In the news

FROM NEW DIRECTIONS IN IMMUNO-ONCOLOGY

Over the past 5 years, immunotherapies have transformed the treatment landscape and the outcomes of patients with cancer. "Such is the impact of these new therapies that all our clinics and treatment chairs are full", explains James Spicer, member of the scientific committee of the New directions in immuno-oncology conference that was held in London in September 2019. This event, a Cancer Research UK initiative, brought together an interdisciplinary group of leaders in the field. In the inaugural address, attendees were reminded that improvements of the current treatment options will only be achieved through collaboration. Indeed, in their presentations, most speakers acknowledged the importance of collaboration in their research.

In this conference, we heard examples of treatments for solid tumours as well as haematological malignancies. All immunotherapy modalities were discussed, from immune-checkpoint inhibition and adoptive cell therapies to vaccine-based approaches and strategies aimed at modulating the microbiome, which was highlighted by Jennifer Wargo as a key element in the response to immunotherapies.

Some sessions were dedicated to discussing the function of several elements of the immune system, such as macrophages, natural killer cells, myeloid-derived stem cells and different subsets of T cells. A common message in these presentations is that, owing to the high degree of adaptability of immunity, immune cell subtypes cannot be considered to have either a tumour-promoting or tumour-suppressing function. A better understanding of distinct immune cell subpopulations will enable the administration of therapies targeting only relevant subsets, with increased efficacy and reduced toxicities.

The concepts of evolution and heterogeneity were addressed by Alberto Bardelli, Joop Jansen, Samra Turajlic and Ash Alizadeh, who presented results of their studies on the molecular mechanisms underlying neoantigen presentation. Other key elements of antitumour immunity, such as the complement pathway, immune surveillance and innate immunity, were presented by Dimitrios Mastellos, Adrian Hayday and Eileen Parkes, respectively. The resulting picture is that of a complex network of immune pathways, all with clinical potential.

Several presentations addressed the growing number of digital tools that are enabling analyses of the intricacies of antitumour immunity. For example, the availability of algorithms that integrate single-cell data could facilitate the design of personalized immunotherapies and real-time monitoring of the response to such treatments.

In summary, the multifaceted nature of antitumour immunity was highlighted throughout the conference. Addressing this complexity in the clinic is not an easy task, but collaborative research has already resulted in favourable outcomes in the field — the facilitation of interactions between researchers can ensure the continuity of this trend.

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Credit: Simon Bradbrook/Springer Nature Limited

GASTROINTESTINAL CANCER

Liquid outperforms tissue

Liquid biopsy is a promising method of monitoring response to treatment, but prospective comparisons of the performance of this approach with single-lesion tissue biopsy in large patient cohorts are needed. Now, such a comparison in patients with gastrointestinal tumours indicates that liquid biopsy might be a more effective tool to monitor acquired resistance to targeted therapy.

A total of 42 patients with gastrointestinal tumours (of seven molecular subtypes across colorectal, gastro-esophageal or biliary tract cancer) with stable disease or a partial response to targeted therapies were involved in this prospective study. Post-progression cell-free DNA (cfDNA) was obtained from peripheral blood samples from all patients. At least one alteration previously validated as being related to resistance was identified in 32 of 42 patients (76%), 17 of whom (40% of all patients) had >1 resistance alteration, with a median of 3 alterations per patient. "These data suggest that the emergence of multiple resistance mechanisms is more common than previously thought and might be the rule rather than the exception", explains co-lead author Gad Getz.

"Liquid biopsy enabled the identification of clinically relevant resistance alterations not detected in the matched tumour biopsy samples in a large proportion of patients, suggesting key advantages over standard tissue biopsy in the setting of acquired resistance", highlights co-lead author Ryan Corcoran. When matched post-progression samples were available, resistance alterations were identified in tissue samples in 11 of 23 patients (48%) and in cfDNA in 20 (87%). In contrast with the results of cfDNA analysis, multiple resistance alterations were identified in tissue samples in only 2 of 23 patients (9%). Only one resistance alteration (an *EGFR* mutation) was identified in tissue samples but not in the matched cfDNA sample by clinical next-generation sequencing. The alteration was subsequently detected with high-sensitivity droplet digital PCR in the cfDNA sample.

Phylogenetic analysis of pretreatment and post-progression cfDNA, and post-progression and autopsy-derived tissue samples from five patients revealed a high degree of intrapatient heterogeneity in the acquisition of resistance mutations. "Liquid biopsies capture the clonal complexity of most of the lesions in the body and can facilitate detection of multiple resistance mechanisms," summarizes Getz.

"In the setting of targeted therapies, liquid biopsies should be incorporated more regularly into clinical practice", concludes Corcoran, adding "the optimal use of liquid biopsies to guide therapy decisions warrants further study." Studies addressing the biological processes underlying the release of cfDNA and other molecules from tumour cells into circulation will also enable the optimal use of liquid biopsies.

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