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