Poster presentations (Mon, 24 Sep, 14:00–17:00)

Translational research

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Real time RT-PCR 3-gene expression signature predicts survival in early-stage squamous cell lung cancer

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Background: Around 50% of early stage squamous cell lung cancer (SqCLC) patients will have recurrence after surgery, with distant metastasis being the main cause of treatment failure. Adjuvant chemotherapy improves survival, but the absolute gain is modest and largely limited to stage II-IIIA. High-risk patients may be selected by gene expression profiles and considered for adjuvant chemotherapy.
Methods: Of the consecutive series of 174 NSCLC patients who underwent complete surgery between 2000 and 2004 we selected 66 stage I-IIIA SqCLC patients (64 pts were stage I and II and 2 pts stage IIIA): 33 pts who developed distant metastases and 33 who were free of distant relapse after a median follow-up of 37 months (range, 24–64 months). Snap frozen primary tumor specimens were obtained at the time of surgery. Sections were taken from blocks of tumor tissue for RNA extraction, and gene expression of 29 genes was assessed by RT-PCR using low density arrays. Expression values were dichotomized using the median as a cut-off value.
Results: The univariate analysis identified 10 genes with significant prognostic value: CSF1, EGFR, CA IX, PH4, KIAA0974, ANLN, VEGFC, NTRK1, FN1, INR1. In the multivariate Cox model, CSF1 [HR = 3.5, p = 0.005], EGFR [HR = 2.7, p = 0.02], CA IX [HR = 0.2, p < 0.0001] and tumor size >4 cm [HR = 2.7, p = 0.02] emerged as significant predictors of survival. A risk score based on the expression of CSF1, EGFR and CA IX was 70% accurate in predicting death risk. This model also performed well in predicting development of distant metastases, with 64% sensitivity and 73% specificity. Biologically significant correlations were observed between some of these genes. For example, high levels of PH4 were related to low or no expression of CA IX (r = −0.33; p = 0.007).
Conclusions: Overexpression of CSF1 and EGFR, and downregulation of CA IX was strongly associated with poor prognosis in SqCLC. Simultaneous assessment of the expression of these genes defines the group of high-risk SqCLC patients who might derive the highest benefit from adjuvant chemotherapy.

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Expression of microRNA-451 is associated with disease-free survival in gastric cancer patients treated with chemoradiotherapy after gastric resection

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Purpose: This study was conducted to evaluate the potential association of miRNA expression with outcome after chemoradiotherapy in patients with resected gastric cancer.
Material and Methods: Data of expression of 250 mature miRNAs were obtained by real-time PCR from paraffin-embedded tumor tissues from patients with gastric cancer stage III treated with surgery following radiation therapy plus 5-fluoruracil/leucovorin based chemotherapy. After median-global normalization, we identified the miRNAs whose expression were significantly related to disease-free survival of the patients. The expression of these miRNA was validated using U6B as an endogenous control and including other independent set of patients.
Results: Our results shown that miRNA expression analysis can be tested in archival paraffin-embedded tissues. Low expression of miR-451 is associated with lower time disease-free survival by univariate analysis as well as multivariate analysis (p = 0.000; risk ratio = 4.74; 95% CI = 1.3–17.3). The miR-451 expression was confirmed as prognostic factor independently of stage including in the study 17 new patients of stage II and IV (p = 0.010, risk ratio = 3.3; 95% CI = 1.3–8.5). Moreover, quantitative data of miR-451 was statistically lower in patients with recurrence of disease than in patients without recurrence.
Conclusions: Our results suggests that miRNA expression can be considered as prognostic markers in gastric cancer patients.

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SNS-314, a selective Aurora kinase inhibitor with potent, pre-clinical antitumour activity, shows broad therapeutic potential in combination with standard chemotherapeutics and synergy with microtubule targeted agents

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Background: SNS-314, a selective small-molecule inhibitor of Aurora kinase A, B, and C, has entered a phase 1 clinical trial for the treatment of patients with advanced solid cancers. Aurora kinases play critical roles during mitosis and cytokinesis. SNS-314 demonstrates significant in vivo activity against a wide range of tumor xenograft models. Of importance, SNS-314 shows remarkable tumor growth inhibition using an intermittent dose-schedule which provides potential for combining SNS-314 with other targeted and conventional anti-cancer therapeutics.
Materials and Methods: A colorectal carcinoma cell line, HCT116 with either intact p53 (p53+/+) or suppressed p53 (p53−/−) protein levels, was treated in vitro with SNS-314 in combination with a panel of chemotherapeutic agents using either co-dosing or sequential dosing schedules. High content cell imaging was used to measure the anti-proliferative effects of the compounds.
Results: The most profound anti-proliferative effects were observed with SNS-314 and agents that disrupt microtubule polymerization such as vincristine and nocodazole. Statistically significant synergy was observed in p53 (−/−) HCT116 cells when SNS-314 was co-dosed with high doses of vincristine. Sequential dosing of SNS-314 followed by each chemotherapeutic compound showed significant synergy with vincristine and nocodazole, a trend toward synergy with docetaxel, and additive anti-proliferative effects with carboplatin, gemcitabine, 5-fluorouracil, daunomycin, and the active metabolite of irinotecan, SN38. The synergy observed between SNS-314 and vincristine and the potentiation seen with docetaxel are consistent with the mechanism of action of an Aurora kinase inhibitor that bypasses an activated mitotic spindle checkpoint resulting in mitotic catastrophe and cell death. These results are currently being explored in xenograft models.
Conclusions: SNS-314, a selective Aurora kinase inhibitor, demonstrates significant synergy in colorectal carcinoma cells with vincristine, and additive activity with docetaxel and all other compounds tested. SNS-314, a novel targeted Aurora kinase inhibitor, shows promise for rationally informed chemotherapeutic combinations for the treatment of human malignancies.

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Comparative analysis of microarray testing and immunohistochemistry in patients with carcinoma of unknown primary – CUP syndrome

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Background: Standard pathological examination including immunohistochemistry (IHC) is considered to be gold standard in the evaluation of tissue specimen in cancer of unknown primary. However, the panel of IHC tests is not standardized between different pathologists. Recently a diagnostic microarray gene expression test has been reported to identify the underlying primary malignancy with an accuracy of more than 80%. In this study we compared the microarray test with IHC performed in a central laboratory.
Methods: 92 pts with histologically/cytologically proven adeno- or undifferentiated CUP were randomized in a prospective phase II trial using two different chemotherapy regimen (results have been reported previously, Proc. ASCO 2005, a4089). IHC and microarray testing (CupPrintTM, Agendia, Amsterdam, NL) using paraffin-embedded tissue was performed retrospectively. So far, 27 cases were available for IHC, 15 of these for CupPrint. In 3 of the 15 cases, more than 1 sample was available,