Results: The frequency of the GG, GA and AA genotypes were 58.2%, 31.2% and 10.6%, respectively. We found that GG/GA genotypes were present in 96.6% of cases with advanced disease (stages III-IV) and in 85.6% of cases with early disease (stages I-II) and these differences were statistically significant (OR = 4.8, $P = 0.026$). After adjustment for gender and age ($\leqslant$62 years), we observed that the G allele were statistically significant associated with advanced disease (OR = 5.1, $P = 0.035$).
Conclusions: Individual differences in cellular microenvironment and in signalling pathways activation may influence cancer development and tumour behaviour. Our preliminary results, suggest that *R497K* functional polymorphism is associated with advanced disease probably because the genetic variant *EGFR 497K* has attenuated functions in ligand binding, growth stimulation, tyrosine kinase activation and induction of proto-oncogenes compared with *EGFR 497R* variant. This genetic profiling may help define higher risk groups and design new target and individualized therapies.

7156 POSTER

HIF1a 1772C/T Polymorphism and Prognosis in Renal Cell Carcinoma

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Background: Hypoxia inducible factor (HIF-1) is a key regulator of the genes involved in the cellular response to hypoxia. Overexpression of HIF-1 has been implicated in the pathogenesis of renal cell carcinoma (RCC) and it is argued that polymorphisms of the HIF1A gene may confer susceptibility to RCC. Purpose: To assess the impact of HIF1A functional polymorphism on RCC progression and prognosis.
Material and Methods: The HIF1A 1772C/T (rs11549465) single nucleotide polymorphism was evaluated in a retrospective cohort study of sporadic RCC patients (n = 179) treated at Instituto Português de Oncologia do Porto from 1999 to 2009. Genomic DNA was extracted from peripheral blood samples. Genotyping was performed by Real-Time PCR allelic discrimination method. Recurrence/progression and cancer-specific survival (CSS) were the clinical outcomes studied. The associations of the HIF1A genotypes with clinicopathological prognostic factors and recurrence/progression were analyzed by the chi-square or Fisher tests. Genotypes influencing survival were compared using Cox proportional hazard regression. CSS was estimated by Kaplan–Meier curves and differences were compared using the Breslow test.
Results: None of the genotypes (CC, CT or TT) were significantly associated with ECOG *performance status* (PS), tumour size, tumour extension, Fuhrman grade, lymph node invasion, distant metastasis, TNM stage, histological necrosis or vessel permeation. The T allele was more frequent in patients with ECOG PS 1 than in those with ECOG PS 0 (OR 1.77; 95% CI 0.91–3.40; p = 0.07). The TT genotype and T allele were associated with recurrence/progression (p = 0.042 and p = 0.02, respectively). The CT and CT+TT genotypes were tend associated with unfavorable CSS (HR 2.79; 95% CI 0.88–8.82; p = 0.08 and HR 2.76; 95% CI 0.93–8.22; p = 0.07, respectively). Patients with CT and CT+TT genotypes showed worse CSS than those with the CC genotype (p = 0.012 and p = 0.018, respectively). CSS rates at 5-years were 88.1% vs 83.9% and 76.6% for the CC vs the CT and CT+TT genotypes, respectively.
Conclusion: These results suggest that HIF1A 1772C/T polymorphism may have effects on RCC progression or prognosis, possibly through altered HIF-1 transcription activity.

7157 POSTER

INT70/09 Phase II Study of Pazopanib (PZP) Monotherapy for Patients (pts) With Relapsed/refractory Urothelial Cancer (UC) − Updated Results

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Background: Discouraging results have been reported in relapsed/refractory UC with the use of either single-agent or combination therapy (Rx), including targeted Rx. In 2nd line setting, median progression-free (PFS) and overall survival (OS) approximate 3 and 6 months, respectively, then having a dramatic fall in 3rd line and beyond. On 10/2010 we reported preliminary, yet encouraging, results of a phase II trial with PZP, a multitargeted drug with distinct anti-angiogenic activity (ESMO 2010, LBA#23). An update of the trial is presented.
Methods: Eligibility included histologically confirmed UC failing $\geqslant$1 CDDP-based Rx for metastatic disease (perioperative Rx excluded). PZP 800 mg once daily until disease progression or unacceptable toxicity was planned. Both CT scan and PET/CT scan were set at baseline and q4weeks thereafter. An optimal 2-stage Simon's design was applied with the 1st stage recruiting 21 pts and, if $\geqslant$2 responses, a full enrollment of 41 pts. RECIST v.1.1 was used; response-rate (RR) was the primary endpoint.
Results: 36 pts were enrolled from 02/10 to 03/11 (28 males, 8 females). Median age was 64 yrs (42−79). 13 pts (36%) had UC of the upper urinary tract and 23 had a bladder primary tumour. 33 pts had multiple disease sites (median 3, range 1−5). Median number of prior cytotoxic agents was 3 (2−8), of prior Rx lines was 2 (1−4) and median number of prior platinum-based cycles was 5 (2−13). 30 pts (83%) had undergone major surgery, 10 pts had received RT. 30 pts had visceral metastases (hepatic in 17 pts). Median baseline ECOG PS was 1 (0−2). 4 pts (11%) had a confirmed RECIST-defined partial response (PR), 26 had a stable disease (83% clinical benefit). 19 pts (53%) had a clear necrotic evolution of multiple metastases and/or a decreased SUV at PET consistent with PR. Of the 34/36 pts having 2 months minimum follow up, median PFS and OS were 3 months (1−11) and 6 months (2−11), respectively. G3 hypertension occurred in 2 pts while G1−2 asthenia in 13, diarrhoea in 5, anemia and hand-foot syndrome in 3 pts each and G2 increase of liver transaminases in 2 pts. No discontinuations/dose reductions were needed.
Conclusions: Activity and potential efficacy of PZP is demonstrated in very highly pre-treated UC pts. Though the PR-rate by RECIST is low, half of pts had a densitometric/metabolic response, the majority of pts had a clinical benefit and PFS-rate is promising (approaching pure 2nd line results). This is consistent with the mechanism of action of PZP, and highlight the need for new criteria or modifications to existing ones to assess response of angiogenesis inhibitors. Final efficacy and safety outcomes with biomarker analysis will be available in 09/2011 (Cancer.gov registry number: NCT01031875).

7158 POSTER

Impact of Targeted Therapies on Muscle Loss and Adipose Tissue in Metastatic Renal Cell Carcinoma (mRCC)

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Background: We previously reported that sorafenib (So) can induce severe muscle depletion (sarcopenia) in RCC. Whether adipose tissue is also involved and whether this phenomenon is due to VEGF inhibition or involves other pathway is unclear. In order to understand the physiopathology of body composition changes with targeted therapies we investigated different drugs, including other VEGF inhibitor (sunitinib [Su]) and mTOR inhibitor (everolimus [E]).
Methods: All patients with mRCC enrolled in 3 previously reported studies: RECORD 1 (E vs placebo [P]), TARGET (So vs. P), and Su continuous dosing were analyzed. Patients were eligible if at least 2 CT scans were available. CT analysis, which has high precision and specificity for evaluation of specific muscles, was used to define change in total skeletal muscle. The 3rd lumbar vertebra was chosen as a landmark. Images were analyzed using Slice-O-Matic software V4.3. Subsequently, tissue cross-sectional areas (cm^2) were computed.
Results: 147 patients (78% male) were evaluable: 36 on E, 37 on So, 36 on Su and 38 on P. Mean durations of treatment were; 136, 172, 142, 117 days respectively on E, So, Su, P. At baseline obesity or overweight were frequent: 42% (P); 55% (E); 55% (So); 66% (Su). Placebo patients had stable body weight (mean$\pm$SD) (+0.9$\pm$3.7 kg), with no changes in muscle mass or adipose tissue. By contrast, patients lost body weight (mean$\pm$SD): −3.5$\pm$5.6 kg, −2.5$\pm$3.8 kg; −3.1$\pm$4.4 kg respectively on E, So, Su. Patients lost skeletal muscle compared with placebo group −3$\pm$8% for E ($p = 0.1$), −5$\pm$8% for So ($p < 0.0001$) and −4$\pm$5% for Su ($p = 0.001$). Interestingly, there were no differences between groups. Muscle loss rate (cm^2/day) was similar for the 3 groups respectively 0.042; 0.045, 0.044 for E; So; Su. No significant changes for adipose tissue were reported: 16$\pm$143% for E; −1$\pm$19% for So; 2$\pm$21% for Su. All combined, after 5 months of treatment, 86 patients were on progressive disease and 33 on stable disease. Loss of adipose tissue but not loss of muscle mass was significantly linked to progressive disease (p = 0.01).
Conclusions: The 3 therapies, everolimus, sorafenib and sutent are responsible for muscle wasting and surprisingly muscle wasting rate is

similar for all three of them (about 0.8 kg of muscle/3 months). Loss of adipose tissue was associated to progressive disease. The pathways between these 3 drugs and body composition changes remain to be investigated.

7159 POSTER

Mutations in FGFR3 and Ras in Urothelial Cell Carcinomas of the Bladder − No Association With MAPK Pathway Activation

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Background: Different members of the PI3K-AKT pathway (*PIK3CA, PTEN, TSC1, AKT1*) are altered in bladder cancer. *FGFR3* mutations characterize the superficial/papillary low-grade tumours and *RAS* genes are mutated in about 13% of all bladder tumours. Interestingly, mutations in *FGFR3* and *RAS* are mutually exclusive in bladder cancer.
Material and Methods: We have analysed the prevalence of somatic mutations in *FGFR3, KRAS*, *HRAS* and *BRAF* genes in 88 Urothelial Cell Carcinomas (UCC) (Parc de Salut MAR Biobank of Barcelona, Spain), and the immunohistochemical expression of phospho-ERK1/2 (Cell Signaling Technology, Beverly, MA) in 80 UCC. The association of these alterations with the pathological features of tumours was also investigated.
Results: About 56% of tumours were mutated, 40 (45.5%) in *FGFR3* and 9 (10.2%) in *RAS* genes (*KRAS* n = 6, *HRAS* n = 3). None of the tumours presented mutations in *BRAF* and there were no $FGFR3^{mut}$-RAS^{mut} combinations. $FGFR3^{mut}$ genotype was associated with low grade bladder tumours (WHO 2004) and according to the three-tiered classification (WHO 1999) grades 1 and 2 tumours did not show statistically significant differences in the percentage of *FGFR3* mutations. *RAS* mutations were not associated with any of the tumour groups. Fifty-six per cent of tumours showed high levels of pERK1/2. There was a marginal association between pERK1/2 overexpression and high grade and stage tumours. Wild-type tumours presented a significantly higher pERK1/2 expression and only *RAS* mutated tumours showed a weak increase in pERK1/2 expression.
Conclusions: Mutations in *FGFR3* characterize low grade bladder tumours (WHO 2004) and with regard to *FGFR3* mutations, grade 2 (WHO 1999) cases are more similar to low grade than to high grade UCCs. *FGFR3* mutations cannot activate MAPK pathway, so other genes different from *FGFR3* may be related with the pERK activation in bladder tumours.
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7160 POSTER

MicroRNA Profiling in Peripheral Blood Predicts Major Response to Sunitinib in Metastatic Renal Cell Carcinoma

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Background: Sunitinib is a standard therapy for metastatic renal-cell carcinoma, but markers to predict drug benefit are needed. In this study, we applied high-throughput microRNA (miRNA) expression profiling in peripheral blood samples to identify predictive markers.
Material and Methods: This multicentre prospective study included patients with clear-cell metastatic kidney cancer and no previous systemic therapy. Peripheral blood samples were taken before initiation of therapy and 2 weeks later. Patients received sunitinib 50 mg/day for 4 weeks every 6 weeks. RECIST criteria were followed to asesss response. Total RNA was isolated from peripheral blood samples and miRNA profiling was performed using microarrays. Patients were stratified according to time to progression of disease. Those with progression before 6 months were included in the “Poor response” group, patients with progression after 18 months were included in the “Prolonged response” group and the remaining patients in the “Moderate response” group. Boosting was applied to filter miRNA expression data according to progression results. Predictive models were built independently for “Poor Response” and “Prolonged response” using binary logistic regression. Predictive accuracy for calibration and discriminant power of predictive models were evaluated.
Results: At the time of the analysis, 44 patients were enrolled and 37 were available for response. Median age was 62, 78% of patients had prior nephrectomy and median follow-up was 9 months. There were 4 complete and 13 partial responses, whereas disease remained stable in 9 (>6 months in 6 of them) and progressed in 11. miRNA profiling of peripheral blood samples showed that 29 miRNAs were differentially expressed between patients in the Poor response group vs. the other groups, and 13 miRNAs were differentially expressed between patients with Moderate response vs. those with Prolonged response. Several predictive models comprising different miRNA sets were generated and evaluated. Differential expression of miR-30b*, miR-370, miR-31, miR-196b, miR-1285 and miR-196−3p was consistently associated with response, so these can be considered relevant biomarkers for sunitinib response.
Conclusion: miRNA profiling in peripheral blood may be a reliable way to identify biomarkes related to sunitinib benefit in patients with metastatic renal-cell carcinoma. Validation of predictive models is ongoing.

7161 POSTER

Prognostic Factors in Patients With Advanced Renal Cell Carcinoma

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Background: Besides to the classical clinical and analytical prognostic factors of advanced renal cell carcinoma (RCC), the prognostic significance of molecular markers and other analytical variables such as one of the actual pathways in the investigation of advanced RCC are also being analysed, although they have not been yet validated for their application in the regular clinical practice.
Materials and Methods: A retrospective cohort of 135 patients with advanced RCC treated with biological agents and/or cytokines (CK) was analysed between July 1996 and February 2010. The expression of several biomarkers by immunohistochemistry and 2 analytical variables were analysed and were correlated with prognosis.
Results: 67 patients were treated only with biological agents and 68 with CK (23 received also biological agents in a sequential manner). The univariate statistical analysis showed that the enhanced expression of HIF-1α correlated with a poor prognosis in patients treated with biological agents (PFS 5.4 vs 13.5 months with low expression, $p = 0.033$) including sunitinib (PFS 5.4 vs 13.4, $p = 0.001$) and CK (PFS 3.3 vs 5.7, $p = 0.003$). The overexpression of CAIX was associated to a better prognosis in patients that received biological agents (PFS 18.3 vs 5.2 months with decreased expression, $p < 0.001$; OS 32.1 vs 7.8, $p < 0.001$) including sunitinib (PFS 16.8 vs 5.5, $p < 0.001$), sorafenib (PFS 8 vs 3.5, $p < 0.001$) and CK (PFS 6.3 vs 2.7, $p = 0.003$; OS 32.9 vs 5.9, $p = 0.001$). Positive PTEN was related to a good prognosis in patients treated with sunitinib (PFS 15.1 vs 6.5 months with negative PTEN, $p = 0.003$) and CK (PFS 7.5 vs 3.8, $p = 0.037$; OS 13.7 vs 7.9, $p = 0.039$). The increased expression of p21 was related to a poor prognosis in patients that received biological agents (PFS 5.9 vs 16.8 months with high expression, $p = 0.024$) including sunitinib (PFS 6.2 vs 18.9, $p < 0.001$), sorafenib (PFS 4 vs 9, $p = 0.013$) and CK (PFS 3.9 vs 7.5, $p < 0.001$). Thrombocytosis was related to a poor prognosis in patients treated with biological agents (OS 15.9 vs 26.7 months without thrombocytosis, $p = 0.007$) and CK (PFS 2.6 vs 5.1, $p = 0.017$; OS 5.9 vs 14.3, $p = 0.010$). Neutrophilia was related to a poor prognosis in patients that received biological agents (OS 17.6 vs 25.4 months without neutrophilia, $p = 0.063$) and CK (PFS 2.6 vs 5.7, $p = 0.019$; OS 5.9 vs 12.8. $p = 0.035$). In the multivariate analysis, the overexpression of CAIX was a favourable prognostic factor independent of PFS with a HR of 0,107 ($p < 0.001$) and OS with a HR of 0,055 ($p < 0.001$).
Conclusions: Our experience has suggested the utility of de HIF-1α, CAIX, PTEN, p21, thrombocytosis and neutrophilia as prognostic factors in patients with advanced RCC. CAIX has shown to be an independent prognostic factor.