predictive of the efficacy of these agents remain elusive. Previously, serial alpha-fetoprotein (AFP) measurement has been found to be useful in prognostication and monitoring treatment response in HCC patients undergoing systemic chemotherapy. Whether AFP changes during therapy are able to predict treatment efficacy of anti-angiogenic therapy in advanced HCC patients is still unknown.
Materials and Methods: Advanced HCC patients who had been enrolled in three prospective phase II clinical trials evaluating a combination of anti-angiogenic therapy (sorafenib, bevacizumab, or thalidomide) and metronomic oral 5-fluorouracil preparations (tegafur/uracil or capecitabine) as the first-line systemic therapy for advanced diseases were included. Early AFP response was defined as a decline in level of more than 20% from baseline after 2 to 3 weeks of treatment. Baseline AFP level and AFP response were analyzed for their associations with treatment efficacy and survival outcome.
Results: A total of 107 patients were enrolled. Baseline AFP level was elevated in 85 (79%) patients. Patients with normal baseline AFP levels, compared to those with elevated levels, had a better disease control rate (77% vs. 39%, $p = 0.001$), median progression-free survival (PFS, 4.0 vs. 2.0 months, $p = 0.024$) and overall survival (OS, 10.7 vs. 4.2 months, $p = 0.013$). Seventy-two patients were evaluable for early AFP response, and 12 (17%) of them were classified as early AFP responders. Early AFP responders, compared to non-responders, had a better overall response rate (33% vs. 8%, $p = 0.037$) and disease control rate (83% vs. 35%, $p = 0.002$). Median PFS (AFP responders vs. non-responders, 7.5 vs. 1.9 months, $p = 0.001$) and OS (15.3 vs. 4.1 months, $p = 0.019$) were also longer in AFP responders. By multivariate analysis, AFP response remained a significant independent predictor for better PFS and OS.
Conclusion: Early AFP response can predict treatment efficacy and survival of advanced HCC treated with anti-angiogenic targeted therapy and metronomic chemotherapy.
The study was supported by the grant of NSC 98-3112-B-002-038.

PP35

Dual use of single WT-1 immunohistochemistry in evaluation of ovarian tumors: a preliminary study of 20 cases

S. Siddiqui[1], Y.-H. Hsiao[2], W. Wang[3], Y.-g. Man[4]. *[1]Pathology Graduate, Howard University Hospital, USA; [2] 2Department of Obstetrics and Gynecology, Changhua Christian Hospital, Changhua, Taiwan; [3]China-Japan Union Hospital, Jilin University, China; [4]Armed Forces Institute of Pathology and American Registry of Pathology, USA*

Background: Our previous studies revealed that a single Wilms' tumor 1 (WT-1) immunohistochemistry could be used to evaluate both the myoepithelai cells and blood vessels of human breast tumors. As the human ovarian tissue is rich in blood vessels and WT-1 has been suggested to be a biomarker for ovarian tumors, our current study intended to assess whether a single WT-1 immunohistochemistry may have dual use in evaluation of the epithelial cells and microvascular density of ovarian tumors.
Materials and Methods: Consecutive sections were prepared from 20-ovarian tumors with co-existing normal and neoplastic components. Consecutive sections were subjected to immunohistochemistry with a mouse monoclonal antibody against human WT-1 protein. To confirm the specificity and sensitivity of WT-1 immunostaining, two adjacent sections from each case were subjected to immunohistochemistry for a well defined ovarian tumor marker, CA125, and a blood vessel specific marker, CD34. From each case, 4−5 randomly selected areas were photographed, and the percentages of positive cells for these molecules were compared.
Results: Distinct immunoreactivities to WT-1 were co-localized with CA 125 in a vast majority of the ovarian tumor foci. Distinct WT-1 expression was also seen in a vast majority of morphologically distinct endothelial cells that were strongly positive for blood vessel marker CD34. WT-1 immunoreactivities appeared to be substantially higher in small vessels near invasive than in normal or pre-invasive lesions, suggesting that WT-1 expression may correlate with tumor progression or invasion.
Conclusion: Our findings suggest that a single WT-1 immunohistochemistry may be used to assess both the tumor cells and micro-vascular density in ovarian tumors. More importantly, the development of agents to target WT-1 expression in vascular structures may have significant therapeutic value.
Supported in part by grant 2006CB910505 from the Ministry of Chinese Science and Technology Department, grants DAMD17-01-1-0129, DAMD17-01-1-0130, PC051308 from Congressionally Directed Medical Research Programs, grant BCTR0706983 from The Susan G. Komen Breast Cancer Foundation, and grant 2008-02 from US Military Cancer Institute and Henry M. Jackson Foundation.

PP95

Predictive mRNA and microRNA markers of response to the HDAC inhibitor PCI-24781 in colorectal tumors

M. Sirisawad[1], L. Tee[2], H. Mamuszka[2], J.J. Buggy[1]. *[1]Pharmacyclics, USA; [2]Exiqon, USA*

Background: PCI-24781 is an oral HDAC inhibitor currently in clinical trials for treatment of solid and hematological malignancies. It has demonstrated very good activity as a single agent in lymphoma with a good safety profile. In solid tumors, there have been several documented stable diseases (SD) but no PRs or CRs to date, as has been noted for other HDAC inhibitors previously. As with EGFR inhibitors, it is possible that clinical success in solid tumors depends upon the selection of the most sensitive tumor type and the most likely responder population within that indication. Interestingly, however, many of the SDs have been durable, with the longest duration of SD (8 months) being observed in a rectal cancer patient. This correlates well with preclinical data showing very good activity of PCI-24781 in colorectal cancer (CRC) cell lines & xenograft models. We therefore examined the activity of PCI-24781 in primary CRC tumors to identify predictive markers of efficacy.
Materials and Methods: Primary CRC samples were obtained from patient biopsies, plated in soft agar and treated with PCI-24781 and the percentage of cell growth inhibition (%GI) was calculated. RNA from these tumors were profiled on whole genome human microarrays, as well as on microarrays containing all known human microRNAs. Validation of mRNA and microRNA hits was performed by RT-PCR. siRNA was used to knock down these mRNA and miRNAs and changes in sensitivity to PCI-24781 as well as in the gene expression profiles were analyzed.
Results: In metastatic primary tumors from heavily pretreated patients, about 38% of the tumors could be classified as resistant to PCI-24781. From the mRNA profiles in the primary tumors resistance markers was identified and validated in a second independent set of primary tumors by RT-PCR. siRNA knockdown of resistant markers sensitized the cells to PCI-24781. From the miRNA profiles, a predictive signature consisting of 6 miRNAs was obtained, two of were also found to be differentially expressed in a separate analysis of colorectal tumor lines. siRNA knockdown of these miRNAs influenced the mRNA expression profile and sensitivity to PCI-24781.
Conclusion: Predicitive mRNA and miRNA markers of resistance to the HDAC inhibitor PCI-24781 in primary human CRC tumors have been developed. Some of these mRNA and miRNAs were shown to be functionally important in the mechanism of action of PCI-24781 and may be useful as predictive markers for patient stratification in clinical trials.

PP27

Expression of microRNA-221 is progressively reduced in aggressive prostate cancer and metastasis and predicts clinical recurrence

M. Spahn[1], S. Kneitz[2], C.-J. Scholz[2], N. Stenger[3], T. Rüdiger[4], P. Ströbel[5], H. Riedmiller[6], B. Kneitz[6]. *[1]Department of Urology and Pediatric Urology, University Hospital Würzburg, Germany; [2]Microarray Core Unit, IZKF (Interdisciplinary Center for Clinical Research), University of Würzburg, Germany; [3]Department of Urology and Paediatric Urology, University Hospital Würzburg, Germany; [4]Institute of Pathology, Community Hospital Karlsruhe, Germany; [5]Institute of Pathology, University Medical Center Mannheim, University of Heidelberg, Germany; [6]1. Department of Urology and Paediatric Urology, University Hospital Würzburg, Germany*

Background: Emerging evidence shows that microRNAs (miR) are involved in the pathogenesis of a variety of cancers, including prostate carcinoma. Little information is available regarding miR expression levels in lymph node metastasis of prostate cancer or the potential of miRs as prognostic markers in this disease. Therefore, we analyzed miR signatures in prostate carcinoma metastasis and studied the role of miR-221 as a novel prognostic marker in prostate cancer.
Materials and Methods: We analysed the global expression of miRs in benign and hyperplastic prostate tissue (BPH), primary prostate carcinoma (PCA), and corresponding metastatic tissues by micro-array analysis. Ninety two samples of radical prostatectomies were subsequently investigated by qRT-PCR to validate the associations between the expression of miR-221, various clinicopathologic factors, and patient survival.
Results: Consistent with the proposal that some microRNAs are oncomirs, we found aberrant expression of several miRs, including the down-regulation of miR-221, in prostate carcinoma metastasis. In a large study cohort, the miR-221 oncomir was progressively down-regulated in aggressive forms of prostate carcinoma. Down-regulation of miR-221 was associated with clinicopathological parameters, including the Gleason score and the clinical recurrence during follow up. Kaplan Meier estimates