News in Brief

European society for medical oncology virtual congress: Molecular analysis for precision oncology, October 9th – October 10th, 2020

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A R T I C L E   I N F O

Article History:
Received 7 January 2021
Accepted 7 January 2021

As with many other conferences over the past year, the 2020 Molecular Analysis for Precision Oncology (MAP) Congress moved online. The conference brought together translational researchers and clinicians with the aim of providing personalised care to patients with cancer. Below are examples of the cutting-edge research that was presented.

On the origin of mutations

The first session, Molecular Targeting, provided a tour of common mutations in various cancers. One of the speakers was François Radvanyi (Institut Curie, Paris, France) who took us through his group’s work on Muscle Invasive Bladder cancer and a mutation within the Fibroblast Growth Factor Receptor 3 gene (FGFR3). The mutation is a single base substitution (a cytosine to a guanine), resulting in the switching of serine 249 for a cysteine (S249C) in the translated protein. The erroneous cysteines allow disulphide bridges to form between FGFR3 monomers causing them to become constitutively active. Once active, downstream signalling from FGFR3 results in a positive feedback loop. Radvanyi then described work published in European Urology and Genome Medicine identifying the probable source of this mutation, a family of proteins that normally protect the cell. The APOBEC family of proteins are anti-viral complexes that have been shown to inhibit HIV infections by introducing mutations into the viral genome during replication. Aberrant APOBEC enzymatic activity may also induce motif-specific and spatially accessible mutations, as shown for the FGFR3 S249C hotspot mutation, favouring carcinogenesis. In both bladder and non-bladder cancers harbouring the FGFR3 S249C mutations, the group also found evidence of other mutations at APOBEC binding sites. APOBEC, or the monitoring of erroneous APOBEC activity, may serve as a marker of special groups of tumours with consequences at the diagnostic, prognostic, and predictive level.

A delicate balance

Mutations not only serve to drive cancer growth, but also contribute to tumour resistance against treatment. Tumours are not homogenous entities but a heterogeneous mix of pathogenic cells with different mutational identities. A treatment that destroys the majority of a cancer may leave behind a subset of cells that have randomly acquired resistance mutations. The resistant cells then rapidly divide, and the cancer returns. Alberto Bardelli (Candiolo Cancer institute and the Department of Oncology, University of Torino, Italy), presented work (published in Science) suggesting that the development of resistance is actively driven by cancerous cells. His group-treated colorectal cancer (CRC) cell lines and CRC patient-derived mice xenografts (PDX) with cetuximab (CTX) and dabrafenib (common treatments for CRC). CRC cells, upon receiving treatment, down regulated transcription of genes involved in mismatched repair (MMR), genes which typically remove mutations that arise during DNA replication. Concentrations of MMR proteins also fell as the cells increased the production of error prone DNA polymerases. These changes prime the cell to accrue mutations. Whole exome sequencing of microsatellite regions (sections of DNA unstable in the absence of MMR) were found to be altered in CRC cell lines and PDX after CTX and dabrafenib treatment. These results were also supported by findings in two patients treated with CTX, who both showed down regulation of MMR proteins. Stunting the efficacy of MMR may allow cancerous cells to expand their mutational landscape, a process referred to as adaptive mutability, increasing the likelihood of developing therapy resistance, but it also introduces a potential Achilles’ heel.

Myriam Chalabi (Netherlands Cancer Institute, Amsterdam, Netherlands) described work that she and her group had done as part of the NICHE trial and recently published in Nature Medicine. The presentation covered the outcomes of 40 patients with colon cancer, 35 of whom had been treated with ipilimumab plus nivolumab. Of these patients, 20 had MMR-deficient tumours and 15 had MMR-proficient tumours. All patients with MMR-deficient tumours showed positive responses to the treatment, and 12 showed no traces of cancer after treatment. Four patients with MMR-proficient tumours showed major or partial positive response to treatment. Alterations to MMR increased the likelihood that a tumour is susceptible to ipilimumab
and nivolumab. It is not clear if the MMR-deficient patients found by Chalabi and colleagues are functionally identical to the downregulation observed by Bardelli and colleagues, but the two talks highlight how a tumour’s response to one treatment can make it vulnerable to another.

**Immune infiltration**

The work presented by Chalabi also found that, for patients with MMR-proficient tumours, infiltration of these tumours by CD8+ PD-1+ T cells was predictive of a positive response to ipilimumab and nivolumab treatment. Both drugs are examples of immune checkpoint inhibitors (ICI). To prevent destruction, cancer cells often evolve mechanisms for blunting the cytotoxic activity of the immune system and ICIs aim to reverse this. The efficacy of ICIs is greatly influenced by the immune component of the tumour microenvironment, therefore understanding the makeup of the tumour milieu is an important step for the development of truly personalised medicine.

Wolf Fridman (INSERM, Paris, France) presented work from his group, published in *Nature*, examining gene expression profiles from 608 tumours across various subtypes of soft-tissue sarcomas. Gene expression profiles were used to classify tumours into one of five groups, based on the predicted tumour microenvironment composition: immune low (A and B), immune high (D and E) and highly vascularised (C) groups. Group E tumours were defined by the presence of tertiary lymphoid structures (TLS). TLSs are composed of T cells, dendritic cells and rich in B cells. In recent years there has been some debate as to the role of B cells in cancer progression, with both pro- and anti-tumour activity being attributed to B cell infiltration. Patients with Class E tumours (the group with the highest concentration of B cells) had the best response to PD-1 blockade and B cells were surprisingly better predictors of survival than the concentration of PD-L1, the ligand for PD-1.

The tumour microenvironment is defined not only by the identity of the cells present, but also their organisation. Leeat Keren (Weizmann Institute, Rehovot, Israel) presented an imaging technique, published in *Cell*, that allows for the visualisation of this organisation. Keren and colleagues tested their technique on biopsies from patients with triple negative breast cancer, an aggressive form of breast cancer with poor prognosis. Biopsies were first stained with a mix of 36 antibodies, raised against proteins associated with immune cells, cancerous cells, cell proliferation and immunotherapy targets (e.g., PD-1). Each antibody was labelled with a specific and unique metal isotope (e.g., Pr-141, Nd-142, Nd-143, etc.). Once labelled, an ion-beam moved across the sample, ionising the metal isotopes attached to the antibodies, these ions (and by extension the antibodies’ targets) can then be identified by mass spectrometry. As the ion-beam sweeps across the fixed sample, pixel by pixel, a 2D image of the antibody target is created. Artificial intelligence-powered cell segmentation allows for the identification of cell boundaries and cell identities. These results showed that breast cancer biopsies could be divided into two groups: cold tumours (without immune cell infiltration) and hot tumours (with infiltration). Hot tumours can be further divided into mixed and compartmentalised tumours. In mixed samples immune and cancer cells are evenly distributed throughout the tissue and, in compartmentalised tumours there are distinct clusters of immune cells forming ordered boarders up against clusters of cancerous cells. Compartmentalisation was associated with an increased expression of PD-1 and PD-L1 on the surface of infiltrating immune cells and (most importantly) with patient survival. These results, quite literally, offer a new dimension to our understanding of the tumour—immune microenvironment.

**Decisions, decisions**

Even with optimal immune cell infiltration, ICIs are not without their downsides. The unshackling of the immune system is not limited to the site of the cancer, and ICIs can result in inflammatory damage to otherwise healthy non-cancerous tissues. These immune-related adverse effects (IRAEs) are particularly common in patients with auto-immune conditions. Not all patients are equally susceptible to IRAEs and prediction of the likelihood of IRAEs before ICI administration would allow for more informed decision making when selecting treatment. Jessica Hassel (University Hospital, Heidelberg, Germany) presented work from her group that sought to provide biomarkers that might allow for the prediction of a patient’s response to ICI. Hassel and colleagues collected pre-treatment serum samples from 333 metastatic melanoma patients receiving ICI at five European centres. Patients were either receiving anti-CTLA4 therapy, anti-PD-1 therapy, or a combination of the two. An antigen array composed of 832 autoimmune and tumour antigens (along with immune and cancer pathway protein antigens) was then used to probe the composition of the serum samples. Of this cohort, 31% of patients would later develop IRAEs after treatment, and the authors were able to find 47 antibodies that correlated with IRAE occurrence. For instance, the presence of antibodies against MAGEB4 (Melanoma Antigen Family B4 also known as Testis Antigen 3) in patient serum before treatment with anti-CTLA4 was associated with an increased chance of survival but also a higher risk of IRAEs. Conversely, patients with antibodies raised against FGFR1 (fibroblast growth factor receptor 1) in serum were less likely to survive but also showed a lower frequency of IRAEs. These results suggest the possibility of developing a blood test that would allow clinicians to better inform patients about the efficacy and likely experience of ICI treatment before initiating therapy.

This conclusion also demonstrates the importance of conferences such as MAP, as only by bringing together clinicians and researchers can we hope to offer patients the most appropriate, and most informed, treatment decisions.