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PROGNOSTIC AND PREDICTIVE VALUE OF CIRCULATING TUMOUR DNA IN PATIENTS TREATED WITH IMMUNE CHECKPOINT BLOCKADE

Immune checkpoint inhibitors are widely used as treatment for an increasing number of solid tumours. Nevertheless, the lack of predictive biomarker represents a limitation across several cancer types.

During the last years, the possibility to dynamically study tumour evolution through circulating tumour DNA (ctDNA) in plasma has opened novel possibility in evaluating disease status and therapeutic response, especially in localised disease to predict the possibility of relapse. However, the specific opportunities for application in the context of immunotherapy remain to be clarified.[1]

In an article recently published in Cancer Discovery by Zhang *et al*,[2] a comprehensive analysis of ctDNA data from about 1000 patients with 16 different solid tumour types, being the most represented non-small-cell lung cancer (NSCLC), urothelial, microsatellite instability high, gastro-oesophageal and ovarian cancers, treated in three phase I/II trials of durvalumab alone or in combination with tremelimumab, was presented.

The aim was to characterise the prognostic and predictive value of pre and on-treatment ctDNA analysis, using training and validation sets. It was shown that ctDNA is detectable in most patients with important disease-specific differences. Pretreatment ctDNA level appears to be an independent, inversely prognostic variable across tumour types, characterised by an association with overall survival and other known prognostic variables, but not with overall response rate. On the other hand, on treatment ctDNA dynamics appear to be predictive of long-term benefit from immunotherapy across tumour types. The last point is of clinical interest as ctDNA fills an important unmet need as a complement to radiological assessments of benefit. Radiological stable disease is a common and particularly challenging clinical category, composed of patients with slowly progressive disease, indolent non-responding disease and radiologically subtle responses to immunotherapy.[3]

It was demonstrated that molecular response, defined by ctDNA dynamics, can help differentiatepatient who will ultimately derive benefit from immunotherapy from those with indolent or progressive disease who are unlikely to derive further benefit from treatment. Although promising, the study has some limitations including the moderate size of the gene panel used, which hinders reliable estimates of Tumor mutational burden, the lack of microenvironment specific biomarkers as well as other potentially relevant molecular features such as clonality and tumour heterogeneity. Moreover, the presence of potential germline and clonal hemopoietic variants was not evaluated. The results of this investigation confirm in a wide population that ctDNA analyses can be an important baseline prognostic feature for stratification in clinical trials, serve as an early biomarker of response.

RET-ALTERED THYROID CANCERS: A NEW PARADIGM FOR TARGETED THERAPY

Targeted therapy has become the cornerstone of precision medicine application in oncology. In recent years, we have notable examples of how an effort to identify relatively rare genomic alterations, such as neurotrophin receptors (NTRK) fusions, that are present in approximately 0.3% of tumours, can have a major impact on their outcome since treatment with NTRK inhibitors achieves responses in 75% of patients regardless of their histological type.[4] This, together with other agnostic indications such as deficient mismatch-repair genes[5] has led to a paradigm shift, both in drug development strategy, and in the framework of regulatory agencies.

The RET proto-oncogene encodes a transmembrane receptor tyrosine kinase that is involved in normal embryonic development and could be constitutively activated through two distinct mechanisms: mutations and structural rearrangements leading to the fusion of

RET to a 5' upstream partner. Germline RET mutations cause hereditary multiple endocrine neoplasia (MEN) 2A and MEN2B, that result for 25% of all diagnosed cases of medullary thyroid cancer. Of the remaining 75% of cases of sporadic medullary thyroid cancer, somatic RET mutations are present in about 60%. RET fusions are oncogenic drivers in fewer than 10% of differentiated or anaplastic thyroid cancers and in 1% to 2% of NSCLC.

In an interesting article recently published in NEJM, Wirth *et al* presented the outcome of the RET-altered thyroid cancer cohort from the LIBRETTO-001 phase 1–2 trial.[6] In the group of 55 RET-mutated medullary thyroid cancer patients previously treated with vandetanib, cabozantinib or both, the progression-free survival (PFS) at 1 year was 82% and the objective response rate (ORR) was 69% (95% CI 55% to 81%). Among 88 patients with RET-mutated medullary thyroid cancer naïve for targeted therapy the 1 year PFS was 92% (95% CI 82% to 97%) and the ORR was 73% (95% CI 62% to 82%). The group of nineteen previously treated RET fusion-positive thyroid cancer patients showed a 1-year PFS of 64% (95% CI 37% to 82%) and an ORR of 79 (95% CI 54 to 94). In addition, the toxicity profile was favourable: the most common adverse events of grade 3 or higher were hypertension, hypertransaminasaemia, hyponatraemia and diarrhoea, and they were present in less than 21% of patients.

In an accompanying editorial,[7] Kurzrock discusses some benefits of using selpercatinib over previously approved multikinase inhibitors such as vandetanib or cabozantinib in patients with RET-altered thyroid cancer. Thus, selpercatinib, a highly potent and selective third-generation inhibitor, stands out for its greater efficacy with a better safety profile, since it avoids off-target effects. Moreover, Kurzrock summarises the impressive data reported by Drilon *et al* in the cohort of patients with RET fusion-positive NSCLC both naïve or previously exposed to platinum achieving durable efficacy with intracranial activity and a favourable safety profile.[8]

In conclusion, selpercatinib has shown great efficacy with long-lasting responses together with scarce toxicity in patients with RET-altered medullary thyroid cancer or NSCLC, both naïve and pretreated. However, perhaps the main take-home message is the need to incorporate the detection of RET alterations into the routine molecular diagnostic panel for thyroid and NSCLC. In this sense, the increasing importance of Molecular Tumour Board to assess molecular alterations detected in next-generation sequencing in academic centre has to be underlined.

PANCANCER COMPUTATIONAL HISTOPATHOLOGY REVEALS MUTATIONS, TUMOUR COMPOSITION AND PROGNOSIS

In the era of precision oncology, histopathological diagnosis remains the core to which an increasing number of molecular tests are added to design personalised patient care. In parallel, there is a raise of interest in artificial-intelligence (AI)-based digital pathology technologies, which involve scanning and analysing digitised whole-slide images. Different AI computational approaches have been applied to tumour diagnosis, classification and prognostic prediction, as well as detection of genetic alterations and biomarkers.[9] Deep learning strategies are able, among others, to classify and predict mutations in lung and liver cancers, and to predict microsatellite instability in gastrointestinal cancer.

In an exciting article, recently published in Nature Cancer, Fu *et al* use deep transfer learning and demonstrate that links between a tumour's morphology and its molecular composition can be found in every cancer type and for nearly every type of genomic and transcriptomic alteration.[10] The authors collected more than 17 000 tissue image slides from The Cancer Genome Atlas, containing 28 cancer types with matched genomic, transcriptomic and clinical outcome data. The pancancer computational histopathology analysis was trained using the pathologist estimate of tumour content to obtain a quantitative representation of 'computational histopathological features'. The algorithm was able to accurately discriminate tissue types and classify in tumour and normal tissue, and deep transfer learning allowed discovering correlations with mutations, transcriptomic signatures and prognosis. Remarkably, conventional histopathological subtypes and grade generally only accounted for a fraction of the associations, which highlights the potential of this approach for discovery.

Automatically learnt histopathological features were associated with a wide range of genetic alterations across cancer types, including whole-genome duplications, chromosomal aneuploidies, focal amplifications and deletions, as well as driver gene mutations. Interestingly, *BRAF* mutations were associated with thyroid carcinomas with papillary morphology, and focal amplification of *EGFR* was characterised by a distinct small cell morphology in glioblastoma. It remains to be elucidated whether morphology is a consequence of the alteration or an indication that these molecular alterations particularly affect specific cell types.

The complex interaction between cancer, immune and stromal cells can be perceived in histopathology. Tumour gene expression not only derives from cancer cells, but also from the associated tumour microenvironment. In this work, a wide range of correlations between histopathology and transcriptomic data reflected stromal content, immune cell infiltration and cell proliferation. Remarkably, even without specifically providing annotated data, the algorithm was able to localise tumour-infiltrating lymphocytes to specific areas. Finally, computational histopathological features also correlated with overall survival for most cancer types, and may even refine existing stage-based prognosis for several tumour types. Interestingly, risk predictions were based on favourable and unfavourable patterns, such as lymphocytic aggregates and necrosis, identified in distinct areas of the same slide.

The analysis was validated on two external breast cancer cohorts from the Molecular Taxonomy of Breast Cancer

International Consortium and the Breast Cancer Somatic Genetics Study consortium, and most associations were reproduced with only minor reduced accuracy. Although computer vision cannot yet replace molecular testing, it may be able to augment histopathological diagnosis adding information to identify novel biomarkers for precision oncology, increasing prognostic information and accelerating diagnosis. The incredible potential of computational histopathological analysis to unravel molecular profiles undoubtedly warrants further refinements, such as future strategies using spatial transcriptomics and sequencing.

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