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PATIENT-DERIVED ORGANOIDS (PDOS) MAY PREDICT PATIENT RESPONSES IN ADVANCED GASTROINTESTINAL CANCERS AND CAN BE IMPLEMENTED IN PRECISION MEDICINE

The most important aim of precision medicine is the selection of the best treatment for each individual patient. To achieve this objective, the analysis of the molecular changes that can occur due to tumour heterogeneity or after anticancer treatment is fundamental. A dynamical study of the disease could lead to the identification of specific targets, which need to be inhibited at time of tumour progression.

By using high-throughput sequencing, it is possible to identify a very limited number of somatic mutations that can be exploited for cancer treatment and drug development. However, the ability to predict response to targeted agents needs to be further improved. To do this, parallel studies, in which drug responses in patients are matched to laboratory preclinical models to personalise treatment and understand mechanisms of chemosensitivity, are fundamental. Organoids are 3D cell-culture systems generated from cancer cells obtained from tumour biopsies from patients. Organoids models make the dynamical study of tumours alterations possible.

A relevant publication on the capability of patient-derived organoids (PDOs) obtained from patients with heavily metastatic gastrointestinal tumours in predicting response to treatment was recently reported in Science.[1] In this article, a total of 110 fresh biopsies obtained from 71 heavily pretreated patients diagnosed with colorectal, gastric cancer or cholangiocarcinoma, enrolled in four Phase I/II clinical trials, were processed by investigators at the Institute of Cancer Research and Royal Marsden Hospital in London. In several cases, PDOs were established from sequential biopsies from metastatic locations at baseline, at the time of best response and at the time of disease progression. Overall, a 96% overlap in mutational spectrum was observed between PDOs, PDO-derived orthotopic tumours (PDO-xenografts) and their parental biopsies. High concordance was also detected in mutational profile, copy number alterations and transcriptomic profiling. Intratumour heterogeneity was also reproduced. Moreover, PDOs were adopted as drug-screening tools. It was showed that response to chemotherapy, cetuximab, regorafenib and TAS102 observed in the POD and in POD orthotopic xenografts was comparable to the one obtained in the treated patients. For the PDOs that were analysed, it was possible to found 100% sensitivity, 93% specificity, 88% positive predictive value and 100% negative predictive value in forecasting response to targeted agents or chemotherapy in patients.

The authors demonstrate as proof of concept that PDOs can be exploited for functional genomics to simulate cancer behaviour and treatment response ex vivo permitting a transposition into the decision making process of early-phase clinical trials. This model could be particularly valuable for drug such as regorafenib or trifluridine/tipiracil with limited impact in outcomes in patients with refractory colorectal cancer and with no defined molecular predictive biomarkers.

IMPROVING CENTRAL NERVOUS SYSTEM TUMOURS DIAGNOSIS BY COMBINING DNA METHYLATION PROFILES AND MACHINE-LEARNING-BASED METHODS

Accurate diagnosis remains challenging in central nervous system (CNS) tumours even with the implementation of integrated diagnosis (*histopathological and molecular characteristics)* proposed by the WHO 2016 Classification. Its main difficulties lie in its high heterogeneity, the interobserver variability and the discordance at the threshold of some molecular tests. To overcome these limitations, an international cooperative effort by several academic institutions led by German researchers has developed a new methylation-based classification of CNS tumours that has been recently published in *Nature*.[2]

These investigators performed genome-wide methylation patterns in freshly frozen or formalin-fixed, paraffin-embedded (FFPE) tumour samples from 2801 individuals with all scope of CNS tumours by

using DNA arrays. Then, the computer used supervised machine learning to recognise methylation patterns present in the pathologist-classified samples, as well as unsupervised machine learning, which involved the computer searching the datasets for patterns that it could use to assign samples into its own computer-generated classification categories.

Through an iterative clustering analysis, 82 methylation-informed CNS clusters were identified. More than two-thirds of these clusters overlapped with existing tumour class or subclass entities from the WHO, while the remaining tumours have not been defined by the WHO classification. Therefore, one of the most relevant findings were tumour classifications that grouped together histologically similar types of tumour comprising more than one tumour type as classified by the WHO or classifications of tumour types that did not match the WHO groupings, since it means that there are tumour similarities that are not related to tumour histology but could contribute to develop new therapeutics.

In order to assess their clinical implementation, authors prospectively analysed 1104 cases that had been diagnosed by pathologists using standard procedures. In the 60.4% of these cases, there was concordance between the computer and the pathologist's classification; for 15.5% of the test cases, the computer and pathologist were concordant but the computer could also identify an additional subclass in the same sample. In 12.6% of the test cases, there was discordance between the computer and the pathologist's diagnosis. It is worth noting that after further analysis (such as gene sequencing), 92.8% of these discordant cases were switched from the initial pathological diagnosis to the computer-based classification. Furthermore, in the 71% of the reclassified tumours, the new classification involved different tumour grade that might have prognostic and therapeutic implications. The remaining cases (11.5%) could not be classified by the computer yet.

In an accompanying perspective article, Wong and Yip highlight some of the strengths and weaknesses of this approach.[3] The utility of obtaining a complete molecular profile of a tumour sample, at low cost, and by using widely available FFPE material is undoubted. Nevertheless, at the moment, histology remains essential in the diagnosis and sample preservation workflow. Thus, even although adaptation of the proposed technique in diagnostic laboratories is relatively straightforward, it could delay its widespread use in daily practice. Therefore, at short term, the most immediate application of this approach would be as a complement in refining diagnosis of rare or ambiguous cases with standard procedures; however, in the medium term, it will improve diagnostic accuracy by providing more comprehensive information.

LIQUID BIOPSIES IN ADVANCED PROSTATE CANCER: A DIGITAL RNA-BASED CIRCULATING TUMOUR CELL SIGNATURES MAY GUIDE THERAPY

Most patients with advanced prostate cancer do present with multiple metastatic bone lesions, making biopsies difficult to analyse molecular aspects, which could be relevant for predictive purposes. This particular point makes liquid biopsies a very relevant emerging strategy for precision medicine in prostate cancer. Most molecular alterations studied in prostate cancer are related to androgen receptors genes, provided that the majority of patients will initially respond to androgen deprivation. In the androgen independent status some other pathways has been also implicated such as the expression of the glucocorticoid receptor, the non-canonical WNT pathway and the transformation to neuroendocrine phenotype.

Circulating tumour cells (CTC) have been frequently isolated in patients with advanced prostate cancer providing material for biological analysis. However, some technical difficulties may hamper its broad clinical application. The development of microfluidic technologies allows efficient processing of blood specimens for CTC capture, including efficient depletion of haematopoietic cells to enable tumour epitope-independent enrichment of untagged CTCs.

In a recent issue of Cancer Discovery a team of investigators from the Massachusetts General Hospital have established an RNA-based molecular signature that allows high throughput and highly quantitative detection of prostate CTCs following microfluidic enrichment.[4] The CTC enrichment was followed by RNA-based digital droplet PCR (ddPCR) and a digital RNA-based scoring system. This resulted in a set of eight genes suitable for developing an RNA-based signature, including four androgen-responsive transcripts (*KLK3* (PSA), *KLK2*, *TMPRSS2* and *AGR2*), two androgen-repressed transcripts (*FOLH1* (PSMA) and *HOXB13*) and two androgen-independent transcripts (*FAT1* and *STEAP2*).

In a prospective trial of men with metastatic castration-resistant prostate cancer treated with first-line abiraterone, they were able to identify predictive CTC-derived molecular markers of clinical outcome. Furthermore, in men with clinically localised prostate cancer undergoing radical prostatectomy, digital detection of CTCs is predictive of pathological seminal vesicle invasion and lymph node dissemination identified at the time of surgery.

These investigators established a sensitive and high-throughput strategy for analysing prostate CTC using microfluidic cell enrichment followed by digital quantitation of prostate-derived transcripts. In a prospective study of 27 patients with metastatic castration-resistant prostate cancer treated with first-line abiraterone, pretreatment elevation of the digital CTC score could identify a high-risk population with poor overall survival and short radiographic progression-free survival. Expression of *HOXB13, a* downstream indicator of the altered

androgen receptor pathway, in CTCs could detect six of six patients with ≤12 month survival, with a subset also expressing the *ARV7* splice variant. *ARV7* is a readily measurable biomarker for acquired androgen pathway independence, predicting resistance to abiraterone or enzalutamide therapy. In a second cohort of 34 men with localised prostate cancer, an elevated preoperative CTC score predicted microscopic dissemination to seminal vesicles and/or lymph nodes.

Although this results should be confirmed in larger series from controlled trials, RNA-based digital CTC scoring may provide a highly sensitive and quantitative blood-based marker to complement standard clinical parameters, with the goal of optimising treatment algorithms in both early and advanced prostate cancer. In summary, there is no doubt that liquid biopsies will evolve to be an indispensable tool in precision oncology, and this study is another big step forward in improving management for the most frequent tumour in men, that is, prostate cancer.[5]

Contributors All contributed equally.

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