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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.