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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