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Percutaneous loco-regional therapy of unresectable hepatocellular carcinoma (HCC) with cisplatin/epinephrine (CDDP/EPI) injectable gel

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Purpose: Patients with unresectable HCC have few, if any, options remaining. We evaluated the effects of CDDP/epi injectable gel, a novel intratumoral chemotherapy, in 58 patients with unresectable HCC.

Methods: Patients (including treatment-naïve, previously resected or relapsed patients) were injected percutaneously with CDDP/epi gel under ultrasound or CT guidance. No more than 3 tumors with a maximum diameter up to 7 cm and total volume up to 200 cubic centimeters were treated. Therapy consisted of up to 10 mL of CDDP epi gel (1 mL contains 4 mg CDDP and 0.1 mg epi) once weekly for 4 weeks with another 4-week cycle at the investigator's discretion. Tumor response and survival comprised the endpoints of the study. Three phase CT scans were used to estimate decrease in 'viable tumor volume' i.e., total treated tumor volume minus total necrotic tumor volume (objective response, greater than 50% decrease sustained for 28 days or longer).

Results: 58 patients (mean age, 65 years) were evaluated for safety and 51 were included in the efficacy analysis. The median baseline tumor volume was 25 cubic centimeters. The median number of treatments ranged from 1 to 8 (median, 4). The median cumulative dose of CDDP was 146 mg. Objective response rate was 53% (27/51): 16 complete responders and 11 partial responders. New tumors were found subsequently in 14/27 responders: of those, 93% had progression only at previously untreated liver sites. The median survival times were 676 days for responders (n = 27) and 357 days for nonresponders (n = 24). The procedure was generally well tolerated with only minor side effects.

Conclusions: CDDP/epi injectable gel may provide an effective treatment for patients with unresectable HCC lesions up to 7 cm in diameter. Results also suggest that efficacy of CDDP/epi gel for local tumor control may be further enhanced by treating emergent tumors or initially treated tumors that progress.

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Randomized phase II study of weekly 24 h infusion of high dose 5-FU ± folinic acid (HD-FU±FA) versus HD-FU/FA/biweekly cisplatin in advanced gastric cancer. EORTC-trial 40953

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Purpose: To investigate the activity and toxicity of high dose infusional 5-FU/± FA with or without biweekly cisplatin as first-line chemotherapy in patients with advanced gastric cancer.

Methods: Histologically confirmed measurable metastatic (M1) or locally advanced (LAD) gastric cancer, age < 75 years, WHO performance status (PS) < 2, no prior chemo- and radiotherapy, adequate organ functions. Treatment: Arm A: FAMTX (prematurely closed), arm B: 5-FU 3.0 g/m2 24 h infusion, weekly x 6 (one cycle), arm C: FA 500 mg/m2 2 h infusion followed by 5-FU 2.6 g/m2 24 h infusion, weekly x 6; arm D: FA 500 mg/m2 2 h infusion followed by 5-FU 2.0 g/m2 24 h infusion, weekly x 6 and cisplatin biweekly 50 mg/m2 1 h infusion.

Results: 153 pts were randomized. Arm A (FAMTX, 7 pts) was prematurely closed after re-evaluation of other trials, arm B (5-FU, 38 pts) was closed after the first interim analysis; arms C and D (54 pts each) were continued. Patients characteristics (arms B, C, D): Median age 59/66/63 years, median PS 1/1/1, LAD (%) 21/9/11, M1 (%) 76/87/87. Median number of cycles (range): Arm B 1 (1-4)/arm C 2 (1-7)/arm D 3 (1-7). Worst toxicity per patient (grade 3 and 4 in %): Leukopenia 3/0/8, thrombocytopenia 0/0/2, diarrhea 3/9/4, nausea 11/4/14, vomiting 5/4/8, neurotoxicity 0/0/8 for arms B, C, D, respectively. Eligibility for response in arm B 33 pts, C 48 pts, and D 43 pts. Confirmed response rate [95%CI]: Arm B 6% [1-20%]/arm C 15% [6-28%]/arm D 37% [23-53%], no change: 30/46/42%, progression of disease: 58/33/12%, respectively. Overall survival [95%CI]): Arm B 7 months [5.7-8.6]/arm C 8.9 months [6.3-11.2]/arm D 9.7 months [7.6-15.8].

Discussion: Infusional HD 5-FU/FA in combination with cisplatin showed high efficacy with a low incidence of severe toxicity and will constitute the control arm of the next EORTC trial of advanced gastric cancer.

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Neoadjuvant herceptin, paclitaxel, cisplatin and radiation for adenocarcinoma of the esophagus: a phase I/II study

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HER-2/neu gene overexpression has been demonstrated in a subset of adenocarcinoma of the esophagus. Herceptin is additive or synergistic with cisplatin, paclitaxel and radiation. We therefore sought to incorporate Herceptin into a neoadjuvant chemoradiation regimen for esophageal cancer. Patients were required to have adenocarcinoma of the esophagus and GE junction and T3, T4 or nodal involvement as staged by CT scan and endoscopic ultrasound. Patients with distant organ metastases were ineligible. HER-2/neu overexpression was determined by immunohistochemistry (DAKO) with 2+ or 3+ classified as positive. Patients with tumors overexpressing HER-2/neu were entered on a phase I/II study of neoadjuvant 50.4 Gy radiation and concurrent weekly paclitaxel (50 mg/m2/week), cisplatin (25 mg/m2/week) and Herceptin for 6 weeks. Herceptin dose level one: 2 mg/kg load followed by 1 mg/kg/week, dose level two: 3 mg/kg then 1.5 mg/kg/week, dose level three: 4 mg/kg then 2 mg/kg/week for 6 weeks. Surgical resection was performed 4-8 weeks after completion of chemoradiation for patients without medical or surgical contraindication; patients could then recieve 1 year of weekly maintenance Herceptin at 2 mg/kg/week. Patients with tumors without HER-2/neu overexpression were treated on a control arm and received the same chemoradiation without Herceptin. Dose limiting toxicities were defined as grade 3 or 4 esophagitis, pneumonitis or cardiac toxicity. Seventeen patients have been entered. Seven overexpressed HER-2/neu (four with 2+, and three with 3+ overexpression). Ten were treated on the control arm. Five of 7 with HER-2/neu overexpression had poorly differentiated tumors with celiac adenopathy, while 2 of 10 patients without HER-2/neu overexpression had poorly differentiated tumors and celiac adenopathy. Thus far Herceptin, paclitaxel, cisplatin and radiation dose levels 1 and 2 have been successfully completed without an increase in toxicity as compared to the control arm. Accrual is continuing at full dose Herceptin to determine the potential role of Herceptin as a component of neoadjuvant and adjuvant therapy in adenocarcinoma of the esophagus.

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An energy and protein dense, high n-3 fatty acid oral supplement promotes weight gain in cancer cachexia

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Introduction: Cachexia is a major factor in the morbidity and mortality of cancer. Pro-inflammatory cytokines and tumour-specific cachectic factors (e.g. proteolysis inducing factor) are thought to contribute to cachexia. N-3 fatty acids, especially eicosapentaenoic acid (EPA), can down- regulate the production or response to such mediators. However, to lay down new tissue and reverse cachexia additional macronutrients are required. In a phase 1 trial increases in weight and lean body mass (LBM) were achieved in patients with pancreatic cancer cachexia taking on average 1.5-2 cans/day of an energy and protein dense formula enriched with n-3 fatty acids and antioxidants [Br J Cancer 1999;81:80].

Methods: This double-blind study compared the same protein and energy dense oral supplement enriched with n-3 fatty acids and antioxidants (experimental:E) with an isocaloric isonitrogenous control supplement (C) for their effect on weight and LBM (bioelectrical impedance analysis). Cachectic patients with pancreatic cancer were asked to consume 1.5-2 cans/d (2 cans:480mls, 32g protein, 620kcal ± 2.2g EPA) for eight weeks. Endpoints were noted at 0, 4 and 8 weeks.

Results: 200 patients (95 E, 105 C) were randomised. Prior to study, patients were losing weight at 3.3kg/month. Overall, patients in both groups (mean D kg, E vs C) became relatively weight stable at 4 (-0.10 vs - 0.13 respectively; NS) and 8 weeks (-0.51 vs -0.75 respectively; NS). However, in view of differences in disease burden between E and C groups, regression analysis was undertaken to explore the relationship between documented intake and study endpoints. The quantity of supplement intake in the E group

correlated with weight (r=0.50, p<0.001) and LBM (r=0.33, p=0.036) and net gain was observed with 1.5-2 cans/d. Similarly, E patients demonstrated positive correlations between increasing total protein intake (meals plus E) and both weight gain (r=0.52, p<0.001) and increased LBM (r=0.46, p=0.004). Such correlations were not observed in C patients. Increased plasma EPA levels were associated with LBM gain (r=0.51, p=0.001).

Conclusion: This study demonstrates that energy and protein dense supplements can stabilise weight in cancer cachexia. Furthermore, net gain of body weight and LBM can be achieved with adequate consumption (1.5-2 cans/d) of such a supplement when it is enriched specifically with n-3 fatty acids and antioxidants.

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Does systemic chemotherapy prior to surgery increase the operative risk of a major hepatectomy ?

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The efficacy of systemic chemotherapy sometimes allows secondary resection of hepatic metastases. The potential hepatic toxicity of anticancer agents may influence the surgical procedure and the post-operative complications of a major hepatectomy. The objective of this study was to assess the impact of preoperative chemotherapy on liver function, the modalities of hepatic surgery, and on postoperative morbidity.

Patients and Methods: Pts without known chronic liver disease, treated by right or left hepatectomy in a curative intent for liver metastasis were analyzed retrospectively. Two groups of pts were compared: 44 non pretreated pts versus 42 pts treated by systemic chemotherapy within 6 months before surgery (median duration of chemotherapy = 6,7 months [extr 1-26]) for the following characteristics using a multivariate analysis: age, gender, body mass index, cancer primary site, number and size of the liver metastasis, existence and duration of preoperative chemotherapy, duration of operative procedure, duration of clamping of the hepatic pedicle, blood loss volume, liver function tests (ASAT, ASAT, ALP, GGT, bilirubine, prothrombin time (PT)) before and just after surgery, existence of postoperative complications and total duration of hospitalization].

Results: The 2 groups were well balanced for all the preoperative characteristics except for age which was statistically different (50 vs 58.7 years, p=0,0002). Preoperative liver function tests, preoperative PT, duration of hepatectomy, duration of clamping of the hepatic pedicle, blood loss volume, postoperative complications, and total duration of hospitalization were not different between the 2 groups. Only the postoperative PT was significantly lower in the pretreated group: 60% versus 49%, p = 0.0002. The duration of preoperative chemotherapy (< 6 mois versus > 6 mois) did not influence those results.

Conclusion: Preoperative systemic chemotherapy, even longer than 6 months, did not seem to have a deleterious effect on the surgical procedure and the post-operative complications of a major hepatectomy for liver metastasis, neither on postoperative morbidity despite macroscopic abnormalities of the liver parenchyma frequently described during surgery. Only the postoperative PT was significantly lower in case of preoperative chemotherapy, but this biologic feature had no impact in terms of post-operative complications.

Lung cancer I

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Cisplatin/gemcitabine (CG) vs cisplatin/gemcitabine/ vinorelbine (CGV) vs sequential doublets of gemcitabine/ vinorelbine followed by ifosfamide/vinorelbine (gv/Iv) in advanced non-small cell lung cancer (NSCLC): final results of a Spanish lung cancer group phase III trial (GEPC/98-02)

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The GECP/98-02 trial was designed to compare a cisplatin-based 3-drug combination vs non-cisplatin sequential doublets vs a cisplatin-based reference regimen in NSCLC. The chemotherapy regimens administered were: Arm A: cisplatin 100 mg/m2 d1 plus gemcitabine 1250 mg/m2 d1&8; Arm B: cisplatin 100 mg/m2 d1 plus gemcitabine 1000 mg/m2 d1&8 plus vinorelbine 25 mg/m2 d1&8 repeated every three weeks; Arm C: gemcitabine 1000 mg/m2 plus vinorelbine 30 mg/m2 d 1&8 for three cycles followed by ifosfamide 3 gr/m2 d1 plus vinorelbine 30 mg/m2 d1&8. Eligibility criteria were measurable stage IV (brain metastases eligible if asymptomatic) or stage IIIB (malignant pleural effusion) NSCLC and PS=0-2. 562 patients (pts) were included between September 1998 and August 2000. Median age 58 (32-76); PS 0-1: 84.2%, PS 2: 15.8%; Stage IV: 79%, Stage IIIB: 21%. The three arms were balanced for the main prognostic features. Response rates were: Arm A: 41%; Arm B: 40%; Arm C: 24.1%. With a follow-up of 12 months median survival was: Arm A: 40.8w (95% CI, 24.5-57.2); Arm B: 34.4 w (95% CI, 27.1-41.7); and Arm C: 44.8 w (95% CI, 31.8-57.9). Toxicities include, in Arms A, B, C, respectively: Grade 3-4 neutropenia 26.3%, 30.1%, and 18.5%, with neutropenic fever in 6.3%, 22.4% and 7.4%; Grade 3-4 thrombocytopenia 18.2%, 23.1% and 7.4%. Nausea and vomiting, neuropathy and renal toxicity were similar in the three arms. Final results will be presented in october 2001.

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Sequential versus concurrent chemo-radiation (RT-CT) in locally advanced non small cell lung cancer (NSCLC): A French randomized phase III trial of GLOT-GFPC (NPC 95-01 study)

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Recent results suggest that concurrent RT-CT is superior to sequential administration in stage III NSCLC. From 10/96 to 05/00, 212 patients (pts) presenting with unresectable locally advanced NSCLC, stage IIIAN2/IIIB, treated in 30 french centers, were randomized in a phase III trial between sequential RT-CT (arm A) and concurrent RT-CT (arm B). The mean age was 57 years (18–70), PS 0 in 110 pts, 1 in 95; stage IIIAN2: 50, stage IIIB: 156, with normal renal, cardiac, hepatic and hematologic function. In arm A pts received induction treatment: Cisplatin (C) 120 mg/m^2 on D 1, 29, 57 and Vinorelbine (V) 30 mg/m^2/d once a week from day 1 to 78 followed by a thoracic radiotherapy (TRT) delivering 66 Gy in 33 fractions, 5 days per week for 6.5 weeks. Pts in arm B, received the same TRT starting on D 1 with 2 concurrent cycles of C 20 mg/m^2/d and Etoposide 50 mg/m^2/d (d1–5 and d29–33), followed by C 80 mg/m^2/d, D78 and 106 and V 30 mg/m^2/d, once a week, D 78 to 127. The total dose of C was equivalent in both arms. Treatment arms were well-matched for baseline characteristics. Survival results are evaluable in 207 pts, toxicity (G3–4 WHO) in 178 pts (Table). Treatment was stopped for toxicity in 18.2% pts (arm A) and 22.3% (arm B). Six toxic deaths occurred in arm A, 10 in arm B.

	Neutropenia	esophagitis	pneumonitis	Median Survival	1-year Survival	2-year Survival
ARM A	88%	1%	1.4%	13.8 mo	56%	23%
ARM B	75%	19%	2.3%	15	56%	35%

This large, randomized study shows an acceptable feasibility, the toxicity of this aggressive regimen reflects the multi-institutional phase III approach; the results, especially in Arm B, compare favorably with other trials, with a clear trend in favor to concurrent RT-CT. An updated analysis will be presented at the meeting.

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Paclitaxel plus carboplatin versus paclitaxel plus gemcitabine in advanced NSCLC. Final results of a randomized phase III study

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Purpose of our multicenter trial was to compare the efficacy and toxicity of the non-platinum combination Paclitaxel (P) plus Carboplatin (C) to the commonly used combination Paclitaxel plus Gemcitabine (G) in advanced inoperable NSCLC.

Patients and Method: Since February 1998, 509 patients were enrolled in the study. Among them, 201 chemotherapy - naïve patients with his-