

785 PUBLICATION Weekly regimen of cisplatin (CDDP), epirubicin(EPI), fluorouracil (5FU) and folinic acid (FA) with G-CSF is active in advanced gastroesophageal(GE) and gastric(G) cancer: results of a phase II study

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Background: We investigated the efficacy of an intensive weekly regimen in patients (pts) with advanced GE and G cancer in terms of response rate and improvement of the resectability rate.

Materials and methods: 28 pts with unresectable and/or metastatic GE or G cancer received a 1 d/week administration of CDDP 40 mg/m², 5-FU 500 mg/m², EPI 35 mg/m², FA 250 mg/m². From day 2 to 5, prophylactic G-CSF was given. After 8 weeks of therapy pts received a restaging of their disease. 16 pts had histologically confirmed diagnosis of G cancer, 12 GE cancer. 12 had locally advanced unresectable disease only; 7 had either primary unresected and metastatic disease (liver 1; nodes 2; peritoneum 2, lung 1; retroperitoneum 1); 5 had metastatic disease (peritoneum 3; retroperitoneum 1; lung 1) and primary tumor resected; 4 pts were treated in an adjuvant setting.

Results: so far 297 cycles have been administered, with a median of 9(2–26)/pt; (at time of writing) all pts were evaluable for toxicity (WHO) and 18 for response (WHO). The overall response rate was 61% with 1 pCR(6%) and 10 PR (55%). A SD was reported in 3 pts (17%) and a PD in 4 (22%). A clinical benefit (ORR+SD+ symptoms relief) was seen in 16/18pts (88%). 7 / 12 pts, with only unresectable disease, underwent surgery and were completely resected with a post-chemo resectability rate of 58.3%. After surgery, 5 out of these 7 pts received the same regimen as adjuvant therapy. G3/4 toxicities were as follows: 43% pts neutropenia, 14% thrombocytopenia, 14% anaemia. Nausea/vomiting(14% G3/4) were the main non-hematologic toxicities. No treatment-related death was reported. The median survival of the whole population was 7.1 months (mo) (95% CI: 1.1–13.1). 4 pts lived >15 mo. The median survival in the responders' group and non responders pts was 12.7 (95% CI: 9.6–15.8) and 3.3 (95% CI:0–8.1) respectively (P001). In the resected pts the median survival was 12.7 mo (95% CI:10.4–15). Median time to progression was 7.1 mo (IC 95%:4.6–9.6) in all evaluable pts and 11.9 mo (IC95%:3–20.7) in resected pts. Median duration of response (14 pts) was 9.4 (IC 95%:3.7–15).

Conclusion: These data confirm the high activity and manageable toxicity of this weekly regimen. Of note is the very good resection rate (58.3%) observed in previously unresectable tumors. These data, although preliminary, suggest that this regimen may be investigated as a neoadjuvant therapy in the treatment of locally advanced G and GE cancer.

786 PUBLICATION Capecitabine and docetaxel in metastatic gastric cancer, an ongoing phase II study

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Introduction: Docetaxel shows promising activity as single agent and in chemotherapy combination regimens against gastric cancer. In a randomized phase II study it has been shown that the dual combination of docetaxel and continuous infusion 5-FU compared to the reference arm epirubicin, cisplatin and 5-FU (ECF) is a well tolerated and very active regimen (Thuss-Patience et. al. JCO 2005). In the current study we replace the 5-FU infusion with oral fluoropyrimidines and evaluate the efficacy of the dual combination capecitabine and docetaxel (CapDoc). Here we report a preliminary analysis of this ongoing prospective multicenter phase II trial.

Methods: *Eligibility:* Metastatic or locally advanced gastro-esophageal junction or gastric adenocarcinoma, ECOG PS 0–2, no prior palliative chemotherapy. *Chemotherapy:* Docetaxel 75 mg/m² d1, capecitabine 2000 mg/m² d1–14, q3w.

Results: 29 patients (pts) are included in this ongoing trial. Data is available for 26 pts. Age: 32–79 years (median 61), M/F 18/8, ECOG PS 0: 6 pts, 1: 18 pts, 2: 2 pts. Number of organs involved by metastases: 1: 4 pts, 2: 7 pts, 3: 10 pts, 4: 4 pts, 5: 1 pts. Measurable disease (RECIST): 26 pts. 128 cycles of chemotherapy are administered so far. *Toxicity:* 23 pts are evaluable for toxicity (worst grade per patient; % of pts): Grade 1/2/3/4: Nausea: 48/9/-/- %, vomiting: 22/17/-/- %, diarrhea: 26/22/13/- %, asthenia: 33/46/4/- %, stomatitis: 9/22/17/- %, alopecia: 22/67/1/- %, fever or infection not neutropenic: 13/26/-/- %, neutropenic fever: -/-/9/- %, nail changes: 22/26/-/- %, atrial fibrillation: 4/9/-/-

%, paresthesia: 9/9/-/- %, dizziness: 22/4/9/- %, hand-foot-syndrome: 30/9/26/- %, leuko-neutropenia: -/30/17/30%, thrombocytopenia: 17/-/-/- %, anemia: 38/13/9/- %, fluid retention: 17/-/-/- %, pulmonary embolism: -/9/4/4, pneumonitis: -/4/-/- %. Dose adjustments of docetaxel had to be made in 38% and of capecitabine in 50% of pts, respectively, during the course of therapy.

Response: 11 of 16 pts with tumor related symptoms showed a subjective improvement of symptoms (69%). 21 pts are so far evaluable for objective response: CR 1 pt, PR 9 pts, NC 9 pts, PD 2 pts, (objective response rate: 47.6%). The median time to tumor progression is 6.0 months. So far only 10% of patients showed primary resistance to CapDoc.

Conclusion: These preliminary data suggest that CapDoc is a well tolerated combination with very promising efficacy

787 PUBLICATION The experience of proton beam therapy for the patient with hepatocellular carcinoma

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Background: Proton beam therapy (PBT) was started from May, 2001 in Hyogo Ion Beam Medical Center (HIBMC). Between May 2001 and April 2004, 27 patients with hepatocellular carcinoma (HCC) were treated with proton beams. This study is to evaluate the efficacy of PBT for the patient with HCC.

Materials and Methods: Eligibility criteria for the patient with HCC in HIBMC as following; solitary tumor, no ascites, performance status of 0 to 2 and no serious comorbidities other than liver cirrhosis. We classified the patient in two groups, Group A; with virus hepatitis, Group B; without virus hepatitis. The back ground of the patients were 23 male / 4 female, median age of 69 years, median size of tumor 39.5 mm in Group A and 19 male / 3 female, median age of 69 years, median size of tumor 71 mm in Group B and 4 male / 1 female. For the planning of PBT, a treatment planning system: FOCUS-M (Mitsubishi Co.) was used by a radiologist. The clinical target volume (CTV) included the gross tumor volume with a 5 to 10 mm margin in all directions by image fusion technique according to CT images and MR images. The planning target volume (PTV) of the initial field encompassed the CTV with a 5 to 8 mm margin. We added because of respiratory synchronization, the caudal margins: 1/3 mm respiratory movements measured by fluoroscopic examination. The accelerated energy of the proton beam is 150 or 190 MeV. The total dosage / fractions were 76 cobalt gray equivalent (GyE) / 20 fractions or 60 GyE / 10 fractions. Median follow-up period was 20 months.

Results: Acute adverse effect (NCI-CTC ver. 2.0) was tolerated in all patients and PBT was completed as planned in all patients. In Group A, 59% of the patients showed the recurrence in the outside of irradiated field but local recurrence was not recognized. In Group B, no patients showed the recurrence in the outside of irradiated field, but only one patient who had maximum tumor size; 119 mm showed the local recurrence. Our results of PBT for the patient with HCC were; 1) the excellent local control, 2) no cure in Group A but the possible cure in Group B. According to this result, we should select the patients before treatment for the purpose of treatment.

788 PUBLICATION Proton beam therapy for hepatocellular carcinoma patients with severe cirrhosis

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Background: Hepatocellular carcinoma (HCC) patients with severe cirrhosis are usually treated with supportive care because of their poor prognosis. However, the survival of severe cirrhotic patients has currently improved due to advanced treatments. We performed a retrospective review to determine the role of proton beam therapy for HCC patients with severe cirrhosis.

Material and methods: Of 197 patients with HCC treated with proton beam therapy between November 1990 and January 2000, 19 patients had Child-Pugh class C cirrhosis. There were 14 men and 5 women and ages at proton beam irradiation ranged from 51 to 69 years (median 61). The hepatic tumors were solitary in 14 patients and multiple in 5, and the tumor size ranged from 25 to 80 mm (median 40) in maximum diameter. No patients had regional lymph node or distant metastasis. A total dose of 50–84 Gy (median 72) in 10–24 fractions was delivered to the tumors.

Results: All tumors but one treated with proton beam therapy were controlled at the median follow-up period of 16 months (range, 3–62). One patient had growth of the irradiated tumor and a new hepatic tumor outside

of the irradiated volume 12 months after treatment. Nine patients had new hepatic tumors, solitary in 1 patient and multiple in 8, exclusively outside the irradiated volume 4–29 months after proton beam therapy. Subsequently, 2 of the 10 patients with new hepatic tumors received second proton beam therapy and the irradiated new tumors were controlled. Consequently, all patients but one died 3–63 months after proton beam therapy; the causes of death were cancer in 6 patients, liver failure in 8, intracranial hemorrhage in 2, and interstitial pneumonitis and trauma in 1 each. The remaining 1 patient was alive with no evidence of disease 33 months after proton beam therapy. The overall and progression-free survival rates were 53% and 47% at 1 year, respectively, and 42% each at 2 years. Performance status and Child-Pugh score were significant prognostic factors for survival. Therapy-related toxicity of grade 3 or more was not observed.

Conclusions: Proton beam therapy for HCC patients with severe cirrhosis was effective and tolerable. It appeared to have achieved good local control and improved survival for the patients.

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PUBLICATION

The FOLFIRI.3 regimen (5-FU/ folinic acid plus CPT-11) in advanced pancreatic carcinoma (PC): results of an AGEO* phase II study

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Background: New therapies are clearly needed to improve the prognosis of patients (pts) with advanced PC. The rationale to develop the FOLFIRI.3 regimen is based on pre-clinical experiments on cell cultures and human tumor xenografts indicating optimal synergy between CPT-11 and fluorouracil when CPT-11 is given before and after 5-FU.

Methods: 35 pts with non pre-treated locally advanced (LA) or metastatic (M) PC were prospectively enrolled. They received a FOLFIRI.3 regimen: CPT-11 90 mg/m² d1 and d3, folinic acid 400 mg/m² on a 2h00 infusion and continuous 5-FU 2000 mg/m² from d1 to d3. Treatment was repeated every two weeks until disease progression or limiting toxicity. Eligibility criteria were: pathologically proven PC, PS (ECOG) 0–2, age ≥18, measurable disease, serum bilirubin <1.5 UNL, adequate hematological and renal functions.

Results: 31 pts are currently evaluable for toxicity and 29 for efficacy. Patient's characteristics were M:18 pts/F:13 pts; LA:7 pts/ M:24 pts; mean age: 58 years (42–77) and initial performance status (WHO) was 0/1/2 in 8/14/9 pts, respectively. No Toxic death occurred. Hematological grade 3–4 toxicities consisted in neutropenia (32%), including two febrile neutropenia. Only 1 grade 3 thrombocytopenia (3%) and anemia (3%) were seen. Grade 3–4 non hematological toxicities were nausea vomiting (35%) and diarrhea (29%). Grade 2 alopecia was observed in 14 pts (45%). Eleven objective responses (35%) were observed, one leading to a surgical resection of the tumor. CA 19.9 decreased (>50%) in 56% of the patients with initially elevated CA 19.9. Nine (29%) stable disease and 9 PD (29%) were observed and 2 pts were not evaluable. With a mean follow-up of 9 months, median progression free and overall survival were 6.7 (CI:5–12.1) and 13.8 months (CI: 5.5–17.9), respectively.

Conclusion: With a 35% overall response rate and manageable toxicity the FOLFIRI.3 regimen seems to be an active regimen in non pre-treated advanced PC pts.

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PUBLICATION

Neoadjuvant chemotherapy can eradicate lymph node micrometastasis for squamous cell carcinomas of the thoracic esophagus

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Background Data: Neoadjuvant chemotherapy has been postulated but not yet proved to eradicate micrometastasis and improve prognosis of patients with advanced squamous cell carcinomas of the thoracic esophagus (ESCC).

Cytokeratin immunohistochemistry of the lymph nodes of ESCC revealed not only Micrometastases (MM) but also Cytokeratin Deposits (CD), which are hyalinized and de-nucleated particles, considered to be the cadaver of carcinoma cells. Successful chemotherapy should convert cancer cells from MM to CD and ESCC patients from systemic disease to regional disease.

Methods: Cytokeratin immunostaining of surgically removed lymph nodes were performed for 100 patients with node-positive ESCC patients,

including 25 patients treated with surgery alone (Surgery Group) and 75 patients undergone neoadjuvant chemotherapy using CDDP, Adriamycin and 5Fu (NACT group). Cytokeratin positive staining was referred to serial hematoxylin-eosin stained sections and classified as metastasis, MM and CD.

Results: CD was less frequently observed in Surgery group than in NACT group (8% vs 47%, $p=0.0024$), while MM tend to be higher in the former (52% vs 40%). MM was a poor prognostic factor in both Surgery and NACT group, while CD was a favorable prognostic factor in NACT group. Effect of NACT on MM were considered to be eradicated: MM(–)/CD(+), persistent: MM(+)/CD(+), no effect: MM(+)/CD(–) and not informative: MM(–)/CD(–). This classification was well correlated with clinical response of main tumor, number of lymph node metastasis in the surgical specimen and post operative survival (3 year survival: 78%, 18%, 0% and 38% respectively). MM(–)/CD(+) was a significant prognostic factor as well as number of lymph node metastasis in the multivariate analysis.

Conclusion: Disappearance of MM and emergence of CD might suggest the eradication of MM by NACT. Clinical benefit of NACT was apparent for these patients with node positive ESCC.

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PUBLICATION

A phase II study of gemcitabine and oxaliplatin in combination with celecoxib in patients with advanced pancreatic tumors overexpressing cyclooxygenase-2 (COX-2)

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Introduction: Overexpression of the COX-2 enzyme has been reported in 90% of patients with advanced pancreatic cancer.

COX-2 contribute to tumor growth through angiogenesis and may be implicated in gemcitabine and oxaliplatin resistance by increasing expression of NK-kB.

Gemcitabine and oxaliplatin (GEMOX) is an active regimen in pancreatic cancer.

The aim of this study is to evaluate the activity and toxicity of GEMOX plus celecoxib in advanced pancreatic cancer.

Patients and methods: A phase II study according to Fleming regimen was used: 43 patients should be included to demonstrate an increase in response rate of 10% in comparison with the response obtained by GEMOX regimen (for an overall response rate of 40%).

Patients with metastatic and/or advanced disease were eligible for the study. All patients should have COX-2 by immunohistochemistry or cytochemistry.

Tumor response was assessed by RECIST criteria with CT imaging every 3 cycles. Ca 19–9, pain assessment and QoL assessment were performed every cycle.

The patients received gemcitabine 1000 mg/mq on day 1 and oxaliplatin 100 mg/mq on day 2 every 14 days. Celecoxib was administered at the dose of 400 mg/mq bid through the entire cycles.

Results: Forty-three patients (median age 57 years) were enrolled of which 15 local and 28 metastatic.

The most common grade 3/4 toxicities included: diarrhea 3/43, nausea and vomiting 4/43, neutropenia 5/43, and 3/43 peripheral neuropathy. A marked decrease in elevated baseline CA19.9 (>50%) was observed in 12 patients (27.9%). 13/43 (30.2%) patients reported an improvement in quality of life. Six patients achieved a partial response (13.9%) and 28 (65.1%) showed a stable disease. The overall median time to progression was 4 months and median survival was 9.5 months.

Conclusion: In conclusion, the addition of celecoxib does not seem to increase the activity even in tumors overexpressing COX-2.

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PUBLICATION

Preliminary results of a phase II trial of dose-intense PEFG (cisplatin, epirubicin, 5-fluorouracil, gemcitabine) in advanced pancreatic adenocarcinoma

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Background: PEFG regimen was superior to standard gemcitabine in a phase III trial (Reni M Lancet Oncol 2005) in advanced pancreatic adenocarcinoma (PA). This regimen was subsequently modified by increasing dose-intensity (Dell'Oro S, Ann Oncol 2004). The aim of the present study was to assess activity and feasibility of dose-intense PEFG regimen.