

Correlation of engraftment, mutation status and response to chemotherapy in primary tumor xenograft models of NSCLC

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Background

Recapitulating the complexity of tumor growth in pre-clinical models is important for mechanistic and functional studies of cancer biology. Primary tumor xenografts may represent the histological complexity of NSCLC better than cell lines. However, not all tumors engraft when implanted into scid mice. We assessed whether histological and mutational profiles affect the ability for tumors to engraft and whether these predict response to chemotherapy.

Methods

Tumor fragments from patients undergoing curative surgery were placed subcutaneously into NOD-scid mice within 24 hours of surgery. Patient characteristics for tumors that engrafted (XG) and did not engraft (No-XG) were compared. Patient tumor DNA was analyzed using the OncoCarta™ Panel v1.0 (Sequenom®). XGs were treated with intraperitoneal cisplatin, vinorelbine, pemetrexed or saline (10 replicates/group). A tissue microarray containing all primary and XG tumors was developed for immuno-histochemical studies.

Results

Of 63/157 (40%) implanted NSCLCs that engrafted, histology was maintained in 97% XGs. Mutations in primary tumors were also detected in XGs. Histological factors significantly associated with engraftment included squamous histology, poor tumor differentiation and larger tumor size. Significantly fewer *EGFR* mutated tumors engrafted ($p=0.012$); conversely, more *KRAS* mutated tumors did engraft ($p=0.062$). In multivariate analysis including age, sex, stage and mutation, patients whose tumors formed XG had significantly shorter DFS compared to no-XG patients (HR 3.43 95%CI 1.21-9.74; $p=0.021$). Response to chemotherapy was seen in 5/21 (23%) cisplatin, 8/18 (44%) vinorelbine and 1/12 pemetrexed treated XGs. pS6RP H-score appeared predictive for response to cisplatin. Mutational status, ERCC1 H-score and P53 did not predict response to chemotherapy.

Conclusions

XGs closely mirror primary tumors histologically and mutationally. Response rates to chemotherapy were similar to that observed clinically. However, tumors that engraft are biologically more aggressive. This should be considered when interpreting results from pre-clinical studies.