outcomes. However, owing to limited data and heterogeneity of the included studies, further RCTs are required to pursue.

6613 POSTER

Exposure-response analysis to identify abt-869 dose in hepatocellular carcinoma (HCC) patients

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Background: ABT-869 is an orally bioavailable, potent and specific inhibitor of all VEGF and PDGF family receptor tyrosine kinases. The objective of this analysis was to identify ABT-869 dose/dosing regimen for a potential phase-3 study in HCC patients.
Methods: An exposure-response (safety/efficacy) analysis was performed for patients (pts) enrolled in a phase 1 (multiple types of solid tumors) and 3 phase 2 monotherapy studies (non-small cell lung cancer (NSCLC), HCC and renal cell carcinoma (RCC)). Studies were conducted internationally in advanced/metastatic solid tumor pts to characterize ABT-869 efficacy/safety profile. Pts received ABT-869 until progressive disease or intolerable toxicity across all studies. Efficacy was assessed by RECIST criteria; safety by NCI-CTCAE, v3.0 and dose/dosing regimen was selected based on acceptable safety/efficacy responses. For drug exposure, plasma concentrations were fitted to a 1-compartmental model by the nonlinear mixed effects modeling (NONMEM) approach and various demographic covariates were tested. Trial abbreviation/registry numbers: Phase 2 trial of ABT-869 in HCC (NCT00517920); ABT-869 in subjects with NSCLC (NCT00716534); ABT-869 in Advanced RCC, after Sunitinib Failure (NCT00486538). All trials: ongoing; not recruiting; sponsored by Abbott Laboratories. ABT 869 is being developed in collaboration with Genentech.
Results: Among 224 pts in the analysis, 45% were Asian, 47% Caucasian and 8% other races; mean body weight was 72 kg (range 35–177 kg). Approximately 95% of pts received drug based on body-weight (mg/kg) while remaining pts had fixed dosing (mg). ABT-869 exposure was significantly ($p < 0.05$) associated with increased hypertension (HT) and skin toxicity events. Under weight-based dosing scheme, heavier pts had greater risk of toxicity as the exposure increased significantly. Transitioning from 0.25 mg/kg weight-based to 17.5 mg fixed dosing, exposure-safety response analysis showed that the predicted HT rate remains similar (33%) for pts with averaged body weight; however in pts with lower and higher body weights, the HT rate range is tighter for the fixed dose (30−36%) as compared to weight-based dose (23−44%). A similar trend was observed for skin toxicity. The model predicted the HT rate for HCC patients successfully and showed lower variability across patients for fixed dose.
Conclusions: A fixed 17.5 mg dose of ABT-869 is recommended for HCC patients based on the exposure predicted safety profile.

6614 POSTER

Clinical features of hepatocellular carcinoma patients underwent resection after concurrent chemoradiotherapy

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Background: This study was to examine the clinical features of the patients who underwent hepatic resection after receiving concurrent chemoradiotherapy.
Materials and Methods: From January 2000 to October 2007, one hundred fifty six patients with hepatocellular carcinoma received concurrent chemoradiotherapy, and those patients who underwent hepatic resection on the primary site during follow-ups were 14 (9%). Most patients were received 45 Gy with the fraction size of 1.8 Gy and 2 patients treated with 43.2 Gy. The chemotherapy was administered by intra-arterial infusion with 5-FU and 3−12 cycles of chemotherapy were performed after the radiotherapy. The tumor size before the concurrent chemoradiotherapy was 5−20 cm and the mean value was 10.4 cm. In radiological examinations, the disease status before the operation was shown to be 2 complete remissions, 6 partial remissions and 4 stable diseases. Two cases showed the suspicious recurrence from imaging studies.
Results: The hepatic resections were performed between 1 month and 21 months after concurrent chemoradiotherapy. A lobectomy was performed in most of the patients (13), and a bisegmentectomy was performed in the remaining 1 patient. In pathological findings, the ratios of necrosis were 5% to 100%. Four patients showed total necrosis and 12 patients (85.7%) showed the ratios of necrosis of 70% or higher. The resection margins were close to the tumor in 5 patients and 1 patient showed positive tumor resection margin. There were vessel invasions in 6 patients and capsular invasions in 5 patients. The median overall survival time was 28 months and the median disease free survival time was 19 months. The number of patients who were disease free after the operation was 3 (21.4%), and the number of patients with intrahepatic metastasis was 6 (42.9%) and distant metastasis was 5 (35.7%). Findings of vessel infiltration and capsule infiltration in univariate analyses were significant for survival rates ($p = 0.006$, 0.043), and disease free survival rates ($p = 0.014$, 0.004). In multivariate analyses, vessel infiltration was a significant factor for survival rates ($p = 0.01$), and capsule infiltration was a significant factor for disease free survival rates ($p = 0.01$).
Conclusions: Unresectable hepatocellular carcinoma could be resectable after concurrent chemoradiotherapy in selected patients. However, more clinical cases and prospective studies are necessary.

6615 POSTER

Advanced biliary tract cancer in Peruvian population

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Background: Biliary tract cancer (BTC) is not common cancer, but there are high incidence in some areas of Latin America and Asia, BTC includes intrahepatic cholangiocarcinoma, Klastkin tumor, extrahepatic cholangiocarcinoma, gall bladder cancer, and ampulla of Vater cancer. The standard treatment has not been established at the moment, traditional chemotherapy (5FU-based) has shown minimal activity and does not prolong survival, and each cancer has different responsiveness to anti-cancer treatment. We evaluated 178 patients (pts) with advanced biliary tract cancer.
Methods: Retrospective reviewed 178 BTC pts between (2000–2005).
Results: 178 pts (112 female, 42 male) were evaluated, median age 60 (range 16−91), median karnofsky performance status 70%. 151 cases (84%) were associated with gallstones, only 1 case present polyps. The clinical feature present most frequently was abdominal pain 81.5% (145 pts), weight loss 48.8% (87 pts), jaundice 43.3% (77 pts), mass in the right upper quadrant 36.5% (65 pts), itching 5.1% (9 pts), anorexia 19.7% (35 pts).
Primary tumor sites were gallbladder (38%), extrahepatic bile duct (29%), intrahepatic bile duct (9%), ampulla of Vater (2%), not specified (22%).
Predominant localizations of metastases were liver 70%, others 30% (lymph nodes, peritoneum).
Only 13.5% (24 pts) received chemotherapy using 5-FU-based chemotherapy the rest received best medical support. The patients that recived chemotherapy had median survival of 4.1 months and the patients that only recived best support had 3.4 months of median survival.
Conclusions: Our analysis showed that in BTC, gallbladder cancer is most common with predominant liver metastases and clinical features similar to previous published articles, treatment with chemotherapy produced modest benefit in survival.

6616 POSTER

Serial alpha-fetoprotein evaluation and survival in hepatocellular carcinoma patients treated with sorafenib

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Background: There is poor correlation between conventional radiologic response criteria and treatment outcomes of patients with advanced hepatocellular carcinoma (HCC). The prognostic value of serial α-fetoprotein (AFP) measurement has not been assessed in HCC patients receing sorafenib. Aim of this study was to examine AFP trends as a surrogate endpoint for survival.
Patients and Methods: Serum AFP was prospectively collected at baseline and during treatment, in conjunction with radiological assessment. In patients with increased AFP levels ($\geqslant$8 U/mL) at baseline, we defined AFP response as a decrease $\geqslant$20% in AFP value after 8 weeks from start of sorafenib treatment. Kaplan-Meier plots were constructed for progression-free survival (PFS) and overall survival (OS), and compared with the Log rank test to evaluate the correlation with AFP response.
Results: Overall 129 patients were evaluated, of which 21 had normal baseline AFP levels, remaining stable throughout treatment course. Median PFS and OS were longer in AFP responders than in non-responders:

6.5 *v* 3.7 months (P = 0.004) and 12.5 *v* 9.0 months (P = 0.026), respectively. In a Cox multivariate analysis, AFP response (responders *v* non-responders; hazard ratio, 0.38; 95% CI, 0.226 to 0.649; P < 0.001) and performance status were identified as contributory prognostic factors for OS. AFP responses or normal AFP levels were observed in 40 of 77 patients with radiologically stable disease and identified a subset of patients with better PFS (8.7 *v* 6.0 months; P = 0.005) and OS (13.8 *v* 9.2 months; P = 0.025). In AFP responders and in patients with normal AFP levels, OS was similar (P = 0.3).
Conclusions: Evaluation of AFP decline is an useful and non-invasive prognostic tool for treatment monitoring in patients with advanced HCC treated with sorafenib.

6617 POSTER

Phase II study of NGR-hTNF, a selective vascular targeting agent (VTA), in previously treated patients (pts) with advanced hepatocellular carcinoma (HCC)

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Background: HCC is a highly vascularised tumor with a median survival of 6 months reported in untreated pts with advanced disease class C according to Barcelona Clinic Liver Cancer (BCLC) staging. NGR-hTNF is a VTA consisting of TNF-a fused to the tumor-homing peptide NGR, which binds an aminopeptidase N overexpressed on tumor vessels.
Methods: Advanced-stage HCC pts received NGR-hTNF 0.8 μg/m^2 infused over 1-hour every 3 weeks (q3w). Progression-free survival (PFS) was the primary study aim with restaging performed q6w. A two-stage design was used with 16 and 27 pts to be enrolled. Subsequently, an additional 12 pts were treated with 0.8 μg/m^2 on a weekly basis (weekly cohort).
Results: Pts with documented progression after loco-regional treatments (59%), systemic therapies (56%; range, 1−3 regimens), or both (33%) received 90 cycles (range, 1−18+). Pt characteristics were: median age 65 years (range, 34−79); M/F 21/6; PS 0/1 18/9; Child-Pugh (C-P) A/B 21/6, BCLC B/C 5/22. No grade 3−4 drug-related toxicities were observed. Main grade 1−2 toxicities were short-lived, infusion-related chills (55%). The median PFS was 2.3 months (95% CI, 1.7−2.9). The disease control rate (DCR) was 30% and the confirmed response rate was 8%. A complete response (4%) lasting 11.5+ months was observed in a 76-year-old sorafenib-refractory, C-P B pt. A partial response (4%) with a 78% tumor reduction was reported in a further C-P B pt. Additionally, a 28% tumor shrinkage was detected in one out of 6 patients (22%) experiencing stable disease. Pts who achieved disease control received a median of 5 cycles (range, 4−18+) and had a median PFS of 4.3 months (range, 3.0−12.8+). With a median follow-up of 14.0 months (95% CI, 12.7−15.3), 8 pts (30%) were still alive and the median overall survival (OS) time was 9.1 months (range, 1.3−21.3+). The survival rates at 12 and 18 months were 34% and 22%, respectively. In the weekly cohort, there was no worsening of toxicity and the DCR was 33%. The subset of 12 sorafenib-pretreated pts reported a response rate of 8% and a DCR of 33%, whereas the median PFS and OS were 2.3 and 9.5 months, respectively.
Conclusions: NGR-hTNF is well tolerated and appears to have promising antitumor activity in previously treated HCC patients. The drug will be further developed in this setting.

6618 POSTER

Results of a multi-center phase II study of imatinib and fluorourcail/leucovorin (FU/LV) in patients with unresectable or metastatic gallbladder or biliary tract cancer

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Background: There are no standard chemotherapeutic regimens for incurable biliary adenocarcinomas. Monotherapies with gemcitabine or FU/LV achieve occasional responses and a median overall survival of about 6 months. By blocking PDGFR a decreased intrastromal pressure may increase therapy effects of chemotherapy. The combination of imatinib and FU/LV has been shown to be safe and feasible in a previous Phase I trial. This multicenter phase II trial was designed to investigate the disease control rate (DCR) of FU/LV and imatinib.
Methods: Eligibility criteria included unresectable or metastatic measurable biliary tract cancer (BTC)/gallbladder cancer (GBC), performance status ⩽2, adequate organ function and no clinically significant cardiovascular disease. Enrollment of planned 44 chemonaive patients (pts.) was completed. Pts. received LV 200 mg/m^2 followed by FU 2000 mg/m^2 as a 24-hour infusion on days 1 and 2 combined with 600 mg imatinib on days −4 to 4 (8 days). Cycles were repeated every 2 weeks up to 12 cycles. Radiological assessments were performed every 4 cycles.
Results: 44 pts (19 GBC; 25 BTC) were enrolled in this phase II study between 05/07−04/09. Median age was 62 years (range 33−77), male/female = 25/19, ECOG 0/1/2=13/26/5. 38 pts. showed metastatic disease at baseline. Treatment was well tolerated. Treatment related grade 3/4 toxicities included (number of pts): diarrhea (2), edema (1), neutropenia (2), nausea (2), transient SGPT elevation (4). 29 pts. were available for response evaluation at time of analysis. The DCR of these 29 pts. available for response assessment was 55.1% (16 pts) (1 CR, 2 PR, 13 SD of at least 4 cycles). 13 pts. (44.9%) showed progressive disease (PD) per RECIST criteria. 3 pts. had disease stabilization after 12 cycles and continue on treatment. Of pts. not available for analysis five are still on treatment before first evaluation of tumor response; pts. were excluded from analysis due to screening failure (3), lost to follow-up (2) withdraw of consent (1), toxicity (2), other (2).
Conclusions: Our data suggest that the combination of FU/LV and imatinib can be safely administrated in pts. with GBC/BTC. Evidence of antitumor activity was seen in majority of patients. Some pts. achieved long term stabilization of the disease.

6619 POSTER

Early skin toxicity as a predictive factor for tumour control in HCC patients treated with Sorafenib

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Introduction: Sorafenib (Nexavar®), an oral multikinase inhibitor that targets Raf kinase and receptor tyrosine kinases, has recently proved to increase median survival and time to progression in patients with advanced HCC. Cutaneous side effects represent one of the most common sorafenib-related toxicities. This study was conducted to assess the link between the antitumour efficacy of sorafenib and its early cutaneous side-effects considering that a confirm of this connection could lead to the identification of an important predictive factor for tumour control in patients with advanced HCC.
Materials and Methods: we retrospectively analysed the incidence of the skin toxicity (rash and hand-foot skin reaction) as definied by NCI-CTCAE criteria v 3.0 (grading criteria) during the first month of treatment with sorafenib. All patients received 800 mg daily of sorafenib and treatment continued until the occurrence of radiologic progression, defined by RECIST criteria, or the occurrence of either unacceptable adverse events or death. We compared tumour control rate (partial response + stable disease) and progression free survival.
Results: sixty-five HCC patients treated with Sorafenib were included in this analysis: forty-seven of them (73.3%) received sorafenib after failure of some local treatment, while 18 (27.7%) received it as first-line treatment. In 48 (73.8%) patients HCC disease was confined in the liver and in 17 (26.2%) the tumor was diffuse to other organs. All patients were classified as Child A and B. During Sorafenib treatment 29 patients developed at least G1 skin toxicity (13 patients rash and 16 HFS). In patients who developed skin toxicity the tumor control rate was 48.3% vs 19.4% in patients without cutaneous side-effects (P = 0.028). Median PFS was 8.6 months (95% C.I.: 6.5−11.6) in the group of patients with skin toxicity vs 4.3 months (95% C.I.: 2.1−6.1) in patients who did not developed skin toxicity (P = 0.002). This difference was statistically significant also in multivariate analysis.
Conclusions: the present results suggest that the skin toxicity should be closely monitored in HCC patients treated with sorafenib also in relation with its potential role as predictive factor of efficacy.

6620 POSTER

Pegylated liposomal doxorubicin (PLD) and gemcitabine (G) in the treatment of advanced hepatocellular carcinoma (HCC)

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Background: Despite Sorafenib represents the new standard therapy for advanced HCC the patient survival remains still poor. Single-agent