Poster presentations (Tue, 25 Sep, 09:00–12:00)
Genitourinary malignancies – prostate cancer

4006 POSTER

Gene profile predicts protection from radio-induced late rectal bleeding in prostate cancer

R. Valdagni[1], M. Gariboldi[2], N. Zaffaroni[3], G. Fellin[4], V. Vavassori[5], S. Barra[6], C. Cozzarini[7], C. Fiorino[8], G. Girelli[9], T. Rancati[1]. [1]*Fondazione IRCCS Istituto Nazionale Tumori, Prostate Program, Milan, Italy;* [2]*Istituto Nazionale Tumori & IFOM, Dept. Experimental Oncology, Milan, Italy;* [3]*Fondazione IRCCS Istituto Nazionale Tumori, Dept. Experimental Oncology, Milan, Italy;* [4]*Ospedale Santa Chiara, Radiation Oncology, Trento, Italy;* [5]*Ospedale di Circolo, Radiation Oncology, Varese, Italy;* [6]*IST, Radiation Oncology, Genova, Italy;* [7]*Ospedale San Raffaele, Radiation Oncology, Milan, Italy;* [8]*Ospedale San Raffaele, Medical Physics, Milan, Italy;* [9]*Ospedale Civile ASL 9, Radiation Oncology, Ivrea, Italy*

Background: Despite the recent sophistication in technology, 5–10% prostate cancer patients (pts) treated with radiation (RT) can still suffer from significant morbidity (tox). Recent findings show abnormal transcriptional responses to DNA damage as associated to acute tox. We tried to identify genetic markers correlated with late rectal bleeding (lrb) in prostate cancer pts treated with 3D conformal RT and selected within the AIROPROS 0101 trial, activated to analyze the correlation between lrb and dosimetric variables.
Materials and Methods: EBV-immortalized lymphocytes (LCL) obtained from blood samples from 30 pts (⩾70–76 Gy CRT; min f-up: 24 mos) and 10 healthy donors were analysed: low risk group [V70 < 15% and V50 < 45%]: 10 pts with G2–3 lrb ("radio-sensitive" pts); high risk group (V70 > 25% and V50 > 60%): 10 pts with G2–3 lrb; high risk group: 10 pts showing no tox ("radio-resistant" pts). Quantitative RT-PCR was performed on each pt, partly irradiated using a 137Cs source (5 Gy), partly left untreated. Inter- and intra-group expression levels with and without RT and class prediction were compared using the BRB ArrayTools, at $p < 0.05$.
Results: 75% of the genes analyzed were RT modulated in at least one of the 4 groups (intra-group comparison). Most of the genes were induced by treatment in all groups but the "resistant", where 4 of the 10 modulated genes were decreased by RT. The other groups presented 18–21 modulated genes, mainly RT induced. The "resistant" and the "sensitive" groups showed many differences before treatment (inter-group comparison) and 10 genes were significantly higher in the "resistant", suggesting a protection from adverse reactions. Only 3 genes were modulated after treatment. Most genes were expressed at the same levels in untreated "resistant" pts and in all the other groups after RT, suggesting their constitutive activation in the "resistant" pts. One of the identified genes was able to distinguish resistant pts from the others.
Conclusions: Pts exhibiting no lrb showed several genes with higher basal levels than other pts/donors. One of these genes might be considered as a potential predictor of late toxicity protection. If validated these results might enable clinicians to use more "flexible" DVH constraints and/or to safely deliver higher RT doses.
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4007 POSTER

Molecular and functional profiling for an improved clinical management of prostate cancer

H. Sültmann[1], T. Schlomm[2], O. Hellwinkel[2], A. Buness[1], M. Ruschhaupt[1], A. Erbersdobler[3], A. Lübke[3], V.D. Luu[1], H. Huland[2], A. Poustka[1]. [1]*German Cancer Research Center, Molecular Genome Analysis, Heidelberg, Germany;* [2]*University Medical Center Hamburg-Eppendorf, Martini-Clinic Prostate Cancer Center, Hamburg, Germany;* [3]*University Medical Center Hamburg-Eppendorf, Institute of Pathology, Hamburg, Germany*

Background: Prostate cancer (PCA) is the most frequent tumor type in males and a major cause of death due to malignancy. The widespread use of the prostate specific antigen (PSA) for the detection of PCA has resulted in an increasing number of men diagnosed with organ-confined, low Gleason-score PCA. However, the high sensitivity of the PSA test is accompanied by a low specificity, causing many patients suffering from unnecessary biopsy taking. Thus, the major aim in current PCA research is to find new molecular markers to improve early diagnosis, prediction of progression, and therapy of PCA.
Materials: To screen for such markers, we applied the cDNA microarray technology to examine genome-wide differences in gene expression in various prostate tissues.
Results: In a first study, we compared normal and tumor prostate from PCA patients. All samples were microdissected and quality-checked before enrollment into the study. We found a large number of differentially expressed genes, including known markers as well as genes whose association with prostate cancer has not been described before. We validated the gene expression patterns of selected candidates with quantitative RT-PCR (qRT-PCR) and derived a gene expression signature for tumor diagnosis and progression. Functional analysis of selected genes by RNA interference in prostate cancer cells revealed several genes, which were conspicuous in cell invasion assays. A second microarray study was designed to compare normal prostate tissue from healthy volunteers to histologically benign tissue from PCA patients. The results were validated by qRT-PCR on an independent sample set taken from tumor-free biopsies.
Conclusions: From these analyses, we derived a diagnostic gene signature, which may be useful to improve patient counseling after negative prostate biopsies, i.e. immediately extended re-biopsy vs. watchful waiting.

4008 POSTER

Bevacizumab/interferon-alpha2a provides a progression-free survival benefit in all prespecified patient subgroups as first-line treatment of metastatic renal cell carcinoma (AVOREN)

S. Bracarda[1], P. Koralewski[2], A. Pluzanska[3], A. Ravaud[4], C. Szczylik[5], C. Chevreau[6], M. Filipek[7], B. Melichar[8], N. Moore[9], B. Escudier[10]. [1]*Azienda Ospedaliera, Medical Oncology, Perugia, Italy;* [2]*Szpital im. Rydygiera, Krakow, Poland;* [3]*Klinika Chemioterapii AM, Lodz, Poland;* [4]*Hôpital Saint André, Medical Oncology and Radiotherapy, Bordeaux, France;* [5]*Wojskowy Instytut Medyczny, Oncology, Warsaw, Poland;* [6]*Institut Claudius-Regaud, Medical Oncology, Toulouse Cedex, France;* [7]*Szpital Wojewodzki im. Sw. Luk, Tarnow, Poland;* [8]*University Hospital Hradec Králové, Oncology and Radiotherapy, Hradec Králové, Czech Republic;* [9]*F.Hoffmann-La Roche, Basel, Switzerland;* [10]*Institut Gustave Roussy, Medicine, Villejuif, France*

Background: Immunotherapy is the current standard of care for patients with metastatic renal cell cancer (mRCC), however only patients with good prognosis typically derive a clinical benefit.Bevacizumab (BEV, Avastin®) is a humanised monoclonal antibody that inhibits tumour angiogenesis by targeting vascular endothelial growth factor. Phase II trials have demonstrated that BEV provides a clinical benefit in both untreated and previously treated patients with mRCC. A multicentre, randomised, double-blind, phase III trial was conducted to compare the efficacy and safety of BEV in combination with interferon (IFN)-α 2a (Roferon®) as first-line treatment in mRCC.
Materials and Methods: Eligible patients had: confirmed clear cell mRCC, undergone nephrectomy, Karnofsky performance status ⩾70%, no CNS metastases, no prior systemic therapy and adequate organ function. Patients were randomized in a 1:1 ratio to IFN-α 2a plus BEV or placebo, stratified by country and Motzer score. Treatment consisted of IFN-α 2a at a recommended dose of 9 MIU 3x/week for up to 1 year, plus BEV 10 mg/kg q2w or placebo until disease progression. Tumour assessments were performed every 8 weeks until week 32 and every 12 weeks thereafter. The effects of baseline demographic and prognostic patient characteristics on progression-free survival (PFS) were analyzed. Cox's proportional hazards model was used to analyze PFS for each level of the baseline variables.

Category	Subgroup	n	Hazard ratio
All		649	0.63
Age	<65	410	0.54
	⩾65	239	0.77
Gender	Female	193	0.60
	Male	456	0.64
Motzer score	Favourable	109	0.77
	Intermediate	433	0.53
	Poor	64	0.69
Lung metastases	No	173	0.77
	Yes	473	0.58
No. of metastatic sites	⩽2	394	0.67
	>2	252	0.54
Body weight loss	⩽10%	501	0.58
	>10%	81	0.76
Baseline VEGF	Below median	191	0.45
	Above median	191	0.67

Results: Between June 2004 and October 2005, 649 patients were randomised (641 treated) at 101 centres in 18 countries. Baseline characteristics were similar in both groups. With a median follow-up of

13 months, the addition of BEV to IFN-α 2a significantly improved duration of PFS in all evaluable patients (10.2 vs 5.4 months, HR = 0.63, p < 0.0001). Analysis of PFS in the prespecified patient subgroups showed that the hazard ratio was consistently <1.
Conclusions: These results demonstrate that BEV plus IFN-α 2a provides a consistent clinical benefit irrespective of baseline prognosis factors and patient characteristics.

4009 POSTER

Urine is the preferred remote body fluid for early identification of prostate cancer using real-time PCR detection of DNA methylation markers

S. Payne[1], J.K. Day[2], S. Cottrell[3], T. deVos[1], S. Yamamura[1], J. Lograsso[1], D. Sarroza[1], Y. O'Campo[1], A. Morotti[1], A. Sledziewski[1]. *[1]Epigenomics Inc., Screening R&D, Seattle WA, USA; [2]Sorenson Genomics, Laboratory Operations, Salt Lake City UT, USA; [3]Amgen Inc., Diagnostics, Seattle WA, USA*

Background: A prostate cancer (PCa) screening biomarker with improved specificity relative to PSA or with the diagnostic ability to discriminate PCa from BPH in patients with elevated PSA would offer a valuable tool for the public health management of PCa. Aberrant DNA methylation occurs early in tumorigenesis, is stable, and can be assayed in tissues and body fluids, making targets of aberrant DNA methylation attractive biomarker candidates. We previously identified candidate DNA methylation markers to discriminate PCa from benign epithelium. We have now validated those markers in a clinical trial and determined the optimal remote body fluid for PCa screening and diagnostics.
Materials & Methods: A clinical study was initiated to determine the optimal remote analyte for a methylation biomarker and to validate the performance of real-time quantitative HeavyMethyl® PCR assays associated with the genes GSTP1, RASSF2, HIST1H4Kand TFAP2E in body fluids. Matched plasma and urine were collected from 100 PCa patients, 51 biopsy negative patients (diagnosed with BPH subsequent to biopsy referral for elevated PSA) and 50 young healthy control males with no known family history of PCa. ROC curves were generated for each marker and cut-off values for methylation were optimized.
Results: In all negative class comparisons and for all markers, urine was the more sensitive analyte. RASSF2 was the best performing screening marker candidate with 74% sensitivity at 96% specificity in urine (37% sens, 100% spec in plasma). HIST1H4K was the best performing diagnostic marker candidate with 28% sensitivity at 95% specificity in urine (16% sens, 96% spec in plasma). None of the markers correlated with PSA values, indicating that they contribute additional information not provided by the PSA value alone. All markers correlated with Gleason score in both urine and plasma DNA. A quantitative screening panel of markers RASSF2 and HIST1H4K yielded 94% sensitivity at 88% specificity. A quantitative diagnostic panel of markers GSTP1 and PSA yielded 83% sensitivity at 45% specificity.
Conclusions: In a series of matched urine and plasma samples we have shown that urine is a superior remote analyte for PCa detection and diagnosis as compared to plasma. We have also shown that a screening panel of only two markers can achieve 94% sens with a spec of 88%. While we have clearly identified markers that discriminate PCa patients from healthy controls, the current markers do not sufficiently discriminate PCa patients from those with BPH as a diagnostic follow-on test to PSA. Identification of markers that improve discrimination of PCa from BPH with elevated PSA is currently underway.

4010 POSTER

Satraplatin increases progression-free survival (PFS) and delays pain progression in hormone refractory prostate cancer (HRPC): Results of SPARC, an international phase III trial with 950 patients

C. Sternberg[1], O. Sartor[2], D. Petrylak[3], J.A. Witjes[4], I. Bodrogi[5], P. Harper[6], J.P. Droz[7], N. James[8]. *[1]San Camillo and Forlanini Hospitals, Medical Oncology, Rome, Italy; [2]Dana Farber Cancer Institute, Lank Center for Genitourinary Oncology, Boston, USA; [3]Columbia University Medical Center, Medical Oncology, New York, USA; [4]Radboud University Nijmegen Medical Center, Department of Urology, Nijmegen, The Netherlands; [5]National Institute of Oncology, Medical Oncology "C" and Clinical Pharmacology, Budapest, Hungary; [6]Guy's Hospital Guy's & St Thomas NHS Trust, Medical Oncology, London, United Kingdom; [7]Centre Léon-Bérard, Geriatric Oncology Program, Lyon, France; [8]University of Birmingham, CRUK institute for Cancer Studies, Birmingham, United Kingdom*

Background: Satraplatin (S) is a novel oral platinum agent with demonstrated activity in many tumors, including HRPC. The SPARC study, a large, randomized, phase III trial, was conducted to compare the effects of S + prednisone (P) and placebo (PL) + P in patients (pts) with HRPC who had failed 1 prior chemotherapy regimen.
Methods: Eligible pts were had stage D2 metastatic HRPC and ECOG performance status 0−2. Pts were randomized to S (80 mg/m^2 qd × 5 d q5w) +P (5 mg bid qd) or to PL+P. The primary endpoint was PFS. Secondary endpoints included time to pain progression (TPP), as indicated by increased present pain index (PPI) score or increased opioid use, and PSA response (⩾50% reduction from baseline). Exploratory analyses measured PFS and TPP for subsets of pts based on prognostic variables: age (<65 or ⩾65 years), baseline PPI score (0 or ⩾1), baseline ECOG score (0−1 or 2), prior docetaxel use, type of tumor progression, and bisphosphonate use.
Results: 950 pts were randomized to S (n = 635) or PL (n = 315). Most pts were Caucasian (89%), age ⩾65 years (71%, median 70 yrs), ECOG score 0−1 (90%), and PPI score 0−1 (65%). In the ITT analyses, pts in the S arm had 33% reduced risk of PFS or death vs the PL arm (median 11.1 vs 9.7 weeks, respectively; HR = 0.67, 95% CI: 0.57−0.77; p < 0.001) and significantly longer median TPP (66.1 vs 22.3 weeks, respectively, HR = 0.64, 95% CI: 0.51, 0.79; p < 0.001). PSA response was also significantly higher in the S arm (25.4% vs 12.4%, p < 0.001). Robust findings across patient subgroups showed significant and comparable treatment effects of S on PFS and TPP irrespective of prior docetaxel use, age, or bisphosphonate use; as well as in pts with baseline PPI scores ⩾1, ECOG scores 0−1, and pts with tumor progression with or without PSA increase. S was well tolerated; the most common adverse events were mild to moderate myelosuppression and GI disturbances. When analyzed by age, neutropenia was more frequent in pts ⩾75 yrs, but no pt in this group had febrile neutropenia and the overall incidence of Grade 3−4 infections remained low.
Conclusions: Second line chemotherapy for pts with HRPC is an unmet medical need. Benefits of satraplatin use on PFS, TPP, and PSA in the ITT population are clear. These results are highly robust. Comparable treatment effects are revealed in different subsets of pts defined by prognostic variables. Satraplatin is well tolerated and will be a welcome addition to the therapeutic armamentarium.

4011 POSTER

Results of a phase 3, randomized study of patients with advanced renal cell carcinoma (RCC) and poor prognostic features treated with temsirolimus, interferon-α or the combination of temsirolimus + interferon-α

P. de Souza[1], K. Maart[2], A. Laurell[3], R.E. Hawkins[4], A. Berkenblit[5], L. Galand[6], A. Thiele[5], A. Strahs[5], J. Feingold[5], G. Hudes[7]. *[1]St. George Hospital, Medical Oncology, Sydney NSW, Australia; [2]GVI Oncology, Clinical Radiation & Oncology, Port Elizabeth, South Africa; [3]University Hospital, Oncology, Uppsala, Sweden; [4]Christe Research Centre, Oncology, Manchester, United Kingdom; [5]Wyeth Research, Clinical Research & Development, Cambridge, USA; [6]Wyeth Research, Clinical Research & Development, Paris, France; [7]Fox Chase Cancer Center, Oncology, Philadelphia, USA*

Background: Temsirolimus is a specific inhibitor of mTOR, a signaling protein that regulates cell growth and angiogenesis. A phase 3, randomized study was designed to determine the effects of first-line treatment with temsirolimus, interferon-α (IFN), or the combination temsirolimus + IFN on patients (pts) with advanced RCC and poor prognostic features. In a second interim analysis, the O'Brien-Fleming Boundary for early success was crossed for the primary endpoint of overall survival (OS; Hudes et al. J Clin Oncol 24: LBA4, 2006). Pts receiving temsirolimus had significantly longer OS compared with IFN (hazard ratio [HR] 0.73; 95% confidence interval [CI] 0.57−0.92; p = 0.007). Pts receiving temsirolimus + IFN did not have significantly longer OS compared with IFN (HR 0.95; 95% CI 0.76, 1.20; p = 0.691). We report the final supportive analysis of this study.
Methods: Pts with previously untreated RCC and poor prognostic features (⩾3 of 6 prognostic factors [Hudes et al. J Clin Oncol 24:LBA4, 2006]) were randomly assigned to 1 of 3 treatment arms: temsirolimus 25 mg IV once weekly (n = 209); IFN 3 million units (MU) escalating to 18 MU subcutaneously (SC) 3 times weekly (n = 207); or temsirolimus 15 mg IV once weekly + IFN 6 MU SC 3 times weekly (n = 210).
Results: This final supportive analysis of 626 pts enrolled was completed when 514 deaths had occurred and confirmed the results of the second interim analysis. Pts receiving temsirolimus continued to have longer OS compared with IFN (HR 0.78; 95% CI 0.63, 0.97; p = 0.0252). OS of pts receiving temsirolimus + IFN was not significantly longer than that for pts receiving IFN (HR 0.93; 95% CI 0.75, 1.15; p = 0.4902). Median OS for temsirolimus, IFN, and combination groups was 10.9, 7.3, and 8.4 months, respectively. Progression-free survival (PFS; investigator assessed) was significantly longer for pts receiving temsirolimus vs. IFN (HR 0.74; 95% CI 0.60, 0.90; p = 0.003). Median PFS was 3.8 and 1.9 months, respectively.