6578 POSTER

Safety and Feasibility of Adjuvant Chemotherapy With S-1 in Korean Patients With Curatively Resected Advanced Gastric Cancer

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Background: Adjuvant chemotherapy with S-1 has been proven effective for patients with curatively resected advanced gastric cancer with D2 lymph node dissection in Japan. We assessed the safety and feasibility of adjuvant S-1 chemotherapy in Korean patients with stage II, III or IV(M0) gastric cancer.
Material and Methods: A total of 305 patients with stage II, III or IV(M0) gastric cancer received adjuvant S-1 chemotherapy following curative gastrectomy with D2 lymph node dissection in Asan Medical Center between October 2007 and December 2009. Adjuvant chemotherapy with S-1 was started 3−6 weeks after surgery and it was administered orally twice daily at the dose of 40 mg/m^2 for 4 weeks followed by 2 weeks of rest, every 6 weeks 8 times for 1 year. We retrospectively reviewed the medical records of the patients and evaluated the safety and feasibility of adjuvant S-1 chemotherapy in Korean patients.
Results: Among the 305 patients, 248 (81.3%) and 198 (64.9%) patients completed 4 and 8 cycles of adjuvant chemotherapy, respectively. The most common reasons for discontinuation of treatment were adverse event (43.9%) and recurrence (26.2%). Among the 305 patients, 75 (24.6%) patients required dose reduction because of toxicities. The most common grade 3/4 toxicities were neutropenia (12.8%), diarrhea (5.3%), abdominal pain (3.8%), and anemia (3.3%). Multivariate analysis showed that total gastrectomy (H.R. 2.50; 95% C.I. 1.32–4.72, p = 0.005) and female gender (H.R. 1.95; 95% C.I. 1.03–3.66, p = 0.039) were independent risk factors for grade 3/4 hematologic toxicities, and old age (>65 years) (H.R. 2.92; 95% C.I. 1.50–5.69, p = 0.002) was an independent risk factor for grade 3 non-hematologic toxicities.
Conclusions: Adjuvant chemotherapy with S-1 for 1 year was safe and feasible in Korean patients. Old age, female gender, and total gastrectomy were independent risk factors for severe toxicities of adjuvant S-1 chemotherapy.

6579 POSTER

Phase II Study of ABI-007 Given as an Every Three Weeks Schedule for Japanese Patients With Unresectable or Recurrent Gastric Cancer Refractory to 5-fluorouracil (5-FU) Containing Regimen

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Background: ABI-007 is a novel Cremophor®-free nanoparticle albumin-bound paclitaxel. Cremophor®-free formulation allows for to be administered using a shorter infusion schedule (30 minutes) and without the need for premedicaion to prevent hypersensitivity reactions.
This single arm phase II study trial was to evaluate the efficacy and safety of ABI-007 given every three weeks for unresectable or recurrent gastric cancer patients (pts) who have received one prior chemotherapy regimen containing fluoropyrimidine and developed disease progression or recurrence.
Patients and Methods: Pts were eligible as follows: histologically or cytologically confirmed gastric adenocarcinoma, received one prior regimen containing fluoropyrimidine analogs and developed disease progression or recurrence, age: 20−74, at least one measurable lesion by RECIST criteria, PS:0−2, adequate organ function and written informed consent. Study duration was until disease progression or unacceptable toxicity develops.
Received one prior regimen containing fluoropyrimidine analogs and developed disease progression or recurrence. Gastric cancer pts received ABI-007(260 mg/m^2, i.v. on day 1 of each 21 day cycle) without premedication.
The primary endpoint was the overall objective response rates (ORR); other efficacy parameters and safety profile.
Results: From April 2008 to July 2010, Total of 56 pts were enrolled, 55 pts received the study treatment, and 54 pts were eligible. Median age was 63.5, Male/Female was 43/13, PS:0/1/2 was 33/23/0 and the presence or absence of primary site was 21/35. ORR as primary endpoint was 27.8% (15 of 54) [95% CI 16.5–41.6] and DCR (disease control rate: rates of CR+PR+SD) was 59.3% (32 of 54) [95% CI 45.0–72.4] for all eligible patients. In addition, other secondary endpoints of efficacy are under investigation.
The most common grade 3/4 toxicities were as follows: lymphopenia, 10.9%; neutropenia, 49.1%; leukopenia, 20.0%; and peripheral sensory neuropathy, 23.6%.
Conclusions: ABI-007 shows promising activity with well-tolerated toxicities. It was suggested that ABI-007 was dose-dense treatment of paclitaxel for unresectable or recurrent gastric cancer refractory to 5-fluorouracil (5-FU) containing regimen.
This trial was supported by Taiho Pharmaceutical CO., LTD. ClinicalTrials.gov Identifier: NCT00661167.

6580 POSTER

Fuoropirimidines(FU) Versus Gemcitabine(Gem) Based Chemotherapy in Locally Advanced and Metastatic Biliary Tract Carcinoma(BTC)

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Background: Between 2004 and 2008, we conducted a prospective study on 96 patients (p) with advanced BTC, nonrandomized, nonblinded crossover to test the effectiveness in every day practice of 2 types of CT:FU and Cisplatin(Cis) (arm A) vs Gem w or w/o Cis (arm B).
Material and Methods: Eligibility criteria included patients with histologically proven locally advanced/metastatic BTC and chemonaive: 57 p (arm A) received FU based CT and 39 p (arm B) Gem based CT. On disease progression, 46 p were crossed over to 2nd line CT (Gem/FU w or w/o platinum compounds). Clinical characteristics (median age: 56.7 y (26−81), F/M 35/61, ECOG at baseline 0/1/2: 47/41/8 and first line CT: 30p 5Fu+Cis, 27p xeloda+Cis, 26p Gem+Cis and 13p Gem), response to CT and survival are in the table.

	All pts	Arm A (FU+Cis)	ArmB (Gem+/−Cis)	p
Number(n)	96	57	39	
First line CT (n)		30 5Fu+Cis; 27 Xeloda+Cis	26 Gem+Cis; 13 Gem	
Age(y)	56.7(26−81)	56.4(26−76)	57(36−81)	
ECOG at baseline(n)	0/1/2:47/41/8	0/1/2:32/20/5	0/1/2:15/21/3	
F/M (n)	35/61	22/35	13/26	
PR/SD(n)	4/71	3/37	1/34	
ORR/DCR(%)	4/78	5.2/70	2.5/90	
PFS(1^{stl}ine CT)	6.0 mo (95% CI 5.5−6.5)	5.9 mo (95% CI 5−6.9)	6.3 mo (95% CI 5.4−7.1)	0.66 (ns)
OS	9.9 mo (95% CI 8.8−11)	10.3 mo (95% CI 7.5−13.1)	9.1 mo (95% CI 7−11.2)	0.09 (ns)
Second line CT (n)	46	29 24 Gem; 5 Gem + platinum compounds	17 FU + platinum compounds	
PFS (2ndline CT)	6.0 mo (95% CI 4.1−7.9)	6.1 mo (95% CI 3.1−9)	3.2 mo (95% CI 0.2−6.9)	0.09 (ns)
OS (2ndline CT)	13.6 mo (95% CI 11.2−16)	19 mo (95% CI 8.9−29)	13.2 mo (95% CI 12−14.4)	0.001 (s)

Results: From 90p evaluable for response: arm A/arm B − 13p/2p had PD; 3p/1p had PR and 37p/34p had SD. Overall response rate (ORR) of arm A was 5.2% and disease control rate (DCR) 70% and ORR of arm B was 2.5% and DCR 89%. PFS for 1st line for all pts was 6 mo (95% CI 5.5−6.5); for arm A − 5.9 mo (95% CI 5−6.9); for arm B − 6.3 mo (95% CI 5.4−7.1) p = 0.66 (ns). 46p received 2nd line CT: 29p Gem based regimen (24p/5p Gem/Gem + platinum compounds) and 17p FU based regimen

(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