when we obtain a partial response (PR) or a stable disease (SD), other 2 cycles were planned. *Results:* a total of 74 courses of chemotherapy were administered with a mean of 2.9 for each patient (1–5). 23 patients are evaluable for response: 10/23 patients had a PR (43%) evaluated by ct-scan, 14/23 had a decrease of Ca 19-9 (61%), 14/23 had an improvement in quality of life (61%). Grade 3/4 hematological toxicity was observed in 5/23 (22%); grade 2/3 gastrointestinal toxicity in 2/23 (9%); alopecia in 2/23 (9%). One sudden death was observed in a patient on day 23 after the third cycle. No complications related to angiographic procedure was noted. At a median follow up of 4 months (1–13), the median survival is 5.6 months and 1-year survival rate is 51% and 9% for responders and non responders respectively. *Conclusions:* this study showed that the FLBC combination given through a celiac axis infusion is well tolerated and active and may become an important strategy both in a palliative and in a preoperative setting in patients with pancreatic carcinoma.

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HYDROXYUREA, FOLINIC ACID, 5FU BOLUS AND INFUSION (HLFP REGIMEN) IN ADVANCED ESOPHAGEAL CANCER

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HLFP regimen is active in advanced gastric cancer. We tested this combination in a phase II study for patients with advanced squamous cell carcinoma of the esophagus. Regimen consisted in hydroxyurea 1.5 to 2 g orally days 0, 1 and 2, folinic acid 200 mg/m^2 in 2-h infusion, followed by 5FU 400 mg/m^2 bolus and 600 mg/m^2 22-h infusion days 1 & 2 every 14 days. Cisplatin was administered at 80 mg/m^2 day 3 every 2 courses. HLFP regimen was given until progression. 32 patients were included, this preliminary report concerns the first 26 (22 males, 4 females) analysed pts (6 too early). Mean age was 62.7 yrs ± 8.8 (44–74). 9 presented an advanced locoregional disease, and 17 a metastatic disease (distant lymph nodes: 17; liver: 6; lung: 3). Initial performance status (WHO) was 0 (11 pts), 1 (11) or 2 (4). 118 courses were administered. Toxicity (> WHO grade 2) was leucopenia (3 pts), thrombopenia (2 pts), vomiting (1 pt), diarrhea (2 pts). Overall, maximal toxicity per pt was gr 0 (1 pt), gr 1 (10), 2 (9), 3 (4) and 4 (2), giving a gr 3–4 rate of toxicity of 23%. Response rate was 69.2%, with 4 CR and 14 PR. 4 pts underwent surgery after chemotherapy, and 8 radiotherapy. 53.8% of pts had a weight gain during treatment, dysphagia disappeared in 67% of pts. Median follow-up is 11 months. At 11 months, 79% of pts are alive, 56% without evidence of progression. This combination is active in advanced esophageal cancer. The study is ongoing.

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DEMONSTRATED EFFICIENCY OF 5FLUOROURACIL (5FU) CONTINUOUS INFUSION (CI) AND CISPLATIN (P) IN PATIENTS WITH ADVANCED BILIARY TRACT CARCINOMA

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Little is known about the efficiency of chemotherapy in advanced biliary tract carcinoma. Accordingly, we conducted a phase II study of combined 5FU CI and P in this disease. 28 patients (pts) (13 M/15 F) were included. Median age: 57 years. ECOG performance status: grade (g) 0–1: 79%, g 2: 18%, g 3: 3%. More than 10% weight loss: 36% Primary tumor: gallbladder: 11, Vater ampulla: 5, cholangiocarcinoma: 5, bile ducts: 7. 25 patients had metastases, 2 had local recurrences of their tumor and 1 a nodulary intrahepatic non resectable form. Sites of the metastases: liver: 12 pts, abdominal lymph nodes: 6 pts, lung: 6 pts, peritoneum: 6 pts, mediastinal lymph nodes: 1 pt. *Treatment schedule:* 5FU CI: 1 g/m^2 × 5 days, P: 100 mg/m^2 day 2 repeated every 4 weeks. *Results:* Median number of cycles: 4. 25 pts are evaluable for the tumor response (1 too early, 2 non evaluable), no complete response, partial response (PR): 8, objective response rate = 29% (CI: 12–46%). Minor response: 2, stabilisation: 10, progressive disease: 6. Toxicity was tolerable: g 3 vomiting: 21% of the pts, g 3 mucositis: 4%. Some pts experienced haematological toxicity: g 3 granulocytopenia: 18%, g 4: 4%; no g 3–4 thrombocytopenia. Other toxicities: g 1–2 renal: 3 pts; g 1 neuropathy: 1 pt. No toxic death. Median survival was 10 months and 1-year actuarial survival 33%.

We conclude that this regimen is tolerable and active in patients with advanced biliary tract cancer.

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PALLIATIVE CHEMOTHERAPY IMPROVES SURVIVAL AND QUALITY OF LIFE IN ADVANCED PANCREATIC AND BILIARY CANCER

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In order to estimate any gain in the quantity and quality of life by chemotherapy, 91 patients with pancreatic or biliary cancer were between Jan 1991 and Febr 1995 randomized to either primary chemotherapy in addition to best supportive care or to best supportive care, where chemotherapy was allowed if the supportive measures did not accomplish palliation. Chemotherapy was 5-FU/leucovorin (FLv) or FLy combined with etoposide. The EORTC QLQ C-30 instrument was used to evaluate quality of life.

In the primary chemotherapy group, 16/39 (41%) had improved/prolonged high quality of life for at least 4 months compared to 4/39 (10%), $P < 0.01$) in patients evaluable in March 1995. Overall survival was longer in the primary chemotherapy group (median 6 vs 3 months, $P < 0.01$). Also the quality adjusted survival time was longer (median 5 vs 2 months, $P < 0.05$). In conclusion, this study shows that chemotherapy can add both quantity and quality of life in advanced pancreatic and biliary cancer.

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POSTOPERATIVE COMPLICATIONS AFTER NEOADJUVANT CHEMOTHERAPY FOR GASTRIC ADENOCARCINOMA

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Multimodality treatment may improve the dismal prognosis of far advanced gastric carcinoma. However, toxicity of the chemotherapy itself as well as increased postoperative morbidity may be significant disadvantages. We analyzed our experience with neoadjuvant chemotherapy in terms of postoperative morbidity and mortality.

Between 1986 and 1993 a total of 61 patients underwent preoperative chemotherapy for advanced, irresectable gastric carcinoma. Chemotherapy consisted of EAP (Etoposid, Adriamycin, Cisplatin) in 56 and ELF (Etoposid, Leucovorin, 5-FU) in 5 patients. Overall remission rate was more than 60%, and 46 patients underwent second-look surgery. In 31 cases, extended total gastrectomy was performed (resectability: 67.4%), while in 15 patients explorative laparotomy, combined with multiple

biopsies, was possible. Morbidity of chemotherapy was primarily characterized by myelosuppression (20% grade 4 according to WHO). Postoperative morbidity was 9%, and only one patient died after explorative laparotomy due to pulmonary complications.

In contrast to the reports of preoperative chemotherapy for esophageal carcinoma, the morbidity and mortality after neoadjuvant chemotherapy and second-look surgery in gastric carcinoma is low and even extended resections do not increase the incidence of postoperative complications.

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HYDROXYUREA, FOLINIC ACID, 5FU BOLUS AND INFUSION (HLFP REGIMEN) IN ADVANCED GASTRIC CANCER

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Hydroxyurea (HU) enhances both 5FU and cisplatin. We designed a phase II study in advanced gastric cancer with the HLFP regimen, based on this dual modulation by HU. Regimen consisted in HU 1.5 to 2 g orally days 0, 1 and 2, folinic acid 200 mg/m^2 in 2-h infusion, followed by 5FU 400 mg/m^2 bolus and 600 mg/m^2 22-h infusion days 1 & 2 every 14 days. Cisplatin was administered at 80 mg/m^2 day 3 every 2 courses. 74 consecutive eligible pts were included (12 too early), this report concerns the first 62 pts (53 M/9 F, mean age 59.8 yrs, range 31–78). Initial PS (WHO) was 0 (17 pts), 1 (31) and 2 (14). 7 pts presented a locally advanced disease without melastases. The 55 remaining pts presented peritoneal carcinomatosis (24), liver (21), lymph nodes (32) or lung (8 pts) metastases, associated with local disease in 41. 800 courses were delivered. Toxicity (> WHO gr 2) was: vomiting (7 pts), neutropenia (8), with only 2 febrile neutropenia episodes, anemia (3), diarrhea (2), thrombocytopenia (1), alopecia (1) and mucositis (1). Maximal toxicity was gr 3–4 in 29% of pts. 10/62 pts with non mesurable peritoneal carcinomatosis or local disease were not evaluable for response. 5 CR and 32 PR were observed in 52 mesurable pts (RR: 71.1%, 95% CI: $5.6–83.6%). $6% of pts had a gain of weight, 77% a rapid disappearance of symptoms. Median follow-up time is 18 months. Median progression-free and overall survival were 9 and 11 months respectively. This combination should be tested in phase III trials.

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ENDOCAVITARY IR-192 HD RADIATION AND LASER TREATMENT FOR PALLIATION IN RECTAL CANCER

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Endoscopic laser therapy (ELT) combined with endocavitary IR-192 HDR is performed in rectal cancer with an anatomical non resectability due to advanced tumor stage and in patients which are unsuitable for resection caused by severe concomitant medical illness.

Patients, Methods and Results: 75 patients (48 males, 27 females) have been treated. 63 patients had ELT only using a Nd-Yag Laser system (wavelength 1064 nm, 100 watts, energy density > 1000 j/cm^2) 24 patients (80.5 yrs) had a severe concomitant medical illness which made them unsuitable for surgery (Group I). 39 patients had an advanced locally inoperable tumor (Group II). 12 patients had a combined therapeutic regime with endocavitary IR-192 afterloading (Gammamed II, 7 Gy at 1 cm distance) following prior ELT (Group III). The interval between the following subsequent treatments was 8.4–9.4 weeks in group I and II compared to 11.5 weeks in group III. Complications mainly laser induced bleedings occurred in 7 patients (9%) and could be dealt by subsequently laser coagulation.

Conclusion: The frequency of treatment was governed by the amount of tumor and the length of time the patient lived. The results suggest, that additional endocavitary radiation significantly prolongs the maintainance of normal bowel function as compared to laser alone.

559 POSTER

A NOVEL THERAPY FOR PATIENTS WITH UNRESECTABLE PANCREATIC CARCINOMA

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Over 80% of patients with pancreatic carcinoma are ineligible for surgical resection at initial diagnosis. At our centre, 30 such patients who received palliative surgery alone survived for a mean of 3.3 months. We therefore treated 34 patients with unresectable pancreatic carcinoma with additional locoregional immunotherapy via transplenic and transtumoural infusion of Interleukin 2 and Interferon-γ combined with locoregional transtumoural chemotherapy.

In early 1995, 17 patients (50%) had achieved a CR or PR, including 7 patients who became eligible for tumour resection following treatment. Overall, patients survived for a mean of 11 months (range 3 to 21 + months) with good quality of life. Updated results on this promising therapeutic approach will be presented.

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INFUSIONAL 5-FLUOROURACIL WITH ALPHA INTERFERON AS A PALLIATIVE TREATMENT FOR PATIENTS WITH SYMPTOMATIC MALIGNANT NEUROENDOCRINE TUMOURS

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Inoperable neuroendocrine tumours are frequently slow growing but occasionally patients can present with rapidly progressive metastatic disease and uncontrolled symptoms. Generally, such patients receive only limited benefit and severe toxicity from chemotherapy regimens. 24 patients with rapidly progressive neuroendocrine tumours were treated with a new regimen of continuous infusional 5FU (200 mg/m^2/day) given via a Hickman line for 20 weeks and alpha Interferon (5 megaunits 3 × week). Maintenance Interferon at the same dose was continued after the initial 20 week period. Of 15 patients with carcinoid tumours 7 (47%) had an objective tumour response (median duration 20.5 months) and 5 (33%) had stabilisation of their disease for a period of between 3.5–42 months. 3 early deaths occurred, all in patients with very advanced disease. An improvement in symptoms was reported by 10 (67%) patients. 3 (33%) of 9 patients with non-carcinoid tumours had an objective response (duration 2.5–24.5 months) and 5 (55%) had stable disease for 2.5–16 months. Toxicity was modest: 3 patients experienced severe gastrointestinal toxicity, 1 patient had a severe skin reaction and 8 patients had subclinical haematological toxicity. These results, particularly for carcinoid tumours are encouraging. This regimen seems to be less toxic and may provide better response rates and palliation than other chemotherapeutic options.

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ECF IS A LOW TOXICITY REGIMEN THAT CAN DOWNSTAGE SQUAMOUS OESOPHAGEAL CANCER

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21 patients with inoperable, locally advanced or metastatic squamous oesophageal carcinomas were treated with epirubicin 50 mg/m^2 and cisplatin 60 mg/m^2 3 weekly and a protracted venous infusion of 5-FU to a maximum of 8 cycles. Response was observed in 12/21 (57%). On radiological criteria 1 patient had CR and 8 PR. Endoscopically there were 4 CRs and 6 PRs. Overall median survival from diagnosis was 14 months and from commencing chemotherapy was 8.4 months. The median relapse free period was 7 months. Symptomatic response was seen in 71–100%. Toxicity was acceptable with no toxic deaths. There was 28% CTC grade 3 haematological toxicity and 38% non-haematological grade 3/4 toxicity. 2 patients underwent potentially curative resection. One remains well 3 years after treatment. We conclude that ECF is a regimen of moderate toxicity which is effective at improving symptoms in most patients. There is a 1 year survival from diagnosis of 55% in our study comparing with 18% in surgical cohorts. Furthermore, a small number of patients are adequately downstaged rendering them amenable to potentially curative surgery.