Atypical patterns of response to immune checkpoint inhibitors: interpreting pseudoprogression and hyperprogression in decision making for patients' treatment

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Introduction

Over the last 5 years, immunotherapy has become one of the backbones for cancer treatment, showing significant improvement in prognosis for several malignancies. Currently, in clinical practice, we have several immune checkpoint inhibitors targeting cytotoxic T lymphocyte associated antigen 4 (CTLA4), programmed cell death 1 (PD-1) and programmed death ligand 1 (PD-L1), while several other drugs, directed toward different co-inhibitory or co-stimulatory molecules, are under evaluation (1). CTLA-4 is the first immune checkpoint to be clinically targeted. Ipilimumab, a fully human anti-CTLA-4 monoclonal antibody, is the first immunotherapeutic drug approved for metastatic melanoma treatment. Subsequently, other drugs were approved for treatment of non-small cell lung cancers (NSCLC), renal cell carcinomas (RCC), urothelial cancers, head and neck tumors, melanoma, Merkel cell carcinomas and microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors. These drugs target PD-1, such as Nivolumab and Pembrolizumab, or PD-L1, such as atezolizumab, durvalumab and avelumab (2). Recently, the combination of nivolumab plus ipilimumab showed a survival advantage in treatment-naive metastatic melanoma, NSCLC and RCC (3-5). Moreover, combination between anti-PD1/anti-PD-L1 and chemotherapy showed a survival benefit and a higher response rate in NSCLC, in small cell lung cancer (SCLC) and in triple negative breast cancer (6-9). The biological basis of this combination is based on the principle that chemotherapy reduces the immunosuppressive activity carried out by the tumor and induces the immunogenic tumor death, with the consequent release of molecules recognized as "non-self" by immune system (10).

Immunotherapy was recently studied also in adjuvant setting in different cancer types. In NSCLC we observed a reduction of the risk of death with Durvalumab after definitive chemoradiotherapy *vs.* placebo (11). In melanoma several phase III clinical trials evaluated ipilimumab, nivolumab and pembrolizumab in completely resected high risk patients, showing a relapse free survival (RFS) benefit (12,13). Further clinical trials are currently ongoing, testing adjuvant immunotherapy in RCC (clinicaltrials.gov: NCT03288532), in esophageal or gastro-esophageal junction cancer (NCT02743494), in gastric cancer (NCT03443856), in head and neck cancer (NCT03406247), in hepatocarcinoma (NCT03630640) and in urothelial cancer (NCT02632409).

Pseudoprogression

Immunotherapy does not generate a rapid response like standard chemotherapy, but the response to treatment, when obtained, will last over time due to the immunological memory.

New patterns of response to immunotherapy have been

described in literature. The first one is pseudoprogression, defined as a response to treatment after initial increase in volume of cancer lesions, due to the infiltration of tumoral tissue by immune cells. Overall, the rate of pseudoprogression do not exceed 10% in patients treated with immune checkpoint inhibitors (14).

The classic response evaluation criteria in solid tumors (RECIST) are not applicable to immunotherapy, leading to formulate the immune related response criteria (irRC) and the immunotherapy RECIST (iRECIST). These immune-specific criteria imply to confirm progression with a second computed tomography (CT) scan and allow the appearance of new lesions in the definition of unconfirmed progression (15). However, most of clinical trials used RECIST 1.1 to assess primary and secondary end-points, while immune-specific criteria were used only for exploratory end-points, introducing a wide variability in the interpretation of data (14).

It is crucial to recognize pseudoprogression from a real progression, to avoid both a premature discontinuation of an effective treatment and the delay of starting a new line of therapy. A tumor biopsy at the time of disease progression could help to assess immune system activation by the treatment. In a study conducted by Di Giacomo and colleagues, a biopsy at progression leads to identify a functional T-cell activation induced by treatment in melanoma patients receiving anti-CTLA-4 (16). Lee and colleagues analyzed circulating tumor DNA, that is associated with poor prognosis in melanoma patients receiving PD-1 inhibitors and showed a decrease from baseline in presence of pseudoprogression (17).

Pseudoprogression seems to be associated with a high likelihood of 1-year survival compared to patients experiencing partial response, stable disease or progressive disease in a retrospective analysis conducted on various cancer type. However, it is important to underline that in this study the number of patients with pseudoprogression was small, with only 21 patients according to irRC. Larger analyses are required to confirm this observation (18).

Hyperprogression

Another uncommon pattern of progression is hyperprogressive disease (HPD), which is characterized by the acceleration of tumor growth during immune checkpoint inhibition. This type of progression can be the explanation of the cross between the survival curves during the first months of treatment observed in some clinical trials, such as that performed in non-squamous NSCLC

patients receiving nivolumab (19). Currently, it is impossible to conclude if HPD is triggered by immunotherapy or is merely a characteristic of an aggressive disease. However, we can observe that HPD seems less common in patients receiving chemotherapy and, therefore, it is likely that it is a specific pattern of response to immune checkpoint inhibitors (20).

HPD incidence in patients receiving immunotherapy range from 4% to 29% in different studies (20-23). This difference could be ascribed to the non-uniformity of the definition of HPD reported in literature, as well as to the heterogeneity of histology included in these studies.

The first report on HPD has been published in 2016 by Champiat *et al.* They defined HPD as a twofold or greater increase of tumor growth rate (TGR) during immunotherapy, compared to baseline. In this study, HPD was reported in 12 of 131 (9%) patients with different tumor types. No difference was observed between anti-PD-1 and anti-PD-L1 across the different histologies, the number of metastasis, the tumor burden, the number and type of previous treatments. An association between HPD and older age has been observed, with a median age of 65.5 years for HPD patients *vs.* 55 years for non-HPD (P=0.007). Patients with HPD showed a worse outcome, with an overall survival (OS) of 4.6 *vs.* 7.6 months in non-HPD progressive patients, although this result was not statistically significant due to the small number of patients (P=0.19) (21).

Kato and colleagues defined HPD as a time to treatment failure (TTF) <2 months, a 50% increase in tumor burden compared to baseline and an increase in progression pace greater than twofold. Notably, they performed a comprehensive genomic analysis, observing a strong association between MDM2/4 amplification and EGFR alterations with TTF <2 months. Overall, in this study 4 of 6 patients (67%) with MDM2/4 amplification and 2 of 10 patients (20%) with EGFR alterations showed HPD. Interestingly they observed that patients receiving anti-CTLA-4 alone or in combination therapy were significantly less likely to have TTF <2 months (22).

Saâda-Bouzid and colleagues defined HPD as a tumor growth kinetic ratio (TGK$_R$) between the value during treatment and at baseline ≥2, where TGK was defined as the difference of the sum of the largest diameters on the target lesions per unit of time. In patients affected by head and neck cancer they observed an HPD rate of 29%, a statistically significant worse progression free survival (PFS according to irRECIST: 2.9 *vs.* 5.1 months, P=0.02) and a trend for shorter OS (6.1 *vs.* 8.1 months, P=0.77) (23).

Ferrara and colleagues reported a retrospective analysis of a large series of NSCLC patients (n=465) (20). To our knowledge, this is the first HPD report with a control arm (406 patients treated with immune checkpoint inhibitors *vs.* 59 patients treated with chemotherapy) and the largest study focusing on a single tumor type. A different definition of HPD compared to that previously described in literature was used. In fact, HPD was defined as difference in TGR during treatment from baseline (ΔTGR) greater than 50%. The authors observed HPD in 13.8% of the patients treated with immunotherapy *vs.* 5.1% in patients receiving chemotherapy. The incidence of HPD is probably underestimated in this study, due to rapid progression and/or death, occurred in about 76 patients, that hindered further CT scan evaluations. Six patients initially classified as hyperprogressors in the immunotherapy group, showed a response to treatment at subsequent CT scan. An association between number of metastatic sites ≥2 and HPD has been observed (P=0.006), but not with tumor burden. A worse OS has been observed in HPD patients (3.4 *vs.* 6.2 months for non-HPD progressive patients; P=0.003), accordingly with what reported in previous studies. In the group of patients receiving chemotherapy no pseudoprogression has been detected, while 3 patients showed HPD (5.1%). The authors observed a not statistically significant longer OS for patients with HPD compared to non-HPD progressive patients in chemotherapy group. However, we estimate that the sample size is insufficient to consider this data reliable. No data about association between pattern of response to immune checkpoint inhibitors and PD-L1 expression or tumor mutational burden (TBM) are available, considering that these molecular tests are not always mandatory in clinical practice. On the other hand, EGFR testing was available, being mandatory in clinical practice for non-squamous histology, but no association between EGFR genetic alterations and HPD has been detected, contrarily to what reported by Kato and colleagues (22). Ferrara *et al.* analyzed also circulating biomarkers such as LDH and neutrophil to lymphocyte ratio (NLR), without finding any association with pattern of progression (20).

A recent study by Zuazo-Ibarra *et al.* concluded that patients non-responding to anti-PD-1/PD-L1, including hyperprogressors, have low number of baselines circulating senescent CD4 T cells (Tsen). In particular, patients with HPD showed an aberrant systemic proliferation of Tsens after the first cycle of therapy, called Tsen burst (24).

The analysis of TGR before starting treatment could help to identify a rapid progressive disease. Unfortunately, no data deriving from clinical trials about pre-treatment TGR are available so far. Nevertheless, some clinical trials showed a better benefit from immunotherapy for patients with a slowly progressive disease, while rapidly progressive NSCLC patients could benefit mostly from other type of treatment, such as antiangiogenetic plus chemotherapy (19,25). These findings, as well as the reported lower incidence of HPD in patients treated with chemotherapy, lead to speculate whether the combination between immune checkpoint inhibitors and chemotherapy could hamper HPD. Another aspect to take into consideration is about the therapeutic attitude in case of HPD. We know that standard chemotherapy lead to rapid tumor shrinkage compared to immunotherapy, but no data about efficacious treatment after HPD are reported in literature.

In conclusion, further studies are required to analyze HPD during chemo-immunotherapy and to study whether a similar atypical pattern of response exist during adjuvant immunotherapy. In this setting, in fact, in which the aim of treatment is merely preventive, it is crucial to precociously identify the subgroup of patients in which immunotherapy could be detrimental. Moreover, molecular biomarkers analysis, baseline TGR association with the pattern of response as well as a unique definition of HDP must be the goals of future studies. HPD should be also included in evaluation criteria and its incidence should be objectively evaluated in future randomized trials.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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