

REVIEW ARTICLE

Hyperprogression after immunotherapy: A comprehensive review

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Summary

Immune checkpoint inhibitors have revolutionized cancer treatment with patient improved survival, quality of life, and a longer response. However, up to 30% of patients experience paradoxical accelerated tumor progression early after immune-checkpoint blockade therapy. This phenomenon is also known as hyperprogression (HP). Unlike other responses, such as pseudoprogression or natural progression, HP causes worse survival outcomes in patients. Older age, higher metastatic burden, and previous radiation have been independently associated with HP. Even though the exact molecular mechanism underlying HP after immune-checkpoint blockade therapy remains unknown, oncogenic signaling activation including MDM2 amplification or EGFR alterations, the modification of tumor microenvironment by radiotherapy

with immune checkpoint inhibitors, and alterations in immune landscape of tumors have been hypothesized as the biological mechanisms behind HP. Patients with HP have been presented with poor prognosis and increased deleterious mutations in cancer genes, along with alterations in the tumor microenvironment. As immune checkpoint inhibitors have been more widely accepted by oncologists, proper assessment of this unique tumor response remains challenging in clinical practice. This work documents the recent findings on epidemiology, biological and clinicopathological factors of HP after immunotherapy.

Key words: hyperprogression, immunotherapy, PD1/PDL1, hyperprogressive disease, immune checkpoint inhibitors

Introduction

Evasion of immune system has been identified as a hallmark of cancer [1]. Cancer cells accomplish “immunoediting” by exploiting several immunity-related processes including regulatory T cell function and antigen presentation [2]. Elucidating the molecular interplay between cancer cells and the immune system has contributed to the development of immune checkpoint inhibitors (ICIs). Clinical engagement of immune checkpoint inhibitors targeting programmed cell death protein 1 (PD-1), programmed cell death ligand 1 (PD-L1), and cytotoxic T lymphocyte-associated protein 4 (CTLA-4) has revolutionized cancer therapy [3]. ICIs have become a standard treatment for multiple malignancies including non-small cell lung

cancer (NSCLC) [4], renal cell carcinoma (RCC) [5], urothelial carcinoma [6], Hodgkin’s lymphoma [7], head and neck squamous cell carcinoma (HNSCC) [8], melanoma [9], and Merkel cell carcinoma [10]. Overall, response rates for immune checkpoint blockade as monotherapy in solid tumors range from 20 to 40% [11-13]. Despite the unprecedented improvements in overall survival rates, some patients present with unconventional responses such as pseudoprogression, mixed response, and hyperprogression (HP) [14]. Distinct response patterns elicited by ICIs have raised clinical concern that immunotherapy may be harmful to some patients. Among these patterns, accumulated evidence from retrospective data and case studies indicated that

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immune checkpoint blockade may accelerate tumor growth in a remarkable subset of patients, with rates ranging from 4 to 29% through multiple malignancies [15-19]. This phenomenon is also known as HP. In contrast to pseudoprogression which is defined as an initial tumor fluctuation followed by tumor shrinkage [20], patients with hyperprogressive disease (HPD) display poor prognosis and survival outcomes. The incidence, molecular basis, and predictive biomarkers of HP have not been fully understood. In this review, we aim to provide recent clinical studies on HP as well as discussing the underlying biological and clinicopathological mechanisms, potential predictors or biomarkers related to this phenomenon.

Hyperprogression: occurrence and clinical significance

HP is a phenomenon characterized by a rapid increase in tumor growth rate after immunotherapy. It was first described by Champiat et al [15] in patients receiving PD-1/PD-L1 inhibitors in phase 1 clinical trial. Moreover, subsequent case studies reported “disease flare” after the initiation of immune checkpoint inhibitors (ICPs) in patients with NSCLC [21,22], squamous cell NSCLC [23], metastatic clear cell renal cell carcinoma (RCC) [24,25], melanoma [26], lymphoma [27] and sarcoma [28]. In addition to the above-mentioned case studies, a number of retrospective studies investigated

Table 1. The incidence of hyperprogression after immune-checkpoint blockade therapy

Authors	Study design	Tumour type	Treatment	Number of evaluated patients	Number of Hyperprogressors	Rate (%)	Definition of Hyperprogression
Champiat et al. (2017)	Retrospective	Multiple tumour types ¹	PD-1/PD-L1 inhibitors	131	12	9.2	<ul style="list-style-type: none"> • RECIST progression at first evaluation • TGR ratio>2 (compared to preimmunotherapy period)
Saâda-Bouزيد et al. (2017)	Retrospective	HNSCC	PD-1/PD-L1 inhibitors	34	10	29.4	<ul style="list-style-type: none"> • TGK ratio>2 (compared to preimmunotherapy period)
Kato et al. (2017)	Genomic Analysis	Multiple tumour types ²	CTLA-4, PD-1/PD-L1 inhibitors	155	6	3.9	<ul style="list-style-type: none"> • TTF<2, 50>increase in tumour burden compared with preimmunotherapy, • >2 fold increase in progression pace
Ferrara et al. (2017)	Retrospective	NSCLC	PD-1/PD-L1 inhibitors	406	56	14	<ul style="list-style-type: none"> • RECIST progression at first evaluation, • ΔTGR increase>1.5 compared with preimmunotherapy
Weiss et al. (2017)	Prospective	Multiple tumour types ³	CTLA-4, PD-1/PD-L1 inhibitors	56	6	11	-
Kanazu et al. (2018)	Retrospective	NSCLC	Nivolumab	87	5	5.75	<ul style="list-style-type: none"> • Multiple predictive biomarkers
Kim et al. (2018)	Retrospective	NSCLC	PD-1/PD-L1 inhibitors	220	37	17	<ul style="list-style-type: none"> • TGK ratio2 (compared to preimmunotherapy period)
Lo Russo et al. (2018)	Prospective	NSCLC	PD-1/PD-L1 inhibitors	152	39	25.7	<ul style="list-style-type: none"> • Combination of Clinical and radiological criteria⁴

HNSCC: head and neck squamous cell carcinoma; NSCLC: non-small cell lung cancer; TTF: time-to-treatment failure; TGR: tumour growth rate; TGK: tumour growth kinetics; TGKR: ratio of post-treatment TGK to pre-treatment TGK

¹Melanoma, renal carcinoma, colorectal cancer, urothelial cancer, hepatocellular carcinoma, head and neck carcinoma, cutaneous squamous cell carcinoma, breast cancer, ovarian cancer, glioblastoma endometrium cancer, glioblastoma, cervix cancer, gastric and oesophagus cancer, mesothelioma, pancreas cancer, sarcoma

²Melanoma, non-small cell lung cancer, squamous cell carcinoma of head and neck, cutaneous squamous cell carcinoma, renal cell carcinoma, and colorectal cancer.

³Breast cancer, colon cancer, lung cancer, pancreatic cancer, renal cancer, melanoma.

⁴Combination of clinicoradiological criteria.

the incidence of HP in cohorts of patients treated with ICIs (Table 1). Champiat et al [15] retrospectively analyzed the prevalence of HP among 131 patients treated with PD-1 and PD-L1 inhibitors. Nine % (n=12 of 131) of patients with multiple tumor types experienced HP, which was defined as RECIST progression at first evaluation and >2-fold increase in tumor growth rate (TGR) early after ICI treatment. In another study investigating the occurrence of HP in 155 patients treated with immunotherapy, 6 advanced cancer patients were presented with HP, defined as time to treatment failure (TTF) less than 2 months, >50% growth in tumor burden compared with pre-immunotherapy period, and >2-fold increase in progression speed [16]. Moreover, Saâda-Bouzid et al [17] reported the highest incidence of hyperprogressive disease (HPD) to be up to 29% (n=10 of 34) in a retrospective analysis of 34 patients with HNSCC. Closer to findings of Champiat et al [15] in NSCLC patients, around 14% (n=56 of 406) of patients with NSCLC were found to have HP in the multicenter retrospective study [18]. Of note, in the study of tumor cell-free DNA copy number for cancer diagnostics, Weiss et al [29] found that 9% (n=11 of 56) of patients with multiple tumor types experienced HP after initiation of immunotherapy. More recently, 17% (n=37 of 220) of NSCLC patients receiving immune-blockade therapy were found as hyperprogressors, whose tumor growth kinetics (TGK) ratio was greater than 2 compared to that in pre-immunotherapy period [19]. Finally, Lo Russo et al [30] reported 25.7% (n=39 of 152) of NSCLC patients treated with ICIs as hyperprogressors. These findings are consistent with results from several phase

3 clinical trials comparing immune checkpoint inhibitors with cytotoxic chemotherapy in patients with NSCLC (Checkmate 057), advanced urothelial carcinoma (Keynote 045 and IMvigor211), HNSCC (Checkmate 141), advanced NSCLC (Checkmate 026), and NSCLC with high tumor mutational burden (Checkmate 227). In these clinical trials, overall survival (OS) and progression-free survival (PFS) declined in the first 3 months after the initiation of ICIs [12,31-34], indicating that a subset of patients receiving immunotherapy experienced unexpected disease progression or death. To illustrate better, the mortality was higher in patients with urothelial carcinoma receiving nivolumab (20%) than in those receiving docetaxel during the first 3 months of treatment in the Checkmate 057 clinical trial [12]. Clinical trials displaying this kinetics can be regarded as remarkable examples of HP. It is significant to emphasize that patients in trials mentioned above had previously received systemic therapies. However, evaluation of HP was not possible due to the lack of pre-imaging data.

Although there hasn't been a universally accepted description of HP, parameters have been proposed by a handful of studies published so far [15-19]. The definition of HP may be depicted as RECIST progression at the first evaluation, TTF less than 2 months, increase in tumor size greater than 50% compared to pre-immunotherapy phase, and increase in progression speed \geq to 2-fold. There have been various parameters for assessing HPD, such as TGR and TTF. TGR incorporates the RECIST, with the sum of target lesions and the time between the tumor evaluations, enabling more dynamic evaluation of tumor kinetics [15]. Another

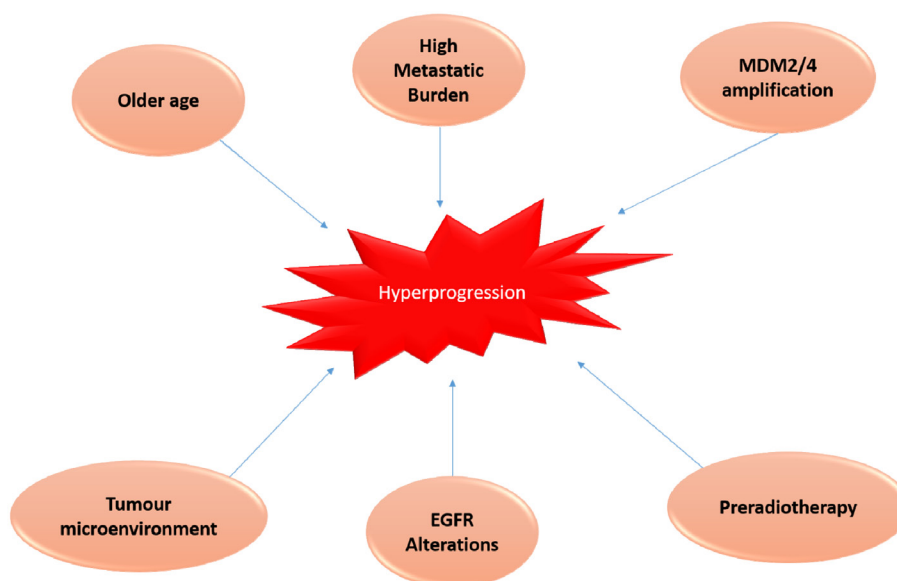


Figure 1. Biological and clinicopathological factors for hyperprogression.

approach, TKG is based on the variations of the sum of largest tumor growth but does not take into account the 3D tumor growth. This can overestimate the rate of HP in patients [17]. Heterogeneity in methodology may contribute to the significant differences in the prevalence of HP among studies. More definitive parameters about pretreatment tumor kinetics are needed for assessing HP.

Biological and clinicopathological factors of hyperprogression

In the above-mentioned studies, immune checkpoint inhibitors may induce an accelerated tumor growth in some patients. It is essential to elucidate the mechanisms of HP, with biological and clinical factors. This may help select patients who might benefit from immune checkpoint inhibitors. Several studies have proposed factors associated with HPD based on retrospective data and case studies (Figure 1).

Older age: One study found that older age (>65 years) was associated with higher incidence of HPD, with worse survival outcomes [15]. This situation can be explained by the differences in the immune system of older patients, such as an increase in the level of inflammatory cytokines or altered protein expression in T cell inhibitory/stimulatory pathways [35,36]. In accordance with the changing immune system in older patients, independent phase 3 clinical trials on ICIs indicated that older patients had less benefit than younger patients [37,38]. Moreover, age-related immunity dysfunction (ARID) causes a decrease in numbers, diversity, and functions of T cells, hence adversely affecting T cell immunity against tumors [39,40]. Up to now, there is limited research on this issue and further prospective studies are highly crucial to elucidate the mechanism of age-related HPD.

High-metastatic burden: HPD was found to be more common in patients with advanced NSCLC having high-metastatic burden compared to those without high-metastatic burden (62.5% ; 35 of 56 vs 42.6% i.e. 149 of 350 ; p=0.006) [18]. The exact mechanism linking the high metastatic burden to HPD is unknown. Additional studies are needed to address this issue.

MDM2 gene amplification: Mouse double minute 2 homolog (MDM2) amplification has been detected in 7% of human cancers [41]. The main role of MDM2 is to inhibit p53 tumor suppressor gene by stimulating its degradation [42]. Even though there has been limited research on the genetic basis of HPD, comprehensive genomic profiling of patients with HPD indicated that MDM2/

MDM4 amplification correlates with the accelerated tumor growth and poor prognosis [16]. In a research by Singavi et al [43], somatic alterations were analyzed in 4 patients with HPD by using next generation sequencing (NGS). MDM2/4 gene amplification has been detected in 66% of patients with HPD. The role of copy number alterations in MDM2 gene as a putative predictive biomarker for HP merits further investigation in large cohorts of patients.

Locoregional recurrence in the irradiated area: A number of studies have reported that previous radiation may predispose to HP. Saâda-Bouزيد et al [17] found that HP occurred in 50% (n=9 of 18) of head and neck cancer patients with a regional recurrence during immune-blockade therapy. It is important to emphasize that almost all patients in this study had previous radiotherapy. In a case study reported by Ogata et al [44], a patient with gastric cancer who received a single dose nivolumab following radiotherapy experienced HPD within the irradiated field. In head and neck cancer as well as in gastric cancer, locoregional recurrence in an irradiated field may play a role in the incidence of HPD. Radiotherapy induces the production of neoantigens in the tumor, which may cause rapid progression in the irradiated field [45]. So far, the exact mechanism linking HP to locoregional recurrence in the irradiated area remains unknown and further prospective controlled studies are needed.

EGFR alterations: Immune checkpoint inhibitors have had limited effectiveness in NSCLC patients with anaplastic lymphoma kinase (ALK) rearrangement or epidermal growth factor receptor (EGFR) mutations. In a phase 3 randomized clinical trials comparing immune checkpoint inhibitors to chemotherapy as a second or subsequent line of therapy in a small number of NSCLC patients with ALK/EGFR alterations, subgroup analyses indicated that patients with ALK/EGFR-positive disease did not benefit from immune-blockade therapy [46,47]. In addition, Gainor et al [48] retrospectively evaluated objective responses among 58 NSCLC patients with ALK rearrangements or EGFR mutations to determine the activity of ICIs within molecular subgroups. They found that objective responses were seen in only 3.6% (n=1 of 28) of ALK- or EGFR-positive patients versus 23.3% of (n=7 of 30) those with ALK-negative/unknown and EGFR wild-type patients. According to preclinical data, lower expressions of PD-L1 and decreased levels of CD8⁺ tumor-infiltrating lymphocytes (TILs) have been found in patients EGFR/ALK-positive patients compared to those with EGFR/ALK-negative, addressing the limited activity of ICIs in these clinically relevant molecular subgroups [48].

Besides MDM2/MDM4 amplification, EGFR alterations have been shown to be independently associated with HP. In a case study presented by Chubachi et al [21], the patient had received multiple lines of chemotherapies and tyrosine kinase inhibitors (TKI) prior to nivolumab administration. The disease was indolent during EGFR-TKIs treatment but progressed dramatically following nivolumab therapy. The authors suggested that the disease flare occurred after the discontinuation of EGFR-TKIs and may be a putative predictive factor for acceleration in disease progression during nivolumab treatment. In the cohort of patients analyzed by Kato et al [16], 20% (n=2 of 10) of patients with EGFR alterations demonstrated HP, with 41.7 fold increase in progression speed. Another abstract presented by Singavi et al [43], 50% (n=1 of 2) of patients with EGFR alterations showed HP. The molecular link between EGFR alterations and HP remains unclear. Further research is needed to address this issue.

Tumor mutational burden: Tumor mutational burden (TMB) has been correlated with greater efficacy of immunotherapies independent of PD-L1 expression [49]. However, the possible utility of TMB in patients with HPD is still unknown. Singavi et al [43] found that patients with HPD have TMB, with score ranging from 4-13 / Mb that is grouped as a low intermediate. More recently, Weiss et al [29] described that chromosomal instability quantification by next-generation sequencing (NGS) from plasma/serum derived cell-free DNA (cfDNA) could be used for predicting hyperprogressive response to immunotherapy. More research is needed to elucidate the relationship between TMB and HPD.

In addition to factors mentioned above, no remarkable differences in the prevalence of HP were reported among patients receiving anti-PD-1 or anti-PD-L1 inhibitors [15,17,18]. Interestingly, no association has been found between HP and CTLA-4 inhibitor monotherapy. Furthermore, there was

no association between HP and disease stage or performance status at baseline [15,17,18]. Mostly, HP is confused with “flare-up” phenomenon related to the discontinuation of previously targeted therapies. However, several studies reported that the types and number of previous therapies had no effect in the prevalence of HP [15,17,18]. There were no significant differences between patients with or without HP in terms of blood characteristics at the baseline (lymphocyte counts, serum levels of albumin or fibrinogen) [15,17]. According to retrospective data, HP was observed in multiple tumor types including NSCLC, HNSCC, melanoma, urothelial cancer, colorectal cancer, ovarian cancer, biliary tract carcinomas and lymphomas, suggesting that HP was independent of tumor histology [15,17]. Finally, no association was found between HP and PD-L1 expression in tumors, tumor burden at baseline, and the number of metastatic sites [15,17]. Interestingly, it has been described that patients with HPD have lower rates of new lesions [15].

Hypotheses about mechanisms behind Hyperprogression

The exact molecular mechanism underlying HP after immune-checkpoint blockade therapy remains unknown. So far, oncogenic signaling activation including MDM2 amplification or EGFR alterations, the modification of tumor microenvironment by radiotherapy with immune checkpoint inhibitors, and alterations in the immune landscape of tumors have been hypothesized as biological mechanisms behind HP (Figure 2).

MDM2 amplification was detected in patients with HPD after immune-checkpoint blockade therapy [16,43]. A possible explanation for the role of MDM2 in HP is related to the inactivation of p53, which is one of the key drivers of carcinogenesis. MDM2 plays a crucial role in the regulation of p53,

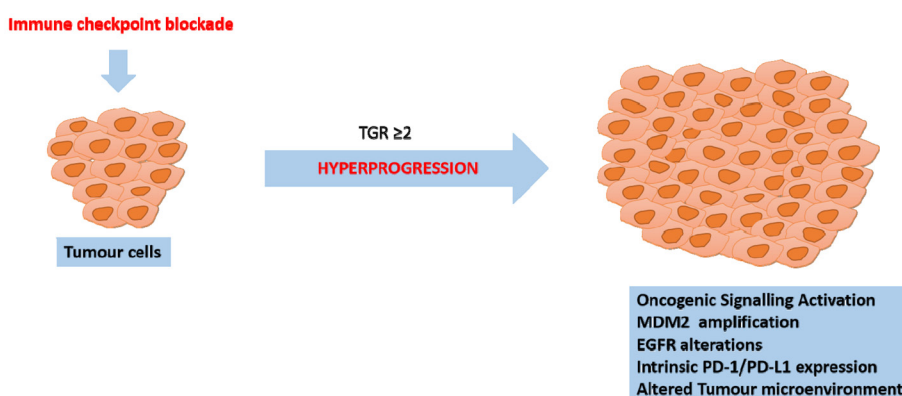


Figure 2. Potentially underlying mechanisms for hyperprogression.

known as the guardian of the genome [50]. MDM2, an ubiquitin protein ligase, directly inhibits N-terminal transactivation domain of p53 and triggers its degradation by the proteasome [51]. Immune checkpoint inhibitors may result in elevated interferon (IFN)- γ which, in turn, activates JAK-STAT signaling pathway [52]. This leads to an increase in the expression of interferon regulatory factor (IRF)-8 [53]. Binding of IRF-8 to the MDM2 promoter induces MDM2 expression [42,54]. This cascade may cause hyperexpression of MDM2 in the presence of MDM2 amplification. On the other hand, the location of a gene on MDM2 amplicon may co-amplify with MDM2 [16]. Combination of MDM2 inhibitors with ICIs might be an effective strategy to avoid the risk of HPD in the future. Further investigation is crucial to clarify this hypothesis.

Beyond MDM2-mediated oncogenic signaling activation, it has been widely known that PD-1/PD-L1 axis exerts intrinsic functions in tumor cells [55]. Intrinsic PD-1 expression in tumor cells has been associated with rapid tumor progression after ICI treatment in preclinical models [55,56]. Consistently, Du et al [56] suggested that PD1 blockade may lead to increase in tumor growth by interfering PD-1-mediated upregulation of proapoptotic proteins such as BIM, G1 phase inhibitor (p15INK4), and cyclin-dependent kinase 2. More importantly, Kleffel et al [55] found that PD-1 inhibition suppressed the growth in PD-1-expressing melanoma cells. Lorenz hypothesized that the differential effects of PD-1 signaling may vary depending on differences in Src homology (SH) domain-containing protein tyrosine phosphatase (SHP) signaling in T cells and melanoma. SHP1 and SHP2 phosphatases are cellular mediators of PD-1 signaling, causing T cell energy [57]. SHP2 is largely demonstrated as a proto-oncogene, whereas SHP1 suppresses tumor growth by degrading JAK kinases and dephosphorylating STAT3 [58,59]. Therefore, SHP differential partnering may take part in the molecular interplay of HP.

The modification of tumor microenvironment by previous radiotherapy with ICIs might be another potential mechanism leading to HP. As described previously, Saâda-Bouzid et al [17] found that almost all patients with HP had at least a locoregional recurrence in an irradiated field. Thus, the previous radiotherapy could contribute to the HPP supportingly, irradiation can decrease the effect of immunotherapy by upregulating PD-L1 expression and depleting tumor infiltrating leucocytes (TILs) [23,24]. Radiotherapy could adversely alter the antitumor immunity, with changes in tumor microenvironment after ICI treatment, leading to HP [60].

Hyperactivation of PD-1/PD-L1 upstream may also lead to HP after immune-checkpoint blockade therapy. Immune activation is known to induce local inflammation, matrix/tissue remodeling, angiogenesis, and anaerobic metabolism, which facilitate tumor progression and spread to the distant parts of the body [61,62]. Reduced activity of PD-1 may induce the levels of oncogenic proteins such as nuclear factor of activated T cells 1 (NFATC1) and pro-oncogenic inflammatory transducers [63,64]. Moreover, downregulated PD-L1 may contribute to activation of proliferation pathways such as RAS MAPK and PI3K/Akt in the presence of enhancing genetic alterations [64].

Alterations of the immune system cells could also mediate the HPD in patients. T cell responses have been at the center of antitumor immunity since immunotherapy in cancer attempts the activation and the expansion of specific cancer T cells [65]. Zuazo-Ibarra et al [66] underlined the role of CD4 T_{HD} cells in identifying the primary resistance to therapy and the risk of HP after immune-checkpoint blockade therapy. They found that low baseline circulating highly-differentiated CD28-CD27- CD4 T cells (T_{HD} cells) in NSCLC patients identify non-responders and hyperprogressors. The authors suggested that profiling of T_{HD} cells in patients prior to immunotherapies could help predict the patients having risk of HP.

Although the main research focused on adaptive immunity, the role of natural immunity in HP could not be underestimated. Accordingly, monocytes and tumor-infiltrating dendritic cells exert immunosuppressive activity through Interleukin (IL)-10 release after anti-PD-1 treatment [67,68]. Moreover, some of the myeloid cells in the tumor microenvironment could lessen the effect of immune-checkpoint blockade therapy through PD-L1 expression or immunosuppression [69,70]. Recently, Lo Russo et al [30] reported the role of TAM programming in mediating HP via Fc/FcR triggering macrophages by anti-PD-1 antibody. Interestingly, all NSCLC patients with HP displayed TM2-like CD163⁺ CD33⁺ PD-L1⁺ clustered epithelioid macrophages. The authors suggested that ICIs promote reprogramming of clustered epithelial macrophages (CD163⁺ CD33⁺ PD-L1⁺) into pro-tumorigenic phenotype via FcR-mediated signaling cascade, eventually inducing HPD.

Changes in mutational and transcriptional landscapes of pre- and post-therapy HPD tumors may explain the underlying mechanism of HP. In a comprehensive genomic study conducted by Xiong et al [71], it was described that two patients with HPD had increased deleterious somatic mutations in cancer genes such as TSC2 and VHL, with up-

regulated oncogenic pathways such as IGF-1, ERK/MAPK, PI3K/AKT, and TGF- β . More importantly, they outlined the significant changes in HPD tumors. Firstly, HPD tumors were less immunogenic, which may be caused by the downregulation of antigen-processing genes such as HLA, B2M, and upregulation of other immune checkpoint genes including CTLA4, KDR, CD96, CD70, TNFRSF18, TNFRSF25, BTNL2, and TNFRS. Secondly, the activity of T cells, dendritic cells, monocytes, natural killer cells, and CD4 helper T cells were weakened, whereas neutrophils were highly active in HPD tumors. Thirdly, natural lymphoid cells (ILC3) were enriched in HPD tumors after anti-PD-1 treatment. It clearly seems that HPD tumors have unique gene expression signature along with changes in their microenvironment. Further genomics and transcriptomics analysis should be done with more patients with HPD to identify unique gene expression signature related to this phenomenon.

Future prospects and concluding remarks

Integration of immune checkpoint inhibitor-based therapies into the oncology field has led to incredible improvements in the clinical outcomes of patients with multiple cancer types. However, accumulated studies revealed that a subset of patients has experienced paradoxically accelerated disease progression early after the initiation of immunotherapy. Until now, a small cohort of patients has been evaluated. Studies with higher numbers of patients and centers are urgently needed to reach a better understanding of HP. Moreover, there has been no universally accepted definition for HP and the methods (TGR, TGK) assessing clinical response have not been widely accepted by the clinical oncology community. Integrating pre-treatment tumor kinetics into clinical practice is critical to objectively discriminate HP from naturally aggressive disease or pseudoprogression. To avoid an ineffective treatment, patients can be evaluated at earlier time periods (4-6 weeks). Future research should focus on achieving consensus for diagnostic criteria of HP and discovering putative biomarkers related to HP. In addition, molecular and immunological basis of HP has remained largely unknown. Genome profiling of patients with HPD might help elucidate biological mechanisms behind HP and design novel therapeutic interventions that would be beneficial for these patients. For this reason, it is highly recommended that the collection of samples including blood or tumor tissue upon disease progression should be considered in the clinical

trials. Even though immune checkpoint inhibitors have been regarded as the primary reason for HP, no benchmarking studies have been conducted to determine whether ICIs induce HPD in patients. Accelerated tumor progression may occur in response to intrinsic cancer biology or due to resistance to immunotherapy. More efforts are needed for comprehensive analysis of various cells on the tumor microenvironment (T cells, Treg or Teff), tumor-associated macrophages (TAMs, M2 type), dendritic cells, myeloid-derived stem cells (MDSC), expression of immune checkpoints, cytokines, and inflammatory or inhibitory mediators with whole genome sequencing of tumor cells. Recently, subsequent studies reported that chromosomal instability quantification by NGS from plasma/serum derived cell-free DNA (cfDNA) and the detection of genome instability number (GIN) by genome-wide sequencing of cfDNA could be used to discriminate clinical responses from progression, pseudoprogression, and HP [29,72]. Complementarily, these attempts contribute to explore the immune landscape in tumors and to discover biomarkers that could predict the HP in patients.

As immune checkpoint inhibitors have been more widely accepted by oncologists, a proper assessment of tumor response remains challenging in clinical practice. Better survival outcomes in patients may lead physicians to fail to notice adverse events of immunotherapy. As mentioned above, an increasing body of evidence reveals that a small subset of patients is harmed by immune-blockade treatment. The distinct nature of HP has been supported by genomic and immunological analysis of HPD tumors. Moreover, patients with HPD have been presented with poor prognosis and increased deleterious mutations in cancer genes, along with alterations in the tumor microenvironment. Accordingly, these findings highlight the possibility of treatment-related adverse event. In conclusion, we suggest that HP should be explored as an adverse event of immunotherapy. This issue warrants further investigation to answer the questions about this undesired phenomenon.

Authors' contributions

All authors have equal contribution to the design and writing of the review. All authors approved the final version of the article.

Conflict of interests

The authors declare no conflict of interests.

References

1. Hanahan D, Weinberg RA. Hallmarks of Cancer: The Next Generation. *Cell* 2011;144:646-74.
2. Vinay DS, Ryan EP, Pawelec G et al. Immune evasion in cancer: Mechanistic basis and therapeutic strategies. *Semin Cancer Biol* 2015. doi: 10.1016/j.semcancer.2015.03.004.
3. Wei SC, Duffy CR, Allison JP. Fundamental mechanisms of immune checkpoint blockade therapy. *Cancer Discov* 2018. doi: 10.1158/2159-8290.CD-18-0367.
4. Puri S, Shafique M, Gray JE. Immune Checkpoint Inhibitors in Early-Stage and Locally Advanced Non-Small Cell Lung Cancer. *Curr Treat Options Oncol* 2018;19:39.
5. Alsharedi M, Katz H. Check point inhibitors a new era in renal cell carcinoma treatment. *Med Oncol* 2018. doi: 10.1007/s12032-018-1147-y.
6. Massari F, Di Nunno V, Cubelli M et al. Immune checkpoint inhibitors for metastatic bladder cancer. *Cancer Treat Rev* 2018;64:11-20.
7. Ansell SM, Lesokhin AM, Borrello I et al. PD-1 Blockade with Nivolumab in Relapsed or Refractory Hodgkin's Lymphoma. *N Engl J Med* 2015. doi: 10.1056/NEJMoal411087.
8. Forster MD, Devlin MJ. Immune Checkpoint Inhibition in Head and Neck Cancer. *Front Oncol* 2018;8:310.
9. Topalian SL, Sznol M, McDermott DF et al. Survival, Durable Tumor Remission, and Long-Term Safety in Patients With Advanced Melanoma Receiving Nivolumab. *J Clin Oncol* 2014;32:1020-30.
10. Uchi H. Merkel Cell Carcinoma: An Update and Immunotherapy. *Front Oncol* 2018;8:48.
11. Robert C, Long GV, Brady B et al. Nivolumab in Previously Untreated Melanoma without BRAF Mutation. *N Engl J Med* 2015;372:320-30.
12. Borghaei H, Paz-Ares L, Horn L et al. CheckMate 057: Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. *N Engl J Med* 2015. doi: 10.1056/NEJMoal507643.
13. Herbst RS, Baas P, Kim DW et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet* 2016;387:1540-50.
14. Queirolo P, Spagnolo F. Atypical responses in patients with advanced melanoma, lung cancer, renal-cell carcinoma and other solid tumors treated with anti-PD-1 drugs: A systematic review. *Cancer Treat Rev* 2017;59:71-8.
15. Champiat S, Derclé 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.
16. Kato S, Goodman A, Walavalkar V, Barkauskas DA, Sharabi A, Kurzrock R. Hyperprogressors after Immunotherapy: Analysis of Genomic Alterations Associated with Accelerated Growth Rate. *Clin Cancer Res* 2017;23:4242-50.
17. Saâda-Bouazid 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.
18. 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.
19. Kim Y, Kim CH, Kim HS et al. Hyperprogression after immunotherapy: Clinical implication and genomic alterations in advanced non-small cell lung cancer patients (NSCLC). *J Clin Oncol* 2018;36:15 (Suppl) 9075-9075.
20. Wolchok JD, Hoos A, O'Day S et al. Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria. *Clin Cancer Res* 2009;15:7412-20.
21. 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;2016:1-3.
22. Kanai O, Fujita K, Okamura M, Nakatani K, Mio T. Severe exacerbation or manifestation of primary disease related to nivolumab in non-small-cell lung cancer patients with poor performance status or brain metastases. *Ann Oncol* 2016;27:1354-6.
23. Yoshida T, Furuta H, Hida T. Risk of tumor flare after nivolumab treatment in patients with irradiated field recurrence. *Med Oncol* 2017;34:34.
24. Alexander GS, Palmer JD, Tuluc M et al. Immune biomarkers of treatment failure for a patient on a phase I clinical trial of pembrolizumab plus radiotherapy. *J Hematol Oncol* 2016;9:96.
25. Kobari Y, Kondo T, Takagi T, Omae K, Nakazawa H, Tanabe K. Rapid Progressive Disease After Nivolumab Therapy in Three Patients with Metastatic Renal Cell Carcinoma. *In Vivo (Brooklyn)* 2017;31:769-71.
26. Faure M, Rochigneux P, Olive D, Taix S, Brenot-Rossi I, Gilibert M. Hyperprogressive Disease in Anorectal Melanoma Treated by PD-1 Inhibitors. *Front Immunol* 2018;9:797.
27. Ratner L, Waldmann TA, Janakiram M, Brammer JE. Rapid Progression of Adult T-Cell Leukemia-Lymphoma after PD-1 Inhibitor Therapy. *N Engl J Med* 2018;378:1947-8.
28. Groisberg R, Hong DS, Behrang A et al. Characteristics and outcomes of patients with advanced sarcoma enrolled in early phase immunotherapy trials. *J Immunother Cancer* 2017;5:100.
29. Weiss GJ, Beck J, Braun DP et al. Tumor cell-free DNA copy number instability (CNI) to predict therapeutic response to immunotherapy prior to cycle 2. *J Clin Oncol* 2016;34:3027.
30. Lo Russo G, Moro M, Sommariva M et al. Antibody-Fc/FcR Interaction on Macrophages as a Mechanism for Hyperprogressive Disease in Non-small Cell Lung Cancer Subsequent to PD-1/PD-L1 Blockade. *Clin Cancer Res* 2019;25:989-99.
31. Powles T, Durán I, van der Heijden MS et al. Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma. *Ann Oncol* 2019;30:1014-23.

- noma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial. *Lancet* 2018;391:748-57.
32. Carbone DP, Reck M, Paz-Ares L et al. First-Line Nivolumab in Stage IV or Recurrent Non-Small-Cell Lung Cancer. *N Engl J Med* 2017;376:2415-26.
 33. Ferris RL, Blumenschein G, Fayette J et al. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. *N Engl J Med* 2016;375:1856-67.
 34. Hellmann MD, Ciuleanu T-E, Pluzanski A et al. Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutational Burden. *N Engl J Med* 2018;378:2093-104.
 35. Goronzy JJ, Weyand CM. Understanding immunosenescence to improve responses to vaccines. *Nat Immunol* 2013;14:428-36.
 36. Solana R, Tarazona R, Gayoso I, Lesur O, Dupuis G, Fulop T. Innate immunosenescence: Effect of aging on cells and receptors of the innate immune system in humans. *Semin Immunol* 2012;24:331-41.
 37. Brahmer J, Reckamp KL, Baas P et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. *N Engl J Med* 2015;373:123-35.
 38. Motzer RJ, Escudier B, McDermott DF et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. *N Engl J Med* 2015;373:1803-13.
 39. Hakim FT, Flomerfelt FA, Boyiadzis M, Gress RE. Aging, immunity and cancer. *Curr Opin Immunol* 2004;16:1516-6.
 40. Fülöp T, Larbi A, Pawelec G. Human T cell aging and the impact of persistent viral infections. *Front Immunol* 2013;4:271.
 41. Momand J, Jung D, Wilczynski S, Niland J. The MDM2 gene amplification database. *Nucleic Acids Res* 1998;26:3453-9.
 42. Zhao Y, Yu H, Hu W. The regulation of MDM2 oncogene and its impact on human cancers. *Acta Biochim Biophys Sin (Shanghai)* 2014;46:180-9.
 43. 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. doi: 10.1093/annonc/mdx376.006.
 44. Ogata T, Satake H, Ogata M, Hatachi Y, Yasui H. Hyperprogressive Disease in the Irradiation Field after a Single Dose of Nivolumab for Gastric Cancer: A Case Report. *Case Rep Oncol* 2018;11:143-50.
 45. Fields EC, McGuire WP, Lin L, Temkin SM. Radiation Treatment in Women with Ovarian Cancer: Past, Present, and Future. *Front Oncol* 2017;7:177.
 46. Lee CK, Man J, Lord S et al. Checkpoint Inhibitors in Metastatic EGFR- Mutated Non-Small Cell Lung Cancer-A Meta-Analysis. *J Thorac Oncol* 2017;12:403-7.
 47. Bylicki O, Paleiron N, Margery J et al. Targeting the PD-1/PD-L1 Immune Checkpoint in EGFR-Mutated or ALK-Translocated Non-Small-Cell Lung Cancer. *Target Oncol* 2017;12:563-9.
 48. Gainor JF, Shaw AT, Sequist LV et al. EGFR Mutations and ALK Rearrangements Are Associated with Low Response Rates to PD-1 Pathway Blockade in Non-Small Cell Lung Cancer: A Retrospective Analysis. *Clin Cancer Res* 2016;22:4585-93.
 49. Bumber Y. Tumor mutational burden (TMB) as a biomarker of response to immunotherapy in small cell lung cancer. *J Thorac Dis* 2018;10:4689-93.
 50. Wade M, Li Y-C, Wahl GM. MDM2, MDMX and p53 in oncogenesis and cancer therapy. *Nat Rev Cancer* 2013;13:83-96.
 51. Moll UM, Petrenko O. The MDM2-p53 interaction. *Mol Cancer Res* 2003;1:1001-8.
 52. Peng W, Liu C, Xu C et al. PD-1 Blockade Enhances T-cell Migration to Tumors by Elevating IFN- Inducible Chemokines. *Cancer Res* 2012;72:5209-18.
 53. Schindler C, Levy DE, Decker T. JAK-STAT Signaling: From Interferons to Cytokines. *J Biol Chem* 2007;282:20059-63.
 54. Zhou JX, Lee CH, Qi CF et al. IFN Regulatory Factor 8 Regulates MDM2 in Germinal Center B Cells. *J Immunol* 2009;183:3188-94.
 55. Kleffel S, Posch C, Barthel SR et al. Melanoma Cell-Intrinsic PD-1 Receptor Functions Promote Tumor Growth. *Cell* 2015;162:1242-56.
 56. Du S, McCall N, Park K et al. Blockade of Tumor-Expressed PD-1 promotes lung cancer growth. *Oncoimmunology* 2018;7:e1408747.
 57. Lorenz U. SHP-1 and SHP-2 in T cells: two phosphatases functioning at many levels. *Immunol Rev* 2009;228:342-59.
 58. Wu C, Guan Q, Wang Y, Zhao ZJ, Zhou GW. SHP-1 suppresses cancer cell growth by promoting degradation of JAK kinases. *J Cell Biochem* 2003;90:1026-37.
 59. Qi C, Han T, Tang H et al. Shp2 Inhibits Proliferation of Esophageal Squamous Cell Cancer via Dephosphorylation of Stat3. *Int J Mol Sci* 2017;18:134.
 60. Demaria S, Golden EB, Formenti SC. Role of Local Radiation Therapy in Cancer Immunotherapy. *JAMA Oncol* 2015;1:1325.
 61. Colotta F, Allavena P, Sica A, Garlanda C, Mantovani A. Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. *Carcinogenesis* 2009;30:1073-81.
 62. Koyama S, Akbay EA, Li YY et al. Adaptive resistance to therapeutic PD-1 blockade is associated with upregulation of alternative immune checkpoints. *Nat Commun* 2016;7:10501.
 63. Xu W, Gu J, Ren Q et al. NFATC1 promotes cell growth and tumorigenesis in ovarian cancer up-regulating c-Myc through ERK1/2/p38 MAPK signal pathway. *Tumor Biol* 2016;37:4493-500.
 64. Dong Y, Sun Q, Zhang X. PD-1 and its ligands are important immune checkpoints in cancer. *Oncotarget* 2017;8:2171-86.
 65. Wang M, Yin B, Wang HY, Wang R-F. Current advances in T-cell-based cancer immunotherapy. *Immunotherapy* 2014;6:1265-78.
 66. Zuazo-Ibarra M, Arasanz H, Fernandez-Hinojal G et al. Senescent CD4 T cells unequivocally identify primary resistance and risk of hyperprogression to PD-L1/PD-1 immune checkpoint blockade in lung cancer. *BioRxiv* 2018;320176.
 67. Said EA, Dupuy FP, Trautmann L et al. Programmed death-1-induced interleukin-10 production by mono-

- cytes impairs CD4⁺ T cell activation during HIV infection. *Nat Med* 2010;16:452-9.
68. Lamichhane P, Karyampudi L, Shreeder B et al. IL10 Release upon PD-1 Blockade Sustains Immunosuppression in Ovarian Cancer. *Cancer Res* 2017;77:6667-78.
69. Antonios JP, Soto H, Everson RG et al. Immunosuppressive tumor-infiltrating myeloid cells mediate adaptive immune resistance via a PD-1/PD-L1 mechanism in glioblastoma. *Neuro Oncology* 2017;19:796-807.
70. Arlauckas SP, Garris CS, Kohler RH et al. In vivo imaging reveals a tumor-associated macrophage-mediated resistance pathway in anti-PD-1 therapy. *Sci Transl Med* 2017;9:eaa13604.
71. Xiong D, Wang Y, Singavi AK, Mackinnon AC, George B, You M. Immunogenomic Landscape Contributes to Hyperprogressive Disease after Anti-PD-1 Immunotherapy for Cancer. *Science* 2018;9:258-77.
72. Jensen TJ, Goodman AM, Kato S et al. Genome-Wide Sequencing of Cell-Free DNA Identifies Copy-Number Alterations That Can Be Used for Monitoring Response to Immunotherapy in Cancer Patients. *Mol Cancer Ther* 2019;18:448-58.