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LIQUID VERSUS TISSUE BIOPSY FOR DETECTING ACQUIRED RESISTANCE AND TUMOUR HETEROGENEITY IN GASTROINTESTINAL CANCERS

Gastrointestinal cancers are a subset of molecularly heterogeneous diseases. In the era of personalised medicine, major efforts are being made towards stratifying patients according to molecular profiling. However, although most treatments are currently based on targeted therapy in relation to specific genomic alterations, acquired resistance emerges during anticancer therapies and subsequently treatment failure occurs. Intratumour heterogeneity plays a significant role in the acquisition of resistance by clonal evolution of tumour cell populations under therapeutic pressure. Despite a single tumour biopsy represents the standard for cancer research and drives our therapeutic decisions, limitations in terms of acquisition and utility, and underestimation of the genomic landscape of tumours are found. Analysis of circulating tumour DNA (ctDNA) overcomes these barriers and allows us a more comprehensive study of tumour capturing intratumour heterogeneity to identify resistance to targeted therapy to better select subsequent treatment.

Parikh *et al*[1] recently published in *Nature Medicine* an article that demonstrates how a single tissue biopsy fails to identify multiple acquired resistance mechanisms compared with ctDNA analysis across different gastrointestinal cancers. This study is the largest comparing ctDNA to tumour biopsy characterisation after disease progression to tailored therapy. ctDNA post-progression from 42 patients diagnosed with different gastrointestinal cancers was analysed by next-generation sequencing (NGS) and/or whole-exome sequencing identifying at least one resistance mechanisms in 32 of 42 (76%) patients and multiple resistance alterations in 17 of 32 (53%) individuals. In contrast, tumour biopsy identified a resistance alteration in 11 of 23 (48%) cases and multiples mechanisms in only 2 of the 23 (9%) patients with tumour tissue available at this time. Interestingly, it was possible to analyse tumour tissue from different regions or metastasis in five patients demonstrating distinct resistance alterations depending on the biopsy site. ctDNA analysis detected all resistance mechanisms identified in the different metastatic lesions again emphasising the ability of ctDNA to reflect heterogeneous molecular alterations present concurrently in distinct tumour lesions in a single patient. Only in one patient harbouring a resistance alteration in the tumour biopsy, this was not detected in matched post-progression ctDNA. However, this alteration was later detected using a higher-sensitive technique called droplet digital PCR (ddPCR). This finding underlines that ddPCR is a sensitive, rapid and affordable method compared with NGS to identify resistance alterations with high accuracy. In conclusion, the present article highlights that ctDNA analysis captures the heterogeneity of resistance after targeted therapy underrepresented across a single tumour biopsy. However, tissue biopsy remains crucial in assessing acquired alterations, specifically for non-genetic resistance mechanisms.

POTENTIAL TO ACCELERATE BIOMARKER DISCOVERY THROUGH CO-CLINICAL TRIALS USING PATIENT-DERIVED XENOGRAFTS: TEMOZOLAMIDE AND OLAPARIB IN SMALL CELL LUNG CANCER

Small cell lung cancer (SCLC) is characterised by a dismal prognosis and little advances in treatment during the last 20 years. Drugs, which seemed promising in early phase trials, have frequently not confirmed their efficacy in larger phase III trials. Furthermore, the scarcity of available tumour tissue and the difficulty of repeating sequential biopsies on progression limit the knowledge on specific molecular alterations and activated pathways implicated. Cisplatin and etoposide (EP) remained the standard first-line therapy for decades. The addition of a checkpoint inhibitor recently proved to increase overall survival in this population. Platinum sensitivity largely determines the expected efficacy of second-line treatment, and few drugs have significant activity in this setting.

Poly-[ADP-ribose]-polymerase inhibitors show limited activity in SCLC models and early phase trials. Despite their single-agent activity being minimal, they seem to have a synergistic effect when combined with inhibitors of DNA damage response.

In an article recently published in *Cancer Discovery* by Farago *et al*, they report on a multi-institutional phase I dose escalation trial and a phase II multi-stage portion of olaparib and temolamide (OT) in patients with SCLC previously treated with platinum-based chemotherapy. The authors developed a series of patient-derived xenografts (PDXs) from patients treated on the phase I portion of the trial, prior to receiving OT and at progression to this therapy. Following treatment of these models, they show comparable efficacy in these PDXs as compared with their donor patients with regards to maximum tumour regression and time to 200% initial tumour volume. This confirmed an accurate recapitulation of the sensitivity and resistance of the PDX models to their matching patients. This allowed them to expand the co-clinical trial to an additional 26 PDX models derived from an unselected cohort of patients representative of a wide biologic diversity of patients with SCLC, not treated on OT therapy. It included 13 models from chemotherapy-naïve patients and 19 generated from patients who had received at least one prior line of therapy. The responses seen in this second cohort again mimicked that seen in the patient cohort.

Farago *et al*[2] correlated transcriptional profiles of the PDX models relative to their treatment regimen and found that gene expression profiles associated with EP sensitivity largely overlap with those associated with OT response. Inflammatory gene sets (interferon-γ and interferon-β, TNF-α, inflammation and TGF-β) enriched for sensitivity to both EP and OT therapy. Increased expression of MYC-regulated transcripts on the other hand enriched for models resistant to EP and OT therapy. These finding are confirmed in a separate OT model validation cohort. In an accompanying editorial,[3] it is said that longitudinal construction of PDX models from samples taken before treatment, at different time points during treatment and at development of progressive disease will further our ability to personalise treatment of SCLC and provide us with information on how resistance develops so that we may better combat it. This experimental system represents a novel approach for patient selection and drug development in a setting where tissue availability is still be an issue.

REMOVAL OF N-LINKED GLYCOSYLATION ENHANCES PD-L1 DETECTION AND PREDICTS ANTI-PD-1/PD-L1 THERAPEUTIC EFFICACY

Immunotherapy has recently and strongly revolutionised the treatment of several solid tumours. However, the selection of patients who will benefit from this approach still represents a challenge. Several factors have been postulated to predict response to anti-PD-1 or anti-PD-L1 inhibitors, such as tumor-infiltrating lymphocytes (TILs), mutational burden and PD-L1 expression. Nevertheless, the results of many trials have questioned the predictive role of PD-L1. In this scenario, the inconsistencies between PD-L1 levels and patient response present a clinical limitation. To address this problem, some researchers focused on post-translational modifications that could alter the capability for standard antibodies in detecting the real expression of PD-L1. Thus, N-linked glycosylation of PD-L1 was supposed to lead to inaccurate immunohistochemical readouts of PD-L1. In an elegant paper published in *Cancer Cell* by Lee *et al*,[4] the possible role of glycosylation in inhibiting the correct evaluation of PD-L1 expression was evaluated. In their work, a panel of cancer cell lines was screened showing that the removal of N-Linked glycosylation enhances PD-L1 detection not influencing the results over PD-L1-negative cell lines. To confirm these results, several biopsies were analysed and, again, it was possible to observe that deglycosylation significantly enhances PD-L1, with a fold for glycosylation of more than 2× in about 37.5%–57.5% of cases. In NSCLC, samples' deglycosylation significantly increased PD-L1 tumour proportion score (TPS) from 5% to more than 49%, the clinically agreed-upon cut-offs to be considered eligible for immunotherapy. Thus, the removal of N-linked glycosylation identified that about 16.4%–24.5% of the patients who could have received anti-PD-1/PD-L1 therapy were excluded based on the current staining method. To analyse whether PD-L1 expression after deglycosylation was reliable to response to anti PD-1 or PD-L1 inhibitors, samples were newly grouped and, finally, the authors demonstrated that deglycosylation renders a more accurate assessment of PD-L1 levels to predict clinical outcomes. For this reason, it seems reasonable that increased PD-L1 signal after deglycosylation is beneficial for therapeutic selection. When, apart from cancer cells, the tumour-associated immune cells were analysed, signal intensity of both TPS and combined positive score (CPS) of PD-L1 varied significantly. These results further suggested that measuring PD-L1 levels either by the TPS or CPS following deglycosylation predicts accurately anti-PD-1/PD-L1 clinical outcome. Moreover, it was demonstrated that antigen retrieval by protein deglycosylation improves predictive ability of PD-L1 as a biomarker for immunotherapy. In conclusion, the deglycosylation of PD-L1 might be an effective method to improve the predictive power of PD-L1 as a biomarker for immune checkpoint inhibitors. Therefore, the removal of the glycan moieties on PD-L1 to expose its polypeptide antigens could potential improve PD-L1 detection providing potential benefits for personalised medicine.

Contributors All authors contributed equally.

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