Negative predictive biomarkers of checkpoint inhibitors in hyper-progressive tumors

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Immune checkpoint inhibitors (ICI) are becoming an integral part of the management of cancer patients. PD-1 and PD-L1 inhibitors led to distinguished clinical responses in patients with different types of cancer ranging from 20 to 30% when used in monotherapy. Anti-PD1 and anti-PDL1 agents are approved by the US FDA in the treatment of multiple malignancies from renal cell carcinoma, classical Hodgkin lymphoma, non-small-cell lung cancer, squamous cell carcinoma of head and neck, metastatic melanoma and urothelial carcinoma of the bladder [1].

Defining predictive biomarker of treatment response and toxicity represents one of the challenges of these new agents. In fact, several biomarkers were evoked in order to explain the response to ICI such as PD-L1 expression/amplification, high tumor mutational burden and mismatch repair gene defect [2]. These immune checkpoint inhibitors were also associated with specific adverse events which were mainly immune related such as colitis, hypophysitis and pneumonitis. Some predictive biomarkers are under investigation to predict these adverse events like neutrophil activation markers (CD117 and CEACAM1), several immunoglobulin genes, IL6 level at baseline and IL17/eosinophil pathway element's level [3]. Interestingly, immunotherapy may also result in a unique tumor response pattern such as pseudo-progression defined as initial tumor increasing size on imaging tools followed by delayed tumor response. Recent anecdotal reports described a subset of patients whose disease paradoxically rapidly progressed after ICI administration suggesting that immunotherapy may have a deleterious effect by accelerating the disease [4,5].

Hyper-progression disease definition & outcome

Two recent reports by Champiat *et al.* and Kato *et al.* described this new pattern of progression in patients treated with PD-1/PD-L1 inhibitors [2,6]. The definition of hyper-progressive disease (HPD) is still not clear and is different according to each study methodology. Kato *et al.* defined HPD as time to treatment failure <2 months, >50% increase in tumor burden compared with preimmunotherapy imaging that was obtained within 2 months of the initiation of immunotherapy, and >2-fold increase in progression pace [6]. However, Champiat *et al.* defined it as RECIST progression after the first evaluation and ≥ 2 -fold increase of the tumor growth rate between the reference and experimental periods, tumor growth rate being a measure to assess tumor growth over time allowing for quantitative and dynamic evaluation of the tumor. Champiat *et al.* reported in their study a prevalence of 9% of HPD (12 patients/131 evaluable patients); these patients were significantly older than patients without HPD which can be due to a different immunological background in older patients such as higher inflammatory cytokines concentrations. HPD was associated with shorter overall survival (4.6 vs 7.6 months; $p = 0.19$). No association was reported between HPD and tumor burden at baseline, tumor type, number of metastatic sites, number of previous lines and type of previous line. No difference was found in HPD between patients treated with PD-1 and PD-L1 inhibitors. The study concluded that blockage of PD-1/PD-L1 pathway could enhance tumor growth or tumorigenesis via alternative signaling pathways or upregulation of alternative immune checkpoints [2].

Primary resistance to ICI

To date, the fact that primary resistance to ICI can explain the hyper-progressive nature of disease cannot be confirmed. Gao *et al.* demonstrated that patients with genomic defects in IFN- α pathway genes were nonresponders to anti-CTLA-4 since IFN- γ is a major cytokine produced by T cells upon recognizing antigens. This suggests that IFN- γ signaling pathway was associated with primary resistance to ipilimumab [7]. Moreover, Shin *et al.* showed that JAK1/2 mutations were implicated in primary resistance to PD-1 inhibitors. JAK1/2 loss of function mutations may have important role in the absence of response to PD-1 inhibitors due to lower ability of immune T cells to recognize tumor cells. It has also been shown that these mutations may result in a lack of T-cell infiltrates due to deficit of chemokine production [8]. Zaretsky *et al.* showed that loss-of-function mutations of JAK1/2 encoding IFN- γ receptor were implicated in acquired resistance to pembrolizumab in the management of metastatic melanoma. It has also been reported that *B2M* gene mutation was identified and led to loss of surface expression of MHC class I [9].

Negative predictive biomarkers of ICI ?

Recently, Kato *et al.* reported retrospectively, the potential biomarkers associated with hyper-progression after monotherapy with immune checkpoints. In fact, stage IV cancers of 155 patients treated with immunotherapy (anti-CTLA-4, PD-1/PD-L1 inhibitors) were genomically evaluated using next generation sequencing. The multivariate analysis showed that EGFR, MDM2/4 and DNMT3A, were independent predictors of poor clinical response with immunotherapies.

According to Kato *et al.*, the link between MDM2 amplification and HPD remains unclear. MDM2 is an oncogene which induces tumorigenicity when overexpressed in rodent cells [10]. In fact, immunotherapy can increase IFN- γ level leading to an elevation of interferon regulatory factor 8 (IRF8) expression (a transcription factor) by activation of JAK STAT pathway. IRF8 binds to MDM2 promoter inducing MDM2 expression. It seems that over-expression of MDM2 which is implicated in tumorigenesis could occur when MDM2 is amplified. Another hypothesis to understand this link evokes the presence of another unknown gene amplified with MDM2 leading to HPD.

In addition, PD-1, PD-L1 and CTLA-1 were upregulated with EGFR activation which can lead to immune escape. It can explain resistance to immunotherapy in EGFR-mutant patients but not hyperprogression. Kato *et al.* concluded that hyperprogression can occur more likely in some histologic subtypes than other since patients with HPD and MDM2/4 amplification or EGFR alterations had breast, bladder, lung, endometrial stromal sarcoma and hypopharyngeal carcinoma. Consequently, can MDM2 amplification or EGFR alterations be considered biomarkers of hyperprogression in patients treated with ICI [6]?

Conclusion & future perspective

In the era of next generation sequencing, determining negative predictive biomarkers of ICI seems necessary to characterize patients who will not benefit from these agents. By validating these biomarkers, we will be able to better select the candidates who will respond to ICI and spare the mistreatment and toxicities in those who will not respond. As a consequence, the exaggerated cost of the use of ICI will be reduced. Alternative anticancer treatment modalities will be suggested to these patients. More translational trials correlating the response of ICI to genomic alterations are important to figure out new biomarkers in this rapidly evolving field.

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