(13p/4p: 5Fu/xeloda w or w/o platinum compounds). From these, 43p were evaluable for response, 33p had SD and 10p had PD. PFS for 2nd line CT was 6 mo (95% CI 4.1−7.9). PFS for FU based regimen 2nd line was 3.2 mo (95% CI 0.2−6.9) and for Gem based regimen 2nd line: 6.1 mo (95% CI 3.1−9) p = 0.09. OS, for all 96pts was 9.9 mo (95% CI 8.8−11) and for 46p with 2nd line CT was 13.6 mo (95% CI 11.2−16) with better OS for pts with FU based 1st line and Gem in 2nd line: 19 mo (95% CI 8.9−2) vs 13.2 mo (95% CI 12–14.4) p < 0.001 (s).
Conclusions: Our results indicate that the FU based CT in 1st line and Gem in 2nd line gave a better survival than the opposite, therefore this nonrandomized trial showed that this regimens' order could be relevant and necessitates a phase III trial randomized to check the impact of CT lines sequence in advanced BTC.

6581 POSTER

Phase II Study of RAD001 Monotherapy in Patients With Non-functioning Carcinoid or Pheochromocytoma/Paraganglioma

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Background: To examine the efficacy and toxicity of RAD001 in patients with non-functioning carcinoid or pheochromocytoma/paragaglioma.
Methods: Patients with histologically confirmed non-functioning carcinoid or pheochoromocytoma/paraganglioma, with at least one measurable lesion were eligible for the study. Other eligibility criteria included; documented disease progression according to RECIST criteria within12 months prior to the entry, not amenable to curative-intent treatment, ECOG PS 0 or 1, and adequate organ function. RAD001 was given at a dose of 10 mg daily every 4 weeks. Response was assessed according to RECIST (v 1.0) every 8 weeks. Primary end-point was 4-month progression-free survival rate. Hypothesis was that 4m-PFSR would be improved from 50% to 65%.
Results: A total of 34 patients were enrolled into this study. 27 patients had nonfunctioning carcinoid, 5 pheochromocytoma, and 2 paraganglioma. Thirty-three patients were evaluable for response. Partial responses were achieved in 3 patients. Twenty-eight patients had stable disease and 3 progressive disease. Response rate and overall disease control rate was 9.0% and 93.9%, respectively. The median PFS was 15.3 months (95% CI, 4.6–26.0 months) and 4-month PFSR was 78%. Mean treatment duration was 9.1 months (range 1.1–30.6 months).
In case of carcinoid, 3 patients had PR and the others had SD (RR 11.1%, DCR 100%), with a median PFS of 17.1 months (95% CI, 11.1–23.0 months) and 4-month PFSR of 90.0%. Twenty-one patients (80.8%) showed tumour shrinkage.
In case of pheochromocytoma/paraganglioma, 5 patients showed SD, 2 PD. Meidan PFS was 3.8 months (95% CI, 0.5−7.0 months) and 4-month PFSR 42.9%. Two patients with paraganglioma showed tumour shrinkage. The most common AEs (all grades) were rash (29.4%), diarrhea (26.5%), and stomatitis (17.6%). The major Gr 3/4 toxicities were thrombocytopenia (14.7%), hyperglycemia (5.9%), stomatitis (5.9%) and anemia (5.9%).
Conclusions: RAD001 showed very promising efficacy (11% PR and 100% disease control rate) in unresectable non-functioning carcinoid and good tolerability in the entire study population. However, RAD001 monotherapy in pheochromocytoma/paraganglioma requires further larger investigation in its efficacy.
Clinicaltrial.gov: NCT01152827

6582 POSTER

Sorafenib Dose Ramp-up Scheme for the Treatment of Advanced Hepatocellular Carcinoma

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Background: Sorafenib is the only drug to date that has shown survival benefit in hepatocellular carcinoma (HCC). Many patients, however, require sorafenib discontinuation or dose reduction due to adverse events (AEs), suggesting the need for a treatment strategy avoids AEs. We have applied a sorafenib dose ramp-up scheme for this purpose.
Materials and Methods: Of 267 patients with HCC treated with sorafenib as first line therapy, 25 had risk factors for increased AEs; advanced liver cirrhosis, post liver transplantation status, or neutropenia and/or thrombocytopenia. These 25 patients were started on a reduced dose of sorafenib, which was increased to the standard dosage according to tolerance. Efficacy and safety were compared in patients treated according to the ramp-up and standard non ramp-up schemes.
Results: Patients were divided into three groups; non ramp-up without risk factors, non ramp-up with risk factors, and ramp-up. There were no significant differences in disease control rate and time to progression among the 3 groups. Grade 3/4 AEs were more frequent in the non ramp-up groups without significant difference. The incidence rates of sorafenib discontinuation and dose reduction related to AEs were lower in the ramp-up group. Sorafenib was ramped up to standard dose in 16 patients (64.0%), and the sorafenib dose intensity in this group did not differ from that in the non ramp-up groups.
Conclusions: Sorafenib ramp-up may be an option in patients at higher risk of AEs or with poorer tolerance. Future trials should test this dosage scheme in patients without any risk factors.

6583 POSTER

Phase I Dose-finding Study of Epirubicin, Oxaliplatin and S-1 (EOS) in Patients With Previously Untreated Advanced Gastric Cancer (AGC)

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Purpose: To determine the recommended dose (RD) and dose-limiting toxicity (DLT) of EOS combination in patients with previously untreated AGC.
Materials and Methods: Previously untreated patients with histologically proven metastatic or recurrent AGC and ECOG performance status 0−2 were enrolled. Fixed dose of epirubicin (50 mg/m^2) and oxaliplatin (130 mg/m^2) was administered i.v. on day 1. The dose of S-1 was escalated as following schedule: Level I: 30 mg/m^2, Level II: 40 mg/m^2, Level III: 45 mg/m^2, Level IV: 50 mg/m^2. S-1 was administered orally twice a day on days 1−14. Each cycle was repeated every 21 days. DLTs were evaluated during the first two cycles of treatment.
Results: Nineteen patients were enrolled: 13 patients in dose-escalation phase and 6 patients in the extension at the RD. Median age was 53 years (range, 40−71 years). At dose level II, 1 DLT (grade 4 neutropenia lasting more than 5 days) was found among 6 patients while at dose level III, 2 DLTs (grade 3 diarrhea and nausea) were observed among 4 patients. Therefore, the dose level II was determined as RD. Cumulative (all cycles) grade 3/4 toxicity included neuropenia (58%), leucopenia (32%), thrombocytopenia (11%), diarrhea (11%), and nausea (5%). Of 13 patients with measurable lesions, 8 achieved partial response and 3 showed stable diseases, and the objective response rate was 62% (95% confidence interval [CI], 36−88%). The median progression-free survival was 6.5 months (95% CI, 4.7−8.2 months).
Conclusions: The RD of the EOS regimen in patients with previously untreated AGC was epirubicin 50 mg/m^2 and oxaliplatin 130 mg/m^2 on day 1 and S-1 40 mg/m^2 twice a day on days 1−14 of every 21-day cycle. This regimen seems to have promising preliminary activity.

6584 POSTER

Epirubicin, Oxaliplatin & Capecitabine Combination for Untreated Advanced Esophagogastric Cancer

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Background: Gastric and esophageal cancers are the fourth most common causes of cancer-related deaths in Bangladesh. The regimen containing epirubicin, cisplatin, and infused fluorouracil (ECF) is used as a standard therapy for untreated advanced esophagogastric cancer in Bangladesh. Combination of epirubicin, capecitabine and oxaliplatin has shown significant results. To confirm we evaluated oxaliplatin and capecitabine as alternatives to infused cisplatin and fluorouracil, respectively for the treatment of untreated advanced esophagogastric cancer in Bangladesh perspective.
Methods: We randomly assigned 122 patients to receive triplet therapy with epirubicin and cisplatin plus either fluorouracil (ECF) or capecitabine (ECX) or triplet therapy with epirubicin and oxaliplatin plus either fluorouracil (EOF) or capecitabine (EOX). The primary end point was overall survival for

the triplet therapies containing capecitabine as compared with fluorouracil and for those containing oxaliplatin as compared with cisplatin.
Results: The hazard ratio for death in the capecitabine group was 0.88 (95% confidence interval [CI], 0.81 to 0.98) in comparison to fluorouracil and the hazard ratio for the oxaliplatin group was 0.93 (95% CI, 0.82 to 1.10) in comparison to cisplatin. Median survival times in the ECF, ECX, EOF, and EOX groups were 9.2 months, 9.3 months, 9.1 months, and 11.5 months, respectively; survival rates at 1 year were 36.6%, 38.9%, 40.1%, and 47.5%, respectively. Overall survival was longer with EOX than with ECF. Toxic effects of capecitabine and fluorouracil were almost similar. As compared with cisplatin, oxaliplatin was associated with lower incidences of grade 3 or 4 neutropenia, alopecia, renal toxicity but with slightly higher incidences of neuropathy.
Conclusions: In our experience, oxaliplatin and capecitabine are more effective than cisplatin and fluorouracil, respectively, in patients with previously untreated esophagogastric cancer.

6585 POSTER

Phase II Study of Low-dose Everolimus Plus Weekly Cisplatin and 24-hour Infusion of High-dose 5-fluorouracil and Leucovorin for First-line Treatment of Metastatic or Recurrent Gastric Cancers

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Background: Cisplatin-HDFL regimen, using weekly 24-hour infusions of cisplatin and high-dose 5-fluorouracil (5-FU) and leucovorin, is commonly used in Taiwan for patients with advanced gastric cancer (GC), showing a satisfactory response rate with favourable toxicity profiles [J Clin Oncol 1994; 12(4): 875; J Clin Oncol (Suppl) 2006; 24(18S): A14063]. Everolimus (RAD001), a derivative of rapamycin, is an orally bioavailable mTOR inhibitor. We have demonstrated that low-dose everolimus (in concentration of 0.5 to 5.0 nM) has a chemosensitizing effect for cisplatin and 5-FU in GC cells [Proc Am Assoc Cancer Res 2007; 48: A4043].
Methods: All patients had pathologically confirmed metastatic/recurrent chemonaive GC, at least 1 measurable lesion, a fasting serum triglyceride level >70 mg/dl, ECOG PS 0/1/2, adequate hepatic, renal, and bone marrow functions. Everolimus 10 mg PO on days 1, 8, and 15; and was given concurrently with the initiation of chemotherapy. Cisplatin 35 mg/m^2 was given as a 24h infusion, days 1 and 8. A 24h infusion of 5-FU 2,000 mg/m^2 and leucovorin 300 mg/m^2 (HDFL) was given on days 1, 8, and 15. Cycles were repeated every 28 days, and response evaluation was performed every 2 cycles & at the end of protocol treatment. The primary end-point was confirmed objective response rate (RR) by RECIST.
Results: Between Mar. 2008 and Mar. 2011, 30 patients (M:15, F:15) with a median age of 55 (33−71) were enrolled and evaluable for response assessment. The overall RR was 60.0% (41−77%, 95% C.I.) with one CR and 17 PRs. Among a total of 201 cycles (median: 6, range: 1 to 25 cycles) given, Gr3/4 neutropenia, infection, nausea, and vomiting developed in 4.0%, 2.0%, 2.5%, and 2.5% of 201 cycles, respectively (data cut-off date: Mar. 31, 2011). None of them developed Gr3/4 stomatitis, diarrhea, or skin rash. Gastrointestinal and skin toxicities were generally mild with addition of low-dose weekly everolimus to cisplatin-HDFL. Gr1/2 nausea, vomiting, stomatitis, and diarrhea developed in 18.9%, 15.4%, 12.9%, and 6.0% of 201 cycles, respectively. Gr1/2 skin rash and Gr1 hand-foot syndrome developed in 7.0% and 30.8% of 201 cycles, respectively. One patient has developed reversible HDFL-related hyperammonemic encephalopathy. Median PFS (range: 1.2 to 24.3+ months) and OS (range: 1.8 to 24.3+ months) was 7.2 and 12.6 months, respectively.
Conclusions: Low-dose everolimus plus infusional cisplatin-HDFL is a highly effective regimen with low toxicity and favorable survival in first-line treatment of metastatic or recurrent GC. Addition of low-dose weekly everolimus to infusional cisplatin and HDFL did not cause any additional gastrointestinal toxicity.

6586 POSTER

Metronomic Combination Chemotherapy With S-1 and Biweekly Paclitaxel for Advanced Gastric Cancer

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Background: The recent phase III chemotherapy trials for gastric cancer have showed the median survival time is prolonged up to 13 months by SPIRITS trial (addition of cisplatin to S-1)and the START trial (addition of docetaxel to S-1).
However, the gastric cancer patients cannot often keep enough oral intakes by primary disease itself. The adverse drug reactions of chemotherapy more strongly develop, and the continuation of the chemotherapy becomes often difficult.
To get the better prognosis, we think the chemotherapy with few side effects and high treatment feasibility is demanded. The metronomic combination chemotherapy with S1 and Paxlitaxel (PTX) has been treated for advanced gastric cancer at our hospital. We aimed to evaluate the efficacy of this treatment.
Materials and Methods: Fifty two advanced gastric cancer patients were examined. S-1 at 80 mg/m^2 daily was given orally, twice daily for consecutive 7 days, and PTX at 80 mg/m^2 was administered by intravenous drip infusion on day 1, followed by a 1-week rest period. This treatment was repeated every 2 weeks (one cycle each) until disease progression or unacceptable toxicity was seen.
Results: A total of 1146 cycles were administered, with a median of 22 cycles (range: 5−76) per patient. Three patients had complete responses and 23 patients had partial responses. Six patients kept in stable desese. The response rate was 61.5% (32/52) and the median time to treatment failure was 9.8 months. The median over all survival time was 21.9 months. The one-year survival rate was 78.8%. The median survival times according to Performance Status (PS) were 25.5 months in PS0, 19.3 months in PS1, and 9.3 months in PS2, respectively. The major adverse reactions were leucopenia and neutropenia. Adverse reactions as gastrointestinal symptoms were few.
Conclusion: The metronomic combination of S-1 and biweekly PTX therapy for advanced gastric cancer appears to be highly efficacious and safe with high treatment continuity and QOL.

6587 POSTER

A Phase 1b, Open-Label Study to Evaluate the Safety of Ganitumab (AMG 479) in Combination With Gemcitabine as First-line Therapy in Patients With Metastatic Pancreatic Cancer

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Background: Ganitumab (AMG 479) is a fully human monoclonal antibody against human IGF-1R that inhibits the survival and proliferative signals driven by IGF-1 and -2. This is the first study to assess the safety and tolerability of ganitumab 20 mg/kg in combination with gemcitabine in Japanese patients (pts) with metastatic pancreatic cancer (mPC).
Material and Methods: Six previously untreated mPC pts were to receive gemcitabine at 1,000 mg/m^2 on days 1, 8 and 15 followed by ganitumab at 20 mg/kg on days 1 and 15, every 28 days cycle. Dose-limiting toxicity (DLT) was assessed in cycle 1.
Results: Six pts [5 male; median age 62 (range, 43 to 69), ECOG PS 0−1] were enrolled, and received >1 dose of ganitumab combined with gemcitabine. The median number of doses administered of ganitumab was 4.5 (range: 3 to 7) and gemcitabine was 6 (range: 4 to 10). The median relative dose intensity of ganitumab was 1.0 (range, 0.6 to 1.0) and gemcitabine was 0.93 (range, 0.7 to 1.0). One pt had a DLT of grade 3 neutropenia with fever >38.5ºC. One pt experienced treatment related serious adverse event of grade 3 nausea and grade 3 decreased appetite in post DLT evaluation period. All 6 pts experienced treatment-emergent adverse events (AEs); the grade $\geqslant$ 3 AEs were neutropenia (4 pts), thrombocytopenia (2), leucopenia (1), lymphopenia (1), nausea (1), blood sodium decreased (1), and decreased appetite (1). Four pts experienced infusion reactions. No developing anti-ganitumab antibodies were detected. Preliminary pharmacokinetic (PK) analysis for ganitumab indicated mean C_{max} and AUC_{0-336} were 309 μg/mL and 1299 day·μg/mL, respectively. Effect of ganitumab on gemcitabine PK was not clearly observed.
Conclusions: Ganitumab 20 mg/kg in combination with gemcitabine 1,000 mg/m^2 (which is one regimen in the phase 3 GAMMA (gemcitabine and AMG 479 in metastatic adenocarcinoma of the pancreas) study) was tolerable for pts with mPC. Updated information will be presented at the meeting.