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Effect of Menatetrenone, a Vitamin K2 Analog, on Recurrence of Hepatocellular Carcinoma After Surgical Resection − Final Results of Randomized Controlled Study

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Background: Since hepatocellular carcinoma (HCC) recurs by intrahepatic metastasis (IM) or multicentric occurrence (MO) after curative surgical resection, it is important to develop treatments for preventing recurrence. A vitamin K2 analog, menatetrenone (MNT) is suggested to have a beneficial effect for suppressing recurrence of HCC. This study was conducted to assess whether MNT suppresses the recurrence of HCC after curative surgical resection.
Materials and Methods: Between January 2005 and September 2009, 101 patients who underwent hepatectomy for the first time were included in the study, and were divided into two groups, Non-MNT group (n = 51); control group that did not take MNT, and MNT group (n = 50); MNT group that were given 45 mg of MNT daily. Primary end-point was recurence of HCC. Disease-free survival rates were compared between the two groups.
Results: There were no significant differences between the two groups in clinical backgrounds [age (67 years vs. 63.5 years), sex (M/F: 23/9 vs. 27/8), viral infection (HBV/HCV/HBV+HCV: 6/34/11 vs. 4/36/10, ICG15: 16.9% vs. 18.3%), PIVKA-II: 106 vs. 66)], operative data [operation time (288 vs. 348 min), blood loss (465 vs. 535 ml), method of operation (Anatomical resection/Non 35/16 vs. 33/17), Max diameter (36 mm vs. 41 mm)], and histological findings [tumour differentiation (well/mod/poorly: 19/29/5 vs. 18/28/4), Edmonson classification (1/2/3: 2/44/5 vs. 2/41/7), vessel invasion (+/−: 17/34 vs. 19/31), IM (+/−: 10/41 vs. 10/40), tumour stage (I/II/III: 8/18/25 vs. 9/17/24)]. During the observation period, recurrence was observed in 33 cases (64.7%) of Non-MNT group and in 28 cases (56.0%) of MNT group ($P = 0.545$), respectively. The cumulative disease-free survival rates at 12, 24, 36, 48, 60 months in Non-MNT group were 70.0%, 48.0%, 23.9%, 23.9%, and 23.9%, respectively, and those in MNT group were 79.4%, 63.1%, 56.4%, 36.3%, and 18.1%, respectively, ($P = 0.111$).
Conclusions: MNT appears to suppress late recurrence of HCC or MO, however, it does not show statistically significant suppressive effect against recurrence of HCC after surgical resection.

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Phase I Study of Gemcitabine as a Fixed Dose Rate Infusion and S-1 Combination Therapy (FGS) in Gemcitabine-refractory Biliary Tract Cancer (BTC) Patients

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Background: Gemcitabine (GEM) contained regimen is often used as the first line chemotherapy for advanced BTC in Japan. But there is no standard regimen for treatment after disease progression. For GEM-refractory BTC, S-1 monotherapy was found to exhibit modest efficacy in a previous phase II trial [response rate: 7.5%, a median progression-free survival: 2.5 months, and a median overall survival time: 7.5 months (E. Suzuki et al, ASCO 2010, #4145)]. This phase I study was conducted to confirm to determine the recommended dose of FGS therapy based on the frequency of its dose-limiting toxicity (DLT) in patients with GEM-refractory BTC.
Materials and Methods: GEM-refractory patients with histologically or cytologically proven unresectable or metastatic BTC were enrolled. GEM was given intravenously (10 mg/m^2/min) on day 1, and S-1 was given orally at a dose of 40 mg/m^2 twice daily from day 1 to day 7, repeated every 2 weeks until disease progression. Patients were scheduled to receive GEM (mg/m^2/week) and S-1 (mg/m^2/day) at three dose levels: 1200/80 (level 1), 1000/80 (level 0), and 800/80 (level-1). DLT was defined as grade 4 hematological toxicities and grade 3 or over non-hematological toxicities during the first 2 courses.
Results: Thirteen patients were enrolled between September 2008 and September 2010. The DLTs were observed in four of six patients at level 1 (four patients: grade 4 neutropenia, and one patient: grade 3 rash), and in two of six patients at level 0 (one patient: grade 4 neutropenia, and one patient grade 3 fatigue). The maximum tolerated dose was level 0. Among evaluable 13 patients, one patient achieved partial response, and seven of thirteen patients achieved stable disease.
Conclusion: The recommended dose of FGS in GEM-refractory metastatic BTC was GEM 1000 mg/m^2 over 100 min on day 1, and S-1 at a dose of 40 mg/m^2 twice daily from day 1 to day 7, repeated every 2 weeks. This regimen was well tolerated, but further evaluation in terms of efficacy will be warranted.

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A Randomized Phase II Study of Gemcitabine (GEM) Plus S-1 Combination Chemotherapy Versus GEM Monotherapy in Patients (pts) With Advanced Biliary Tract Cancer (BTC) − GS-COMBI Study

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Background: Our previous phase II study demonstrated that GEM/S-1 combination chemotherapy was tolerable and showed good efficacy in pts with advanced BTC (Sasaki et al, Cancer Chemother Pharmacol 2010). This randomized phase II study compared GEM/S-1 combination chemotherapy and GEM monotherapy in pts with advanced BTC (UMIN000001705). The interim analysis was reported at 2011 ASCO-GI Cancer Symposium Meeting (Abstract 250).
Materials and Methods: Pts with advanced BTC who had at least one measurable lesion were randomized into two groups. GEM/S-1: GEM 1,000 mg/m^2 (day 1, 15) and S-1 80 mg/m^2 (day 1−14) repeated every 4 weeks. GEM: GEM 1,000 mg/m^2 (day 1, 8, 15) repeated every 4 weeks. Treatment was continued until disease progression. The primary endpoint was objective response according to RECIST version 1.0.
Results: From November 2008 to March 2010, 62 pts were enrolled from 13 institutions. Thirty patients were allocated to GEM/S-1 combination chemotherapy and thirty-two patients were allocated to GEM monotherapy. Patient characteristics of GEM/S-1 combination chemotherapy were: Median age 68 (range 47−83); Male/Female 16/14; Performance status 0/1−2 18/12; Gallbladder/Intra-hepatic bile duct/Extra-hepatic bile duct 16/8/6; Locally advanced/Metastatic/Recurrent 7/20/3. Patient characteristics of GEM monotherapy were: Median age 75 (range 55−86); Male/Female 20/12; Performance status 0/1−2 18/14; Gallbladder/Intra-hepatic bile duct/Extra-hepatic bile duct 14/8/10; Locally advanced/Metastatic/Recurrent 7/21/4. All baseline characteristics were comparable between two groups. Response rates of GEM/S-1 and GEM were 20.0% and 9.4%, respectively. The median time-to-progressions of GEM/S-1 and GEM were 5.6 months and 4.1 months, respectively.
Conclusions: GEM/S-1 combination chemotherapy is more active than GEM monotherapy in pts with advanced BTC. Updated data will be presented at the meeting.

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A Phase II Study of Epigenetic Therapy Using Belinostat for Patients With Unresectable Hepatocellular Carcinoma − a Multicenter Study of the Mayo Phase 2 Consortium (P2C) and the Cancer Therapeutics Research Group (CTRG)

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Background: Patients with unresectable hepatocellular carcinoma (HCC) carry a dismal prognosis. Epigenetic aberrations have been reported in HCC. Belinostat is a novel, low molecular weight, histone deacetylase inhibitor. The purpose of this study was to assess the efficacy of epigenetic therapy with belinostat in patients with unresectable HCC.
Patients and Methods: Major eligibility criteria included histologically confirmed HCC that is not amenable to curative treatment; ECOG $\leqslant 2$; adequate organs functions. The belinostat dose used was 1400 mg/m^2/day i.v. on day 1−5 every 3 weeks, as defined in a prior phase I study. The primary endpoint was progression-free survival (PFS) and the secondary endpoints were response rate (RR) according to RECIST and overall survival (OS). Adverse events were reported using CTCAE v3.

Results: 42 patients were accrued. Prior therapies included surgery (36%), radiofrequency ablation (7%), transarterial therapy (50%); prior systemic therapies (38%). Median follow-up was 20.0 months. Median cycle no. was 2 (range: 1−12). The PR and SD rate was 2.4% (1/42) and 45.2% (19/42) respectively. Median PFS was 2.64 months (95%C.I. 1.55–3.17) and OS was 6.60 months (95%C.I. 4.53–11.60). Grade ⩾3 toxicities that occurred in ⩾5% included: 4 (9.5%) abdominal pain, 4 (9.5%) hyperbilirubinemia, 4 (9.5%) raised alanine transaminase, 3 (7.1%) anemia, 3 (7.1%) vomiting, 2 (4.8%) distension, 2 (4.8%) hemorrhage, 2 (4.8%) prolonged QTc and 2 (4.8%) dehydration. One patient developed sudden death but it was determined not likely due to study medication.
Conclusions: With the majority of patients having failed prior therapy, epigenetic therapy with belinostat demonstrates tumour stabilization and is generally well-tolerated. Further studies including combinational study with other agents is warranted.
Acknowledgement: The study was sponsored by the Division of Cancer Treatment and Diagnosis, National Cancer Institute, U.S.A, and its collaborator TopoTarget.

6598 POSTER

Combination of Capecitabine and Oxaliplatin (CAPOX) is an Effective Option for the Treatment of Neuroendocrine Tumours (NET)

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Background: The role of chemotherapy in advanced NET is questionable. While carcinoid tumours are resistant to cytotoxic chemotherapy, streptozocin-based regimens are acceptable for treatment of pancreatic NET. Recently, it was demonstrated that Everolimus and Sunitinib have activity in low and intermediate grade advanced pancreatic NET, with a median progression free survival of 11 months and partial response rate (PR) between 5% and 9%. The aim of this retrospective analysis was to evaluate the activity of the CAPOX combination in treating NET in an unselected population.
Material and Methods: We retrospectively evaluated 24 patients diagnosed with metastatic NET treated with CAPOX at two Brazilian institutes that are reference in cancer care.
Results: Median age at diagnosis was 56 years (range 23 to 73), 71% were male, 71% had ECOG 0 or 1, 63% tumours were primary from pancreas, 17% lung, 8% small intestine, 4% rectum, 8% unknown primary and 29% were functional. According to WHO classification criteria, 25% were grade 1, 37.5% grade 2 and 37.5% grade 3. Local treatments as embolization, chemoembolization or hepatic surgery were performed in 29% of patients. Most patients received CAPOX in 2nd line (1st to 4th line), with a median of 6 cycles. 29% of patients had PR by RECIST criteria. No association was observed between response rate and tumour grade, primary site or line of CAPOX. The median time to progression was 9.8 months and median time to treatment failure was 12.1 months. 75% patients remain alive, so median overall survival was not reached. Toxicity grade 3 was observed in 21% of patients, mainly neuropathy and hand-foot syndrome. Dose reduction was necessary in 33% patients, but only 1 discontinued treatment due to toxicity.
Conclusions: The CAPOX combination is active in an unselected population with metastatic NET and may be a good platform for the incorporation of the newer molecular targeted agents being investigated for the treatment of NET.

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Phase II Trial of Gemcitabine and an Omega-3 Rich Lipid Infusion in Advanced Pancreatic Cancer

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Background: Omega-3 fatty acids (n-3FA) have been shown to reduce cell proliferation and viability and induce apoptosis in pancreatic cancer cell lines and xenograft models. Oral preparations in human trials have shown mixed results but display a trend towards stabilisation of tumour-related cachexia and improved quality of life. Poor compliance and bioavailability of oral preparations is a recurrent problem. Novel biological agents which significantly improve survival, radiological response, quality of life (QOL) and tumour cachexia are currently unavailable.
Materials and Methods: A phase II single-arm (Simon's two-stage design) trial of gemcitabine (1000 mg/m3 weekly for 3 weeks followed by a rest week) plus intravenous n-3FA rich infusion (up to 100g, Lipidem ®, BBraun Melsungen) was administered to patients with histologically proven locally advanced or metastatic pancreatic cancer. Inclusion criteria were identical for single-agent gemcitabine. Historical data from a matched cohort of 24 patients receiving single-agent gemcitabine prior to trial initiation were obtained. Tumour assessment by RECIST criteria on CT was performed every 2 cycles. CA19-9 at baseline and every 2 cycles was measured. Primary outcome measure was objective response rate, with secondary outcome measures of overall and progression free survival, changes in QOL, weight and pain scores. Adverse events were recorded by CTCAE V4.0 criteria. The trial is registered with clinicaltrials.gov: NCT01019382 and sponsored by University Hospitals of Leicester.
Results: Twenty-six patients underwent 76 cycles (median = 3) of treatment, with 20 evaluable for response. 11/20 (55%) had liver metastases (LM) and 18/26 (69%) were male. Partial response (PR) rate was 3/20 (15%) overall and LM PR rate was 6/11 (55%). Disease control rate (best response of Stable Disease+PR) was significantly better in the n-3FA+gemcitabine group than historical controls: 15/20 vs 6/17 ($p = 0.002$). Mean change in overall target lesion and LM diameters was −12% (95% CI −2 to −23%) and −19% (95% CI −47 to +9%) respectively. Mean peak change in CA19-9 was −48% (95% CI −21 to −76%). Median overall survival and progression free survival (experimental group vs historical controls) was 6.0 vs 4.1 months ($p = 0.44$) and 3.6 vs 2.3 months ($p = 0.02$) respectively. Grade 3 or 4 thrombocytopaenia and neutropaenia rates were 16% and 8% respectively.
Conclusions: n-3FA rich lipid infusions in combination with gemcitabine may have activity in advanced pancreatic cancer. A phase III double blind randomised controlled trial is planned to assess this activity further.

6600 POSTER

A Randomized, Multicenter, Open-label, Phase III Study to Compare the Efficacy and Safety of Capecitabine Plus Paclitaxel Followed by Capecitabine Maintenance (PX-X) With Capecitabine Plus Cisplatin (XP) as a First-line Chemotherapy for Recurrent or Metastatic Gastric Cancer (PAC-C Study)

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Background: Our previous open label, phase II, multi-center prospective study (ML20312) has shown the efficacy and safety of paclitaxel plus capecitabine with subsequent capecitabine maintenance (PX-X) as first-line treatment for advanced gastric cancer (AGC). In this randomized, phase III, multi-center prospective study (PAC-C study), we would like to confirm the efficacy and safety of PX-X in treatment of AGC by comparing it with that of standard regimen of cisplatin/capecitabine (XP).
Methods: The study is registered with ClinicalTrials.gov ID of NCT01015339. Patients with previously untreated metastatic or recurrent gastric adenocarcinoma, signed informed consent, evaluable lesion(s) by RECIST 1.0, KPS⩾70 and adequate organ functions are eligible. No prior taxanes, or more than 2 cycles of capecitabine, or more than 300 mg/m^2 total dose of cisplatin is allowed in adjuvant or neoadjuvant chemotherapy. All eligible patients are randomized to 2 arms, PX-X or XP. In PX-X arm, Paclitaxel is given with 80 mg/m^2 for 3-hour infusion on day 1, 8, capecitabine is given with 1000 mg/m^2 twice daily day 1−14 (every 3 weeks) until progression/intolerance, or maximum 4 cycles. Subsequently, the patients with no progression were given maintenance therapy of capecitabine monotherapy with same dose/schedule as the combination therapy until progression or intolerance. In XP arm, cisplatin is given with 80 mg/m^2 for 2-hour infusion on day 1, capecitabine is given same to PX-X arm, until progression/intolerance, or maximum 6 cycles. The primary endpoint is progression free survival (PFS), and secondary endpoints are Disease Control (DCR), overall response Rate (ORR), overall survival (OS), safety, quality of life (QoL) and biomarker detection of TP, DPD, TS and β-tubulin. Our predicted PFS in PX-X arm is 6.5 months, the PFS in XP arm is 4.5 months according to China clinical practice in recurrent/metastatic gastric cancer treatment. 160 patients per arm was needed to provide an 80% chance of observing a difference of 2 months in PFS at significance level of 0.05. The patients will be followed up for 1 year after treatment end of last patient or death occurred in 75% patients. The protocol was amended in April, 2011 to include an interim safety analysis at the time of 160 patients enrolled.