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Research Article

Differences between Hyperprogressive Disease and Progressive Disease in Patients Receiving Immunotherapy

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Abstract

Objectives: Although immune checkpoint inhibitors (ICIs) became a vital part of cancer care, many patients do not respond to treatment. In this group, a few of the patients with a hyperprogressive disease (HPD) have shorter overall survival (OS) compared with those having a progressive disease (PD). Therefore, biomarkers are needed to differentiate HPD and PD.

Methods: Ninety-five patients treated with ICIs with progression according to response evaluation criteria ın solid tumors criteria in the first control imaging were included. HPD was defined according to Russo's work. The PILE scoring system, which includes pan-immune-inflammation value, lactate dehydrogenase, and Eastern Cooperative Oncology Group PS, was followed. The relationship between PILE score and HPD was analyzed.

Results: The median OS of all cohorts was 11.18 months. The patients in the HPD group had decreased OS (4.77 vs. 13.94 months, p<0.001) and progression-free survival (PFS) (1.89 vs. 3.16 months, p<0.001) compared with those in the PD group. The risk of HPD was higher than the risk of PD in patients with a high PILE score (p=0.001).

Conclusion: In this study, we showed that patients treated with ICI with a higher PILE score are at greater risk for HPD. The PILE score may be a biomarker to differentiate HPD from PD.

Keywords: Hyperprogressive disease, immun checkpoint inhibitors, immunotherapy, PILE score

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With the widespread use of immune checkpoint inhibitors (ICIs), we encounter unexpected treatment responses. Hyperprogression and pseudoprogression are the new treatment procedures we are encountering.[1] A few patients treated with ICI experience rapid treatment unresponsiveness and progression that cannot be defined by the response evaluation criteria in solid tumors (RECIST). This situation is considered hyperprogression. Although there is no universally accepted norm for hyperprogression, it has been found to be between 4% and 29% in studies.[2–11] A few studies showed that patients with a hyperprogressive disease (HPD) show less survival time than those with a standard progressive disease (PD).[3, 5, 7, 9] Therefore, there is a need for predictive factors that can differentiate HPD from PD.

Methods

In our retrospective cohort study, patients with any cancer subtype treated with ICI at Hacettepe University Cancer Institute between September 2014 and July 2019 were retrospectively screened. All patients with baseline and at least

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one follow-up cross-sectional imaging with contrast after the first dose of immunotherapy were included. In total, 95 patients who progressed according to the RECIST criteria at the first follow-up imaging were included in the study.

Baseline patient demographics, patient weight and height, Eastern Cooperative Oncology Group (ECOG) performance status, tumor histology, ICI types, comorbidities, baseline lactate dehydrogenase (LDH), neutrophil levels, and thrombocyte levels, pan-immune-inflammation value (PIV) and PILE score were recorded with survival data. PIV was calculated as follows: (neutrophil count × platelet count × monocyte count)/lymphocyte count. PILE is a prognostic score consisting of PIV(< median=0, ≥median=1), LDH (≤ULN=0, >ULN=1) and ECOG PS (<2=0, ≥2=1). A PILE score of 0-1 was defined as a low PILE score and a 2-3 as a high PILE score.

Patients with HPD are defined by RECIST progression and at least three of the following symptoms: time-to-treatment failure <2 months (time-to-treatment failure is defined as the time from the start of treatment with ICI to ICI discontinuation for any reason); increase of ≥50% in the sum of target lesions major diameters between baseline and first radiologic evaluation; the appearance of at least two new lesions in an organ already involved between baseline and first radiologic evaluation; spread of the disease to a new organ between baseline and first radiologic evaluation; clinical deterioration with a decrease in ECOG performance status ≥2 during the first 2 months of treatment.[10]

The baseline characteristics were expressed in percentages, medians, and interquartile ranges as appropriate. The baseline characteristics of the patients were compared using Chi-squared and Mann–Whitney U tests. The association of hyperprogression risk and possible predisposing factors were evaluated using Chi-squared and Fischer's exact tests. Survival analysis, according to the presence or absence of hyperprogression and other clinical parameters, was performed via the Kaplan–Meier method and Cox regression analysis. Statistical Package for Social Sciences version 20 program was used in the analyses. p-values below 0.05 were considered statistically significant.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the ethics committee of Hacettepe University.

Results

A total of 95 patients were included in the analyses. The median age of all cohorts was 58.87±10.08 years, and 56.8% of the patients were males. The malignant melanoma (30.5%) and renal cell carcinoma (27.3%) comprised more than half of the patients. Most patients had a good ECOG performance status (ECOG 0–1, 83.1%). Of the total patients,

Table 1. Baseline clinical and laboratory features of patients with HPD and PD

	HPD	PD	p
Median age	58.81±11.62	60.28±9.49	0.530
Sex			
Female	7 (26.9%)	34 (49.3%)	0.050
Male	19 (73.1%)	35 (50.7%)	
Age (years)			
>65	11 (42.3%)	20 (29%)	0.201
<65	15 (57.7%)	49 (71%)	
LDH			
Normal	7 (30.4%)	44 (68.8%)	0.001
>ULN	16 (69.6%)	20 (31.3%)	
Albumin			
>4	6 (24%)	28 (41.2%)	0.127
<4	19 (76%)	40 (58.8%)	
ECOG score			
0–1	23 (88.5%)	56 (82.4%)	0.353
2–4	3(11.5%)	12 (17.6)	
Liver metastasis			
Present	11 (42.3%)	22 (31.9%)	0.341
Absent	15 (57.7%)	47 (68.1%)	
Immunuotherapy plus CT			
Present	7 (26.9%)	13 (18.8%)	0.389
Absent	19 (73.1%)	56 (81.2%)	
Neutrophil/lymphocyte ratio			
>3.375	16 (61.5%)	35 (50.7%)	0.346
<3.375	10 (38.5%)	34 (49.3%)	
Diagnosis			
Melanoma	10 (38.5%)	19 (27.5%)	0.071
RCC	4 (15.4%)	22 (31.9%)	
NSCLC	6 (23.1%)	8 (11.6%)	
Other	6 (23.1%)	20 (29%)	
Line of treatment			
1–3	22 (84.6%)	51 (73.9%)	0.270
>3	4 (15.4%)	18 (23.2%)	
PILE score			
0-1	5 (21.7%)	39 (60.9%)	0.001
2-3	18 (78.3%)	25 (39.1%)	
Type of ICI			
Ipilimumab	4 (15.4%)	8 (11.6%)	0.898
Nivolumab	16 (61.5%)	45 (65.2%)	
Pembrolizumab	2 (7.7%)	4 (5.8%)	
Atezolizumab	4 (15.4%)	12 (17.4%)	
Albumin			
Normal	6 (24%)	28 (41.8%)	0.116
<4	19 (76%)	39 (58.2%)	

HPD: Hyperprogressive disease; PD: Progressive Disease; LDH: Lactate dehydrogenase; ECOG: Eastern Cooperative Oncology Group; CT: Computed tomography; RCC: Renal cell carcinoma; ICI: Immune checkpoint inhibitor.

27.3% patients had HPD, 37.8% had high LDH levels, 62.1% had low albumin, and 33.7% had liver metastases. Approximately 53.6% of patients had NLR scores above 3.375. The basic clinical and laboratory characteristics of patients with HPD and PD are shown in Table 1.

After follow-up for a period (median, 6.6 months), 79 (83.1%) patients died. The median overall survival (OS) and progression-free survival (PFS) for all cohorts were 11.18±1.36 months and 2.81±0.12 months, respectively. Patients in the HPD group had significantly decreased OS and PFS compared with patients in the PD group. (OS: 4.77±0.89 vs. 13.94±1.80 months, p<0.001; PFS: 1.89±0.11 vs. 3.16±0.12 months, p<0.001) (Figs. 1, 2).

The patients were categorized into low-risk (0–1 point) and high-risk groups (2–3 points) according to the PILE score. HPD was higher than PD in patients with a high PILE score (p=0.001). High LDH level is at high risk for HPD (p=0.001).

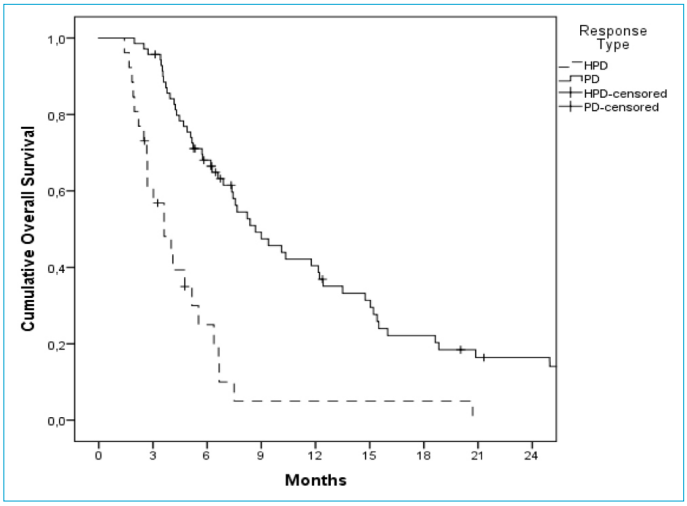

Figure 1. Comparison of overall survival according to HPD and PD.

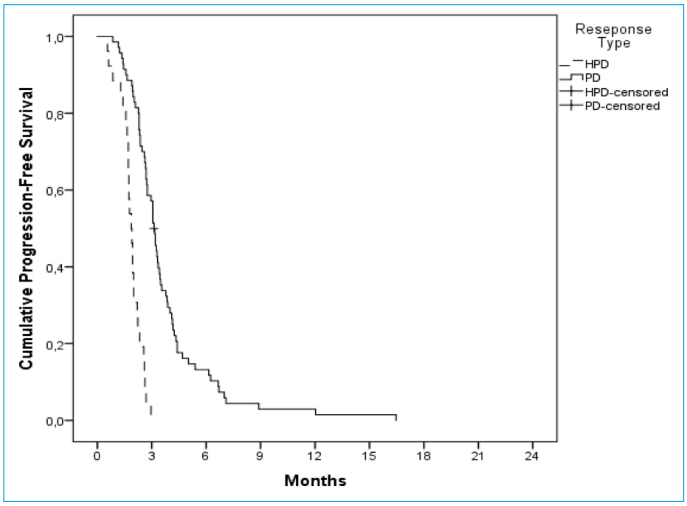

Figure 2. Comparison of progression-free survival according to HPD and PD.

Sex (female vs. male, p=0.050), age (>65 vs. <65 years, p=0.201), ECOG (0–1 vs. 2–4, p=0.353), presence of liver metastases (present vs. absent, p=0.341), the line of treatment (1–3 or more, p=0.270), and diagnosis (p=0.071) were not found to be associated with HPD.

A multivariable model for OS was constructed with sex and PILE score. In multivariate analyses, a high PILE score was found to be associated with HPD (HR: 4.992, 95% CI: 1.615–15.425, p=0.005) (Table 2).

Discussion

In our study, we evaluated patients who showed progression according to the RECIST criteria at the initial follow-up imaging and classified them as HPD or PD according to Russo's criteria. We found the OS in HPD to be significantly shorter than that in PD without HPD (4.77±0.89 vs. 13.94±1.80 months, p<0.001). Patients with a high PILE risk score were found to be significantly more at risk for HPD than patients with a low-risk score (p=0.001).

Although ICIs have promising results in many cancer types, desired treatment responses have not been achieved in many patients.[12–14] It is known that the OS time in the case of HPD is quite short compared with that in the standard PD case.[3, 5, 7, 9]

Studies are conducted to evaluate the continuation of immunotherapy for patients who have progressed under immunotherapy. In the study by Ge et al., the immunotherapy beyond progression (IBP) group had longer OS and PFS compared with the non-IBP group (median OS – 26.6 vs. 9.5 months, HR: 0.40, 95% CI: 0.23–0.69, p<0.001; median PFS – 8.9 vs. 4.1 months, HR: 0.41, 95% CI: 0.26–0.65, p<0.001).[15] Therefore, we need to determine which patients have HPD and which patients have PD.

In their study, Sasaki et al. evaluated nivolumab treatment in patients with advanced gastric cancer. Progression according to the RECIST criteria was detected in 53% of the patients in the initial response evaluation, and 39% of these patients met the HPD criteria. In this study, PFS was 0.7 months and OS was 2.3 months in patients with HPD.[7] In the study by Kim et al., PFS and OS were significantly shorter in patients with HPD than in patients with PD with-

Table 2. Multivariate analysis of factors associated with HPD

Clinical factor	Risk of hyperprogression	
	HR (95%)	p
Sex (female–male)	2.449 (0.810–2.449)	0.113
PILE category (low–high)	4.992 (1.615–15.425)	0.005

HPD: Hyperprogressive disease; HR: High risk.

out HPD (48 days and 205 days vs. 19 days and 50 days).[5] Similarly, in our study, PFS and OS were shorter in patients with HPD than in patients with PD who did not have HPD. In the two studies mentioned here, predictive factors to be used in differentiating HPD from PD were not investigated.

Blood cells around the tumor have effects on tumor carcinogenesis, and biomarkers created with neutrophil, lymphocyte, platelet, and monocyte values yielded prognostically significant results.[16, 17] In the study of Guven et al., in which clinical data were added to these laboratory parameters, PILE risk category, which consisted of ECOG status, was seen. The pan-immune-inflammation value and LDH level predict the response to immunotherapy.[18] In this study, it was observed that the OS and PFS of the PILE high-risk group were shorter than those of the low-risk group. After this study, Zeng et al. showed that PILE score could play a predictive role in patients with extensive stage NSCLC in their study.[19] In our study, we examined the relationship between the PILE risk group and the difference between PD and HPD. We found that patients in the PILE high-risk group were statistically significantly at risk for HPD compared with patients in the low-risk group. We found that the PILE score, which has been shown to predict the immunotherapy response in the above-mentioned studies, also predicts hyperpogression.

Concomitant administration of immunotherapy drugs and chemotherapy does not reduce the risk of hyperprogression. Similarly, we found that it was not important for hyperprogression in which step of the treatment immunotherapy was given. From this, we can deduce that there is no relationship between pre-immunotherapy disease burden and hyperprogression.

The limitations of our study are its retrospective nature and the inclusion of patients from different patient groups. There is a need for disease-specific multicenter prospective studies investigating HPD.

Conclusion

We showed that patients treated with ICI with a higher PILE score are at greater risk for HPD. If prospective studies confirm our results, the PILE score may be a biomarker to differentiate HPD from PD.

Disclosures

Ethics Committee Approval: In our retrospective cohort study, patients with any cancer subtype treated with ICI at Hacettepe University Cancer Institute between September 2014 and July 2019 were retrospectively screened.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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