Editorial Commentary

Who will suffer from hyperprogressive disease in patients with advanced non-small cell lung cancer treated with PD-1/PD-L1 inhibitors

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The development of immunotherapy has resulted in a paradigm shift for the treatment of advanced non-small cell lung cancer (NSCLC). Immune checkpoint inhibitors (ICIs) [i.e., programmed cell death 1 (PD-1)] and programmed cell death ligand 1 (PD-L1 inhibitors) are particularly important in the treatment of NSCLC, which is associated with poor prognosis. These agents have become a cornerstone of lung cancer treatment.

Following the administration of ICIs, a proportion of patients may obtain a durable response through activation of the immune system of the patient, whereas others may be non-responsive to treatment. In addition, unlike conventional anti-cancer chemotherapy, immunotherapy is occasionally linked to an unconventional response pattern (i.e., pseudoprogression) or very rapid progression (i.e., hyperprogression, HPD). Pseudoprogression is defined as an initial increase in the tumor burden or number of tumor lesions prior to a decrease. The reported rate of pseudoprogression is 0.6–5.8% (1). HPD is characterized by drastic progression of disease, reducing patient quality of life and becoming life-threatening. Chubachi *et al.* reported a case of "disease flare" in NSCLC after treatment with nivolumab. This may have been the first report of HPD following the administration of immunotherapy (2). HPD is often defined as ≥2-fold increase in the tumor growth ratio (TGR) or tumor growth kinetics ratio (TGKR) during treatment with ICIs compared with that observed prior to treatment (3,4). Previous studies investigating HPD in multiple types of cancer showed that the frequency of HPD induced by ICIs is 2.5–29.4% (3-5).

According to Champiat *et al.* (3) and Saâda-Bouzid *et al.* (4), there is no association between HPD and tumor burden at baseline, the number of previous lines of treatment, the number of metastatic sites, or the expression of PD-L1 in tumors. Thus far, two clinical factors, namely regional recurrence in an irradiated field in head and neck squamous cell carcinoma and elderly patients, have been associated with HPD. Kato *et al.* (5) suggested that epidermal growth factor receptor (*EGFR*) mutations and mouse double minute 2 homolog (*MDM2*) amplification may act as molecular predictors of HPD. Moreover, the investigators showed that the rate of HPD in patients with an *EGFR* mutation was 20% (2/10). Singavi *et al.* reported that the rate of *EGFR* amplification and *MDM2/MDM4* amplification in patients was 50% (1/2) and 66.7% (2/3), respectively (6). However, the underlying mechanism remains unclear and further investigation using larger cohorts of patients is desired. In addition, it has been reported that the prognosis of patients who develop HPD is shorter compared with that observed in those who do not. The development of HPD may explain the initial dip in Kaplan-Meier curves observed in several phase III trials (7,8). However, the etiology, prevalence, characteristics of patients prone to HPD, and predictive factors of HPD remain to be determined.

A recent study investigated the development of HPD in patients with advanced NSCLC treated with PD-1/PD-L1 inhibitors compared with single-agent chemotherapy. Moreover, the investigators examined the potential association between treatment and HPD (9). This research is valuable because it: (I) targeted only advanced NSCLC; (II) included patients treated using only PD-1/PD-L1 inhibitors; (III) recruited >400 patients at multiple centers; and 4) conducted a comparison with historical cohorts of patients who received chemotherapy. Moreover, the study calculated tumor progression using the peculiar ΔTGR (i.e., TGR prior to and during treatment, and variation per month). HPD was defined as disease progression at the first evaluation, with a ΔTGR exceeding 50%.

In the immunotherapy cohort, 62 patients (15.3%) were initially classified as having HPD. However, pseudoprogression was eventually reported in four of those. Finally, 56 patients (13.8%) and 19 patients (4.9%) were classified as having HPD and pseudoprogression, respectively. Of note, in the chemotherapy cohort, the incidence of HPD and pseudoprogression was 5.1% and 0%, respectively. The investigators concluded that the development of HPD is more common in response to treatment with PD-1/PD-L1 inhibitors versus chemotherapy in pretreated patients with NSCLC.

Moreover, they examined the association between the HPD status and clinical variables. HPD was significantly associated with the presence of more than two metastatic sites prior to the administration of PD-1/PD-L1 inhibitors. However, there was no association with the tumor burden at baseline. The increased number of metastases and the increase in tumor burden appear to be correlated. However, this may be due to the fact that the target lesions defined by the response evaluation criteria in solid tumors (RECIST) do not completely influence the whole tumor burden. It has been reported that a high tumor burden is associated with an inferior prognosis and effect of ICIs (10,11). Huang *et al.* found that clinical failure was the result of an imbalance between Ki67+ CD8 T-cell reinvigoration and tumor burden. The bulk of circulating Ki67+ CD8 T cells determined in relation to the baseline tumor burden correlated with clinical response (11). Older age (≥65 years old) was not associated with HPD in this study. And, it was not possible to evaluate the association between the expression of PD-L1 and HPD due to missing data.

In the landmark survival analysis performed at six weeks, patients experiencing HPD exhibited significantly lower overall survival versus that observed in patients with progressive disease [median overall survival: 3.4 months; 95% confidence interval (CI): 2.8–7.5 months *vs.* 6.2 months; 95% CI: 5.3–7.9 months, respectively; hazard ratio =2.18; 95% CI: 1.29–3.69; P=0.003]. Consistent with the results reported by previous studies, the prognosis of patients who developed HPD was poor (2-4). This suggests that HPD is a special poor prognostic factor, which may be life-threatening mainly during the first two months of treatment.

Currently, there is no consensus regarding the definition of HPD. HPD is usually defined as ≥2-fold increase in the TGR or TGKR. Nevertheless, this definition is merely indicative of a very rapid-growing tumor, and does not provide information regarding the involvement of ICIs in triggering and promoting this progress. The definition used in this study—an increase in the TGR by ≥50%—determines the exact rate of tumor growth. This assists in distinguishing between progression due to the natural history of the disease and that induced/accelerated by the administration of ICIs. In that sense, it can be said that ΔTGR more than 50% captures the original HPD phenomenon more.

Unfortunately, currently, there are no biomarkers to accurately predict the response of an individual to treatment with ICIs. Therefore, determining the patients who will not benefit from treatment with ICIs and those who will be super-responders is of crucial importance. Considering that patients with HPD are associated with poor prognosis, it is urgent to promptly identify those at high risk of developing HPD. At least, we need to recognize that HPD occurs in >10% of patients with advanced NSCLC. Notably, this rate is higher than expected. Furthermore, it is important to promptly decide the subsequent administration of salvage chemotherapy in response to the development of HPD. Biopsy performed in patients with pseudoprogression reveals the infiltration of inflammatory cells (12,13). Therefore, this approach may be useful in distinguishing between HPD and pseudoprogression. However, it is difficult to perform a biopsy in patients with a poor performance status at HPD. Further studies, involving liquid biopsy in patients at risk of developing HPD, are warranted to determine the mechanism involved in the development of HPD and identify clinical characteristics, genomic profile, and the immune environment. Ultimately, candidates for immunotherapy may be screened prior to initiating therapy.

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Footnote

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

References

1. Wang Q, Gao J, Wu X. Pseudoprogression and hyperprogression after checkpoint blockade. Int Immunopharmacol 2018;58:125-35.
2. Chubachi S, Yasuda H, Irie H, et al. A Case of Non-Small Cell Lung Cancer with Possible "Disease Flare" on Nivolumab Treatment. Case Rep Oncol Med 2016;2016:1075641.
3. Champiat S, Dercle L, Ammari S, et al. Hyperprogressive Disease Is a New Pattern of Progression in Cancer Patients Treated by Anti-PD-1/PD-L1. Clin Cancer Res 2017;23:1920-8.
4. Saâda-Bouzid E, Defaucheux C, Karabajakian A, et al. Hyperprogression during anti-PD-1/PD-L1 therapy in patients with recurrent and/or metastatic head and neck squamous cell carcinoma. Ann Oncol 2017;28:1605-11.
5. Kato S, Goodman A, Walavalkar V, et al. Hyperprogressors after Immunotherapy: Analysis of Genomic Alterations Associated with Accelerated Growth Rate. Clin Cancer Res 2017;23:4242-50.
6. Singavi AK, Menon S, Kilari D, et al. Predictive biomarkers for hyper-progression (HP) in response to immune checkpoint inhibitors (ICI) – analysis of somatic alterations (SAs). Ann Oncol 2017;28:1140PD.
7. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med 2015;373:1627-39.
8. Lopes G, Wu YL, Kudaba I, et al. Pembrolizumab (pembro) versus platinum-based chemotherapy (chemo) as first-line therapy for advanced/metastatic NSCLC with a PD-L1 tumor proportion score (TPS) ≥ 1%: Open-label, phase 3 KEYNOTE-042 study. J Clin Oncol 2018;36:abstr LBA4.
9. Ferrara R, Mezquita L, Texier M, et al. Hyperprogressive Disease in Patients With Advanced Non-Small Cell Lung Cancer Treated With PD-1/PD-L1 Inhibitors or With Single-Agent Chemotherapy. JAMA Oncol 2018;4:1543-52.
10. Katsurada M, Nagano T, Tachihara M, et al. Baseline Tumor Size as a Predictive and Prognostic Factor of Immune Checkpoint Inhibitor Therapy for Non-small Cell Lung Cancer. Anticancer Res 2019;39:815-25.
11. Huang AC, Postow MA, Orlowski RJ, et al. T-cell invigoration to tumour burden ratio associated with anti-PD-1 response. Nature 2017;545:60-5.
12. Chiou VL, Burotto M. Pseudoprogression and Immune-Related Response in Solid Tumors. J Clin Oncol 2015;33:3541-3.
13. Tanizaki J, Hayashi H, Kimura M, et al. Report of two cases of pseudoprogression in patients with non-small cell lung cancer treated with nivolumab-including histological analysis of one case after tumor regression. Lung Cancer 2016;102:44-8.

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