Results: Age-, tobacco- and body mass index (BMI) - adjusted logistic regression analysis showed an overrepresentation of *LEPR* Gln223Arg Gln homozygous genotype in overall PC cases, compared with controls ($P = 0.040$). Moreover, an earlier onset of disease was verified in *LEPR* Lys656Asn Asn/Asn carriers ($P = 0.049$). Cumulatively, we observed an association between *LEPR* Gln223Arg Arg/Arg carriers and a higher Gleason score ($P = 0.022$). In patients submitted to curative intent treatment, Kaplan-Meier curves and function plots showed a shorter time-to-relapse in *LEPR* Gln223Arg Arg/Arg ($P = 0.006$).
Conclusions: Results from the present study suggest a role for *LEPR* Gln223Arg in PC susceptibility, aggressiveness and in the time-to-relapse. Furthermore, *LEPR Lys656Asn* polymorphism may be a marker of earlier onset of PC. The apparently dual role of LEPR 223 variant, might be due to the higher Arg/Arg binding affinity of LEPR to leptin supporting a peripheral interactome in initiation and a direct effect during development and tumor reactivation. Further studies are warranted to understand the functional role of these variants in leptin pathway activation.

7022 POSTER

Genetic profile of IL-6/IL6R pathway predicts susceptibility, agressiveness and response to hormonal treatment in prostate cancer patients

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Background: Interleukin-6 (IL-6), a pleiotropic cytokine with critical roles in inflammation and immune response, seems to be involved in Prostate Cancer (PCa) development and in androgen-independence (AI) mechanisms. Our purpose was to investigate the potential role of functional *IL6* and *IL6R* genetic variants in PCa patients, which have been found to directly affect the *IL6* transcription rate *in vitro* and IL-6 levels *in vivo*.
Material and Methods: We conducted a study in biopsy-proven PCa patients and controls (without malignant cells) ($n = 983$ and $n = 239$, respectively). Genotyping was performed through PCR-RFLP and Real Time-PCR allelic discrimination. Genotypes from *IL6* polymorphisms were individually combined with *IL6R* Asp358Ala polymorphisms according to a functional rationale: Low/intermediate signalling genetic profile and higher signalling gentic profile.
Results: In the *IL6* polymorphism at locus −174 we found an increased risk for C carriers to present a PSA level $\geqslant 20$ ng.mL-1 at the time of diagnosis ($P = 0.02$). Moreover, results show an association of *IL6*−174 C carriers with development of distant metastasis ($P = 0.049$). Carriers of the C allele of *IL6* polymorphism in locus −174 of the promoter region are at higher risk of developing biochemical relapse ($P = 0.035$) and of dying from the disease ($P = 0.008$). Kaplan-Meier survival analysis showed a borderline association of *IL6*−174 C carriers with an earlier AI development ($P = 0.056$). *IL6* −597 A carriers are overrepresented in the group of patients who developed biochemical relapse ($P = 0.013$) and is associated with an earlier onset of PCa development ($P = 0.019$). When *IL6* −174 and *IL6R* polymorphisms were combined, we observed an overrepresentation of higher IL-6 signalling genetic profile in the group of patients with PSA$\geqslant$20 ng.mL-1 ($P = 0.049$), with metastatic disease ($P = 0.049$) and death from cancer ($P = 0.026$). Kaplan-Meier function plots with Breslow test showed an earlier development of AI in higher IL-6 signalling genetic profile ($P = 0.008$).
Conclusions: Functional polymorphism in *IL6* and *IL6R* may contribute to earlier relapse in PCa hormonal-treated patients, supporting the involvement of *IL6*/*IL6R* pathway as an alternative pathway in AI of PCa. Conversely, our results lend support to *IL6*/*IL6R* pathway as an additional therapeutic target during hormonal treatment. The *IL6* and *IL6R* functional polymorphism might be a useful molecular marker for PCa aggressiveness and as a predictive factor for AI relapse.

7023 POSTER

Osteopontin functional genetic polymorphism is associated with prostate cancer biochemical recurrence and androgen independence

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Background: Understanding the molecular mechanisms that underlie endocrine instigation of indolent tumours may help to clarify several processes in cancer. Elevated osteopontin (OPN) transcription often correlates with increased metastatic potential of transformed cells and have key roles in inflammation and immunity. With the aim to evaluate a genetic variant with functional effect on transcription in *OPN*, we have analysed its association with prostate cancer (PCa) recurrence-free survival and in androgen-independence development.
Materials and Methods: This study was conducted in histologically confirmed PCa patients ($n = 406$). We used Real-Time PCR in order to investigate the genotype and allelic distributions of the polymorphism *OPN* −66 T>G.
Results: Biochemical recurrence risk was significantly associated with OPN functional polymorphism ($P = 0.03$) and Kaplan-Meier function plots analysis with Breslow test showed a lower time to recurrence in G carriers ($P = 0.021$). Furthermore, in those patients submitted to hormonal therapy ($n = 209$), we observed an increased hazard ratio for TT carriers to develop androgen independence (HR = 3.57, 95% CI = 1.5−8.8, $P = 0.005$), after adjustment for relevant prognostic clinical variables.
Conclusions: Results suggest that this functional polymorphism in OPN gene may influence osteopontin expression and therefore instigate the growth of otherwise indolent tumors.

7024 POSTER

Phase Ib dose-finding trial of intravenous (i.v.) panobinostat (PAN) with docetaxel (DOC) and prednisone (PRED) in patients (pts) with castration resistant prostate cancer (CRPC)

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Background: Panobinostat is a potent pan-deacetylase inhibitor that has shown anti-tumor activity in prostate cancer model systems, both in vitro and in vivo, which is potentiated by DOC.
Material and Methods: Open-label, multicenter, dose-finding trial of i.v. PAN given on Days 1 and 8 (10, 15, and 20 mg/m^2) with fixed-dose DOC on Day 1 (75 mg/m^2) and PRED (5 mg bid) in a 21-day cycle in pts with CRPC. All but 3 patients were chemonaive. Pts are required to have adequate organ function and ECOG PS $\leqslant 1$. Pts with cardiovascular abnormalities or QTcF >450ms are excluded. Treatment is continued until disease progression or intolerability. The primary endpoint is determination of maximum tolerated dose (MTD) of i.v. PAN with standard dose DOC using the Bayesian statistical model. Dose-limiting toxicities (DLTs) are defined in Cycle 1.
Results: 27 pts (Cohort 1, $n = 8$; Cohort 2, $n = 10$; Cohort 3, $n = 9$) have been treated, median age of 66 yrs (range 26−88), median Gleason score of 8 (range 7−9), and median PSA of 63.7 ng/mL (range 1.3–672). DLTs included: Gr 4 bradycardia in Cohort 1 ($n = 1$, pt had bradycardia as past medical history) and Gr 4 neutropenia resulting in Day 8 PAN dose omission ($n = 2$, Cohort 2; $n = 1$, Cohort 3). The MTD has not been reached. The maximal dose of PAN allowed by the protocol is 20 mg/m^2. Gr 3/4 adverse events included: neutropenia (19 pts), febrile neutropenia (7 pts), syncope (2 pts), DVT (2 pts). Gr 3 or 4: fatigue (1 pt) and no thrombocytopenia, or diarrhea have been reported. Among the 891 ECGs performed, 2 pts had QTcF increase >60ms from baseline, with no QTcF >480ms reported. In Cohorts 1 and 2, the median number of cycles was 6; 2 pts in Cohort 1 received $\geqslant$15 cycles and 5 pts in Cohort 2 received $\geqslant$6 cycles. In Cohorts 1 and 2, 10 pts had PSA declines, 7 of whom had a >50% decline in

PSA from baseline. In Cohort 3, 7 of 9 pts are still on treatment after 2 cycles, with 1 patient having a 99% PSA reduction at Cycle 4. Of the 13 pts enrolled with measurable disease, 2 pts have achieved an unconfirmed partial response and 6 pts have unconfirmed stable disease using RECIST criteria.
Conclusions: The maximal dose of panobinostat allowed by the protocol in combination with docetaxel and prednisone is 20 mg/m^2. The combination is well tolerated and has shown promising activity both for PSA reduction and tumor shrinkage. The combination warrants further exploration in a randomized Phase II setting.

7025 POSTER

Prognostic value of hypermethylation for retinoic acid receptor beta (RARB) and p-16 genes in patients with prostate cancer

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Background: Correlations between specific gene hypermethylation and clinicopathologic features suggestive of aggressive disease characteristics indicate that these genes may have prognostic potential. Such molecular markers may help to identify men who will undergo recurrence, so that they can be targeted for more aggressive therapy. we investigated hypermethylation of promoter genes, retinoic acid receptor β (RARB) and p-16, prostate cancer patients with different prognostic features who referred to three hospital in Iran between Jan 2007 and April 2008.
Methods: 63 prostate biopsy specimens from three different groups of patients, 21 benign prostate hyperthrophy (BPH) as control group, 21 prostate cancer who had good prognostic features, and 21 patients with poor prognostic feature were evaluated. The prostate biopsy specimen examined for hypermethylation of promoter genes RARB and p-16 with Methylation Specific PCR (MSPCR) and odds ratio for any association with patients' prognosis were tested by Chi-square and Fisher exact test.
Results: There was no RARB methylation in BPH specimens. In patients with good prognostic features 7 (33.3%) were positive for RARB methylation which was significantly more common than control group ($p < 0.000001$).RARB methylation was found in 15 (71.4%) of patients specimens with poor prognostic features, that were more common than control group (0.000001). The RARB methylation in patients with poor prognostic factors were significantly more common than in patients with good prognostic features ($p < 0.02$). There was no p-16 positive subject in BPH group. In patients with good prognostic features 19% had methylation of p-16 and of those with poor prognostic features 47.6% were positive for RARB methylation. The P16 methylation in patients with poor prognostic factors were significantly more common than in patients with good prognostic features($p < 0.00001$).
Conclusion: Methylation of RARB and p-16 are good indicator for early detection and predicting prognosis of prostate cancer in Iranian patients.

7026 POSTER

Deriving prostate alpha-beta ratio using carefully matched groups, long follow-up and the Phoenix definition of biochemical failure

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Background: Prior studies derived a low value of a/β for prostate cancer (e.g. 1−2 Gy) using outcome data from external beam radiotherapy (EBRT) and permanent prostate brachytherapy (PPB). However, these values are associated with wide confidence intervals and inaccuracies such as poorly-matched groups, differing definitions of biochemical failure and insufficient follow-up.
Materials and Methods: Patients with Canadian Consensus Risk Group low- or low-tier intermediate risk prostate cancer, treated with either EBRT or PPB, were matched for PSA, Gleason score, T-stage, percentage of positive cores, androgen deprivation therapy duration and era, yielding 118 pairs. The Phoenix definition of biochemical failure was used. The best value for a/β was found using maximum likelihood analysis, and 95% confidence intervals using the profile likelihood method. The linear quadratic formalism was applied with radiobiological parameters set at RBE = 1, Tpot = 45 days, and repair half-time = 1 hour. Sensitivity analysis was performed using extreme values of these parameters.
Results: PPB and EBRT groups were well-matched with respect to all known risk factors. Median follow-up or time to failure was 60 months. Kaplan-Meier estimates of freedom from biochemical failure (bNED) showed superiority of PPB compared to EBRT (log-rank test $p = 0.001$): Estimates of probability of bNED were 82% and 95% at 72 months for EBRT and PPB; and 63% and 95% at 90 months. The value of a/β that best fitted the outcome data was >30 Gy, with a lower 95% confidence limit of 3.2 Gy. This was confirmed on bootstrap analysis. Varying the parameters to extreme values yielded a best-fit a/β of at least 3.0 Gy.
Conclusions: Our result of >30 Gy as the best estimate of a/β for low and low-intermediate risk prostate cancer directly contrasts with prior best estimates of 1−2 Gy. Obtained values of a/β result from superior outcomes for PPB observed for long follow-up time. If the true value of a/β is not less than the rectal a/β then radiation hypofractionation may not improve the therapeutic ratio.

7027 POSTER

Interim results of a phase II trial of oxaliplatin and pemetrexed as 2nd/3rd line therapy in castration resistant prostate cancer (CRPC)

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Background: There is no standard of care for men with metastatic CRPC after disease progression on docetaxel. Pemetrexed and oxaliplatin have each shown modest single-agent response rates in CRPC and have non-overlapping toxicities; this trial evaluates their efficacy in combination.
Methods: Men with CRPC whose disease progressed on docetaxel were eligible. A two-stage design ($\alpha = 0.1$, $\beta = 0.1$) was used to determine the response rate as primary endpoint (RECIST, or PSA if no measurable disease present); 47 patients are planned. After giving written informed consent, 31 men enrolled from July 2006 - November 2008. Treatment was pemetrexed 500 mg/m^2 IV and oxaliplatin 120 mg/m^2 IV every 3 weeks, with folate and B12 supplementation.

Response	Number (%)
Overall (N = 31)	
PR (>50% decrease PSA or RECIST)	10 (32%)
SD	12 (39%)
PD	6 (19%)
Inevaluable – off treatment	4 (13%)
RECIST (N = 26)	
PR	4 (15%)
SD/unconfirmed PR	18 (58%)
PD	4 (13%)
Inevaluable	5 (16%)

Toxicity	Grade 1/2	Grade 3/4
Allergic	7	1
Auditory	12	0
Bone Marrow	22	8
Constitutional	22	6
Dermatologic	5	0
Gastrointestinal	24	0
Hemorrhage	5	0
Hepatic (including alk phos)	23	4*
Metabolic/Laboratory	12	0
Neurologic (dizziness, confusion, ataxia)	18	5
Pain	7	3
Pulmonary	2	1
Renal	4	0

*2 grade 3 AST/ALT

Results: Median age was 66 (41−81), 72% were Caucasian and 97% had ECOG performance status 0−1. Median baseline PSA was 286 ng/mL (range 4.8−2290). All had metastatic disease with 1 (55%) or 2 (45%) prior chemotherapy regimens; 94% had bone involvement. Subjects received a median of 6 treatment cycles (range 1−21); 3 continue on study. Responses are summarized in the table; 8 of the 31 patients (26%) have achieved a PSA response, and 4 objective PRs by RECIST, out of 26 evaluable patients. Eighteen (58%) had stable disease. After 15 deaths, median survival is 11.8 months (95% CI 7.5−23.5+). Toxicities are presented in the table; the only grade 4 event was thrombocytopenia. Common grade 3 events included fatigue (6 subjects), hematologic (7), and neurologic (5). Two patients died while on study, one due to disease progression and the other one due to cardiopulmonary arrest.