8014 POSTER

Genes differentially expressed in therapeutic response and non-response cervical carcinoma

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Background: Cervical cancer is the second most common cancer in women worldwide. The most important risk factor in the development of cervical cancer is persistent infection with a high-risk human papillomavirus. The standard regimen for treatment of advanced stage cervical cancer is radiotherapy. Although combination of radiotherapy and cisplatin-based chemotherapy is better than radiotherapy alone, 5-year overall survival remains only 52% suggesting that intrinsic and acquired tumor resistance impedes the improvement of standard treatment. To date there are no markers for predicting treatment outcome in cervical cancer. We thus investigated differential gene expression profiling in therapeutic response and non-response cervical carcinoma using the human whole genome microarrays.
Materials and Methods: Total RNA was prepared from cervical tissues obtained from 22 normal and 15 cervical cancer patients, FIGO stage IIIB which were separated into 2 groups based on response to therapy; 7 responses and 8 non-responses. Total RNA in each group was pooled and used to determine gene expression profiles by microarrays. Genes differentially expressed were uploaded and generated the networks using the Ingenuity Pathways Analysis (IPA) software.
Results: The top 10 up-regulated genes expressed in non-responses compared to responses were *REG1A, PLA2G2A, SAA2, LGALS4, IGLL1, CXCL10, FCGBP, IL1B, OVOL1*, and *CHI3L1*. The network generated by IPA with top functions involved in connective tissue disorders, inflammatory diseases, and skeletal and muscular disorders. The top 10 down-regulated genes were *IVL, LCE3D, SPRR3, SLURP1, KRT4, CNFN, CLIC3, SPRR2A, RHCG*, and *CRABP2*. The network generated by IPA with top functions related to cell death, skeletal and muscular disorders, and cellular development.
Conclusions: Genes differentially expressed in non-responses compared with responses in our study are involved in poor prognosis or clinical outcomes of cancer patients suggesting their role as predictive biomarkers for treatment outcome in cervical cancer patients.

8015 POSTER

NKTR-102 demonstrates nonclinical and phase 1 clinical anti-tumor activity in ovarian cancer

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Background: NKTR-102, a novel prodrug of irinotecan (IRI), is currently in phase 2 development in patients with platinum resistant ovarian cancer. NKTR-102 uses Nektar's novel small-molecule advanced polymer conjugate technology to improve the pharmacokinetics and tumor distribution of IRI and its active metabolite SN38. Objective: To investigate the nonclinical and clinical anti-tumor activity of NKTR-102 in metastatic platinum resistant ovarian cancer.
Methods: Mice bearing A2780 ovarian tumors that are minimally responsive to cisplatin, received NKTR-102 or IRI in 3 weekly doses of 50, 100, or 150 mg/kg. Anti-tumor efficacy was evaluated based on tumor growth delay (TGD) in mice and response rate in mice and humans. In the phase 1 study of NKTR-102, 5 patients with ovarian cancer were enrolled in weekly $\times 3$ q4w, q14d and q21d regimens. Patients with measurable disease were assessed for tumor response using RECIST 1.0 every other cycle.
Results: In mice, NKTR-102 and IRI were equally well tolerated. Control tumors grew rapidly and uniformly to the 2000 mm^3 endpoint in a median of 14 days. IRI administered at 50, 100, and 150 mg/kg resulted in TGD of 12, 15, and 16 days, respectively, with one partial response (PR) at the highest dose. NKTR-102 at IRI-equivalent doses resulted in TGDs of 33, 32, and 34 days, respectively, with 100% regression response rate (PRs + CRs) in each group. Increasing NKTR-102 doses were associated with increased numbers of CR responses (5, 8, and 9 CRs, respectively). NKTR-102 was superior to the equivalent IRI dose at all doses tested and the lowest dose of NKTR-102 was superior to the highest IRI dose. In the phase 1 clinical study, tumor response could be assessed in 2 of 5 patients with ovarian cancer. Of these two patients, one patient receiving 145 mg/m^2 q14 (sixth line) had an unconfirmed partial response (37% reduction in target lesions) but terminated from the study prior to confirmation, and one patient on the weekly regimen receiving 172.5 mg/m^2 had a mixed response that included a 21% reduction in target lesions.
Conclusions: NKTR-102 shows superior activity compared to IRI in the A2780 ovarian tumor model, inducing a 100% response rate at all doses and dose-related increases in CRs versus PRs. Anti-tumor activity was observed in heavily pre-treated patients with ovarian cancer. A phase 2 study in patients with platinum resistant ovarian cancer is ongoing

8016 POSTER

Gene expression profile as a diagnostic tool for synchronous ovarian/endometrial cancer

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Background: Since the histological diagnosis of synchronous endometrioid ovarian/endometrial epithelial tumors lacks of sufficient reliability, the aim of this study was to demonstrate that gene expression profiling can provide additional support to traditional diagnostic procedures.
Material and Methods: Within our patients' cohort of 24 women affected by endometrioid epithelial ovarian cancers (EOC-END), ten patients had received a pathological diagnosis of synchronous ovarian/endometrial epithelial cancer. Genetic profiles of flash-frozen tissue biopsies from 22 ovarian, 2 matched ovarian/endometrial adenocarcinomas (EC-END), 15 normal endometria (NE) and 14 human ovarian surface epithelium (HOSE) short-term cell cultures were generated using Affymetrix U133 plus 2.0 oligonucleotide microarrays. The GCOS1.3 algorithm was used to convert array intensities into expression signals and Present calls. Probe sets were retained for comparisons of EOC-END to HOSE or NE if the higher-expressing group had >75% samples called Present and an average log2(signal) >6. EOC-END cases were compared separately to HOSE and NE controls using the two-class-unpaired procedure in SAM Version 3.05. Probe sets were significant by SAM if expression changed >4.0$\times$ with $q < 5\%$. Probe sets significant in both comparisons were used to cluster the samples hierarchically via average linkage, and the two EC-END samples were included in the clustering to examine their relationship with EOC-END samples.
Results: Three hundred forty probe sets met the significance criteria in both SAM analyses and were used to cluster the samples. The hierarchical clustering cleanly divided the EOCs, NEs, and HOSE samples into three major branches, and both EC-END samples clustered with EOCs. Of interest, one EC-END formed a two-member cluster with its ovarian counterpart, indicating that the two cancers from this patient were very similar to each other. By contrast, the other EC-END clustered much closer to other EOCs than it did to its ovarian counterpart, indicating a relative lack of similarity between the two cancers from this patient. These clustering results strongly suggested the presence of metastatic disease in the first patient and of multiple tumors in the second one. Since in both cases pathology reports were ambiguous, our findings demonstrate that cancer genetic profiles can help to clarify the final diagnoses.
Conclusions: Genetic analysis may represent a powerful additional tool for synchronous ovarian/endometrial cancer diagnosis.

8017 POSTER

Tspan13 expression in epithelial ovarian cancer

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Background: Epithelial ovarian cancer (EOC) is a major cause of gynaecologic cancer mortality in the western world. The lack of specific markers and the few early symptoms that characterize EOC, cause that 80% of patients are diagnosed at advance staged of the disease, when the percentages of survival are very low.
Methods: An affinity-purified polyclonal rabbit antibody against tspan13 was raised using a peptide corresponding to amino acids 116−128 in the large extracellular region of the tspan13 protein (sequence accession number: NP_055214) (Pacific Immunolgy, San Diego, CA, USA). Paraffin embedded ovarian cancer tissues were cut at 5 μm serial sections and were deparaffinized in xilene, rehydrated in graded ethanol (100−80%) and then boiled in 10 mM sodium citrate buffer containing 0.05% Tween-20 for antigen retrieval. After incubating the sections in blocking solution, were