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MICROSATELLITE INSTABILITY AND EPSTEIN-BARR GASTRIC CANCER SUBTYPES DO LARGELY BENEFIT FROM ANTI-PD-1 INHIBITION

Several trials with the check-point inhibitors pembrolizumab or nivolumab demonstrated some antitumour efficacy in chemorefractory advanced gastric cancer with a response rate ranging from 10% to 26%. However, no clear predictive biomarkers were found to facilitate a proper selection of patients. A series of 61 patients with advanced gastric cancer received second-line or third-line treatment with pembrolizumab in a prospective phase 2 trial.[1] In a cooperative effort carried out by Korean and American investigators, a molecular characterisation of all tumours was performed including whole-exome sequencing and RNA sequencing of tissue biopsies, as well as circulating tumour DNA (ctDNA) from plasma. Six out of seven (85%) patients with microsatellite instability (MSI) showed very good responses (three complete and three partial responses). Moreover, all six cases with Epstein-Barr positive (EBV+) tumours showed partial responses. The only MSI case in which pembrolizumab failed was presenting heterogeneous areas with or without MLH1 immunohistochemical staining. These areas did show specific features of MSI when MLH1 positive and, in those in which MLH was lost, the biological features indicated microsatellite stability. When the rest of the six responding MSI patients were explored for this heterogeneity phenomenon, the pattern was very homogeneous in all of them and no heterogeneity at all was observed among them.

Mutational burden and PD-L1 positivity have been associated with responses to anti-PD1 antibodies in many tumour types. In gastric cancer, mutational burden is particularly high in MSI subtypes, and PD-L1 is generally overexpressed. However, the mutational burden was low in five of the six responding patients who were EBV+, indicating that EBV+ gastric tumours respond to anti-PD1 antibodies, regardless of the low mutational load. When responses were associated with the gastric cancer molecular subtypes, all MSI high and EBV+ patients responded, while only 12% and 5% of the chromosomal instability and genomic stable, respectively, responded. Another relevant observation was the low responses observed when individual tumours presented indications of mesenchymal activation. None of the six cases presenting with a high epithelial-mesenchymal transition (EMT) signature did respond to pembrolizumab in this study, while 30% of those with low EMT profile responded.

Another interesting observation of this study is the potential value of ctDNA in assessing the mutational burden of patients with gastric cancer as a positive predictor of the effect of pembrolizumab. A high concordance with the mutational load in tissue and in plasma was confirmed. Moreover, patients in the upper tertile of ctDNA mutational load had 83% response rate versus only 7.7% in the rest. Also, the dynamic of ctDNA was indicating a potential relation with the efficacy of treatment. Post-treatment changes were powerful predictors of both response and progression in gastric cancer. A decrease in ctDNA variants 6 weeks after pembrolizumab is related with response. On the other hand, an increase in ctDNA variants at that time relates with early progression in the four observed cases.

In summary, MSI high and EBV+ are strong predictive biomarkers of a positive response to anti-PD1 antibodies in patients with advanced gastric cancer. Patients with these features could be offered treatment with anti-PD1 antibodies at an earlier status of their disease.

TANDEM DUPLICATOR PHENOTYPE IS A PREVALENT GENOME-WIDE CANCER CONFIGURATION DRIVEN BY DISTINCT GENE MUTATIONS

The systematic application of whole-genome sequencing to the study of cancer genomes has uncovered complex scenarios, showing that large portions of the genome are affected by a multitude of somatic structural variations. Although not always associated with a discernible driver mutation, these variation patterns have the potential to deregulate several

oncogenic elements. Among them, DNA segmental duplication consists in the increased expression of the genes that are entirely comprised within the rearrangement, whose copy number is thus augmented. Recently, it was described an enrichment of head-to-tail somatic segmental tandem duplications (TDs) which is commonly referred to as the tandem duplicator phenotype (TDP).[1]

Menghi *et al*, in an elegant article published in *Cancer Cell*,[2] demonstrated, expanding on their original discovery,[3] that TDP was not an ubiquitous finding among solid tumours and it occurred in 50% of triple negative breast cancer, and ovarian and endometrial cancers. Moreover, the authors stratified and validated TDP tumours by classifying their TDs into three span intervals, with modal values of 11 kb, 231 kb and 1.7 Mb or different combinations of these. Group 1 TDPs were found to lose TP53 and BRCA1. Unlike it, BRCA2 was not linked to any TDP configuration. When focusing on TDP group 2 tumours, the CCNE1 pathway was strongly activated. Specifically, in each one of the individual triple negative breast cancer, and ovarian and endometrial cancers, CCNE1 activation was found to explain at least 40% of TDP group 2 tumours. CDK12 emerged as the strongest candidate linked to the TDP group 2/3mix profile. p53 and BRCA1 conjoint abrogation drives TDP induction by generating short-span TDP mammary tumours in genetically modified mice lacking them. In 91% of TDP cancers with full genomic mutational ascertainment definitively involving one of these three driver genes, concomitant mutations of TP53 were observed, implying that defective DNA damage checkpoint control facilitated tumourigenesis, TD formation or both. These data suggest a mechanistic scenario for TDP induction, where specific HR defects and excessive replicative stress in the presence of replication fork stalling enhance TD formation. These results provide a detailed view of a specific chromosomal configuration in cancer characterised by genomically distributed TDs, that unifies a number of reports focused on individual cancer types. This new classification may improve the understanding of pathway alteration improving tailored treatment in patients diagnosed with breast and gynaecological tumours.

QUANTITATIVE ANTICIPATION OF TUMOUR PROGRESSION WITH A MATHEMATICAL MODEL BASED ON LIQUID BIOPSIES IN METASTATIC COLORECTAL CANCER

In an interesting article published in *Cancer Discovery*, Khan *et al* presented a prospective trial, exploring new ctDNA and tissue biomarkers to assess response and resistance to anti-EGFR therapies in metastatic colorectal cancer (mCRC). They included 47 patients with chemorefractory RAS WT mCRC. In a first cohort of patients, ctDNA and tissue was tested using digital PCR, while they subjected all baseline samples in the second cohort of patients with mCRC to next-generation sequencing (NGS) of a broad panel of 77 cancer-related genes.[4] As the main contribution of this paper, the authors demonstrated for the first time in a prospective trial that the combination of longitudinal plasma biopsies and solid-tissue samples can be coupled with mathematical modelling of tumour evolution to quantitatively anticipate tumour progression. This is an important finding which may affect future clinical decisions and patient therapy.

Nevertheless, as the authors outlined in this publication, ctDNA samples should be taken every 4 weeks or even more frequently in order to be adequately analysed with this new mathematical model. In addition, it requires an experienced and trained multidisciplinary team including bioinformaticians, clinicians and radiologists. Moreover, they concluded, as observed by others, that RAS-mutant clones emerged during anti-EGFR treatment and disappeared once treatment was discontinued.[5] More importantly, the authors showed that approximately 50% of patients with mCRC considered KRAS WT, and as such eligible for anti-EGFR treatment, in fact presented some RAS aberrations which we detected using ultra-deep sequencing technology. These patients did not benefit from anti-EGFR antibodies therapy. This observation confronts recent studies proposing hot-spot mutational analysis that suggested high concordance between the mutational status of RAS in tumour tissue and ctDNA in patients with mCRC.[6 7]

Another relevant finding is the observation of polyclonal resistance as a common feature in anti-EGFR refractory patients. The authors do suggest a hierarchical structure of resistant clones that could justify heterogeneity on tumour progression. In conclusion, Khan *et al* showed that combining liquid biopsies with mathematical modelling of tumour evolution allows quantitative anticipation of tumour progression. The validation of this concept in prospective trials is ongoing.

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