What’s the difference between hyperprogressive disease and progressive disease for patients with treated immune checkpoint inhibitors?

Hasan Çağrı Yıldırım (hasan-cagri@windowslive.com)
Hacettepe Üniversitesi Tıp Fakultesi
https://orcid.org/0000-0003-3060-377X

Deniz Can Guven
Hacettepe Üniversitesi Tıp Fakultesi

Oktay Halit Aktepe
Hacettepe Üniversitesi Tıp Fakultesi

Hakan Taban
Hacettepe Üniversitesi Tıp Fakultesi

Feride Yilmaz
Hacettepe Üniversitesi Tıp Fakultesi

Serkan Yasar
Hacettepe Üniversitesi Tıp Fakultesi

Burak Yasin Aktaş
Hacettepe Üniversitesi Tıp Fakultesi

Gürkan Güner
Hacettepe Üniversitesi Tıp Fakultesi

Ömer Dizdar
Hacettepe Üniversitesi Tıp Fakultesi

Sercan Aksoy
Hacettepe Üniversitesi Tıp Fakultesi

Mustafa Erman
Hacettepe Üniversitesi Tıp Fakultesi

Suayib Yalcin
Hacettepe Üniversitesi Tıp Fakultesi

Saadettin Kilickap
İstinye Üniversitesi: İstinye Üniversitesi

Research Article

Keywords: Immun checkpoint inhibitors, hyperprogressive disease, progressive disease, PILE
Abstract

Background

Although the immune checkpoint inhibitors (ICIs) became a vital part of cancer care, many patients do not respond to treatment. Some of the patients in this group, which is considered to have hyperprogressive disease (HPD), have a shorter overall survival compared to progressive disease (PD). Therefore, biomarkers are needed to differentiate between HPD and PD. Here, we evaluated PILE score to differentiate HPD from PD in patients treated with ICI.

Methods

Ninety-five patients treated with anti-PD-1 or anti-PD-L1 inhibitors for any type of cancer with progression according to RECIST criteria in the first control imaging were included. HPD was defined according to Russo's work. The PILE scoring system was calculated, including PIV (< median vs. ≥ median), LDH (normal and > normal), and ECOG performance status (0 vs. ≥ 1). The relationship between PILE score and HPD was examined.

Results

The median follow-up was 6.6 months and the median OS of all cohort were 11.18 ± 1.36 months. The patients in the HPD group had decreased OS (4.77 ± 0.89 vs. 13.94 ± 1.80 months, p <0.001) and PFS (1.89 ± 0.11 vs. 3.16 ± 0.12 months, p <0.001) compared to 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. If prospective studies confirm our results, the PILE score may be a biomarker to differentiate HPD from PD.

Introduction

With the widespread use of immune checkpoint inhibitors (ICI), we encounter unexpected treatment responses. Hyperprogression and pseudoprogression are the new treatment responses we are encountering [1]. Some patients treated with ICI's experience rapid treatment unresponsiveness and progression that cannot be defined by the RECIST criteria. This situation is considered as hyperprogression. Although there is no universally accepted definition of hyperprogression, it has been found to be between 4% and 29% in studies [2-11]. Some of these studies showed that hyperprogressive
disease (HPD) is associated with worse survival time than the standard progressive disease (PD) [3, 5, 7, 9]. Therefore, there is a need for predictive factors that can differentiate HPD from PD.

**Method**

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 one follow-up cross-sectional imaging with contrast after the first dose of immunotherapy were included. 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, ECOG performance status, tumor histology, ICI types, comorbidities, baseline lactate dehydrogenase (LDH), neutrophil levels, thrombocyte levels and were recorded together with survival data.

Patients with HPD defined as RECIST progression and at least 3 of: 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 $\geq 50\%$ 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 decrease in Eastern Cooperative Oncology Group (ECOG) performance status $\geq 2$ during the first 2 months of treatment[10].

The baseline characteristics were expressed with percentages, medians, and interquartile ranges (IQR), wherever appropriate. Baseline characteristics of the patients were compared with chi-square and Mann-Whitney U tests. The association with hyperprogression risk and possible predisposing factors were evaluated with chi-square 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 analyses. 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 the all cohort was $58.87 \pm 10.08$ and 56.8% of the patients were males. The malign melanoma (30.5%) and RCC (27.3%) comprised more than half of the patients. Most patients had a good ECOG performance status (ECOG 0-1, 83.1%). 26 (27.3%) patients had HPD. 37.8% of the patients had high LDH levels and 62.1% had low albumin. 33.7%
of the patients 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 a median 6.6 months of follow-up, 79 (83.1%) patients died. The median OS and PFS all cohort were 11.18 ± 1.36 and 2.81 ± 0.12 months, respectively. Patients in the HPD group had significantly decreased OS (4.77 ± 0.89 vs. 13.94 ± 1.80 months, p <0.001) and PFS (1.89 ± 0.11 vs. 3.16 ± 0.12 months, p <0.001) compared to PD group. (Fig. 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)

Sex (female vs. male, p:0.050), age (>65 vs <65, p:0.201), ECOG (0-1 vs 2-4, p:353), presence of liver metastases (present vs. absent, p:0.341), the line of treatment (1-3 or more, p:0.270), diagnosis (p:0.071) were not found to be associated with HPD.

A multivariable model for OS was constructed with the following parameters: sex and PILE score. In multivariate analyses, high PILE score 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 and we found the overall survival in HPD to be significantly shorter than 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 ICI’s have promising results in many cancer types, desired treatment responses have not been achieved in many patients [12-14]. It is known that the overall survival time, especially in the case of HPD, is quite short compared to the standard PD [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 overall survival (median OS, 26.6 vs. 9.5 months; HR, 0.40; 95% CI: 0.23–0.69; P<0.001) and progression-free survival (median PFS, 8.9 vs. 4.1 months; HR, 0.41; 95% CI: 0.26–0.65; P<0.001), compared with the non-IBP group [15]. Therefore, we need to determine which patients have HPD and which patients have PD.

In the study by Sasaki et al., in which they 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 patients with PD without HPD (48 days, 205 days and 19 days, 50 days, respectively) [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 above, predictive factors to be used in differentiating hyperprogressive disease from progressive disease 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, it was seen that the PILE risk category, which consists of ECOG status, The Pan-Immune-Inflammation Value (PIV) and lactate dehydrogenase (LDH) level, predicts the response to immunotherapy [18]. In this study, it was observed that the overall survival and progression-free survival of the PILE high-risk group were shorter than 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 progressive disease and hyperprogressive disease. We found that patients in the PILE high-risk group were statistically significantly at risk for hyperprogressive disease compared to 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 hyperprogression.

Hyperprogressive disease is an issue that needs to be investigated because it is a response that we will encounter more frequently with the widespread use of ICI’s and that we have not encountered with previous standard chemotherapy and tyrosine kinase inhibitors. As the mechanism of hyperprogressive disease should be clarified, we should also know in which patients we encounter hyperprogressive disease. We should also understand from the obvious difference in our data on overall survival and progression-free survival that hyperprogressive disease and progressive disease are not the same.

Concomitant administration of immunotherapy drug 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 hyperprogressive disease.
Table 1
Baseline clinical and laboratory features of patients with or without hyperprogression

|                          | HPD          | PD           | p score |
|--------------------------|--------------|--------------|---------|
| Median age               | 58.81 (±11.62) | 60.28 (±9.49) | 0.53    |
| Sex                      | Female       | 7 (26.9%)    | 34 (49.3%) | 0.050   |
|                          | Male         | 19 (73.1%)   | 35 (50.7%) |
| Age                      | >65          | 11 (42.3%)   | 20 (29%)  | 0.201   |
|                          | <65          | 15 (57.7%)   | 49 (71.2%) |
| 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%) |
| KC metastasis            | Present      | 11 (42.3%)   | 22 (31.9%) | 0.341   |
|                          | Absent       | 15 (57.7%)   | 47 (68.1%) |
| Immunotherapy plus CT    | Present      | 7 (26.9%)    | 13 (18.8%) | 0.389   |
|                          | Absent       | 19 (73.1%)   | 56 (81.2%) |
| NLR                      | >3.375       | 16 (61.5%)   | 35 (50.7%) | 0.346   |
|                          | <3.375       | 10 (38.5%)   | 34 (49.3%) |
| Diagnosis                | Melanom      | 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   |
|                | HPD          | PD           | p score |
|----------------|--------------|--------------|---------|
| Nivolumab      | 16 (61.5%)   | 45 (65.2%)   |         |
| Pembrolizumab  | 2 (7.7%)     | 4 (5.8%)     |         |
| Atezolizumab   | 4 (15.4%)    | 12 (17.4%)   |         |
| Albümin        |              |              |         |
| Normal         | 6 (24%)      | 28 (41.8%)   | 0.116   |
| <4             | 19 (76%)     | 39 (58.2%)   |         |

Table 2
Multivariate analysis of factors associated with HPD

| Clinical Factor        | Risk of hyperprogression |
|------------------------|---------------------------|
|                        | HR (95%)                  | p score     |
| Sex (female-male)      | 2.449 (0.810-2.449)       | 0.113       |
| PILE Category (low-high)| 4.992 (1.615-15.425)     | **0.005**   |

Declarations

**Funding:** The authors received no financial support for this article.

**Conflict of Interest:** The authors declare that they have no conflict of interest.

**Compliance with Ethical Standards:** 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.

References

1. Borcoman, E., et al., *Novel patterns of response under immunotherapy.* Annals of Oncology, 2019. **30**(3): p. 385-396.

2. Champiat, S., et al., *Hyperprogressive disease is a new pattern of progression in cancer patients treated by anti-PD-1/PD-L1.* Clinical Cancer Research, 2017. **23**(8): p. 1920-1928.
3. Ferrara, R., 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 oncology, 2018. 4(11): p. 1543-1552.

4. Kanjanapan, Y., et al., *Hyperprogressive disease in early-phase immunotherapy trials: clinical predictors and association with immune-related toxicities.* Cancer, 2019. 125(8): p. 1341-1349.

5. Kim, C., et al., *Hyperprogressive disease during PD-1/PD-L1 blockade in patients with non-small-cell lung cancer.* Annals of Oncology, 2019. 30(7): p. 1104-1113.

6. Saâda-Bouzid, E., et al., *Hyperprogression during anti-PD-1/PD-L1 therapy in patients with recurrent and/or metastatic head and neck squamous cell carcinoma.* Annals of Oncology, 2017. 28(7): p. 1605-1611.

7. Sasaki, A., et al., *Predictive factors for hyperprogressive disease during nivolumab as anti-PD1 treatment in patients with advanced gastric cancer.* Gastric Cancer, 2019. 22(4): p. 793-802.

8. Kato, S., et al., *Hyperprogressors after immunotherapy: analysis of genomic alterations associated with accelerated growth rate.* Clinical Cancer Research, 2017. 23(15): p. 4242-4250.

9. Matos, I., et al., *Incidence and clinical implications of a new definition of hyperprogression (HPD) with immune checkpoint inhibitors (ICIs) in patients treated in phase 1 (Ph1) trials.* 2018, American Society of Clinical Oncology.

10. Russo, G.L., 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.* Clinical Cancer Research, 2019. 25(3): p. 989-999.

11. Tunali, I., et al., *Novel clinical and radiomic predictors of rapid disease progression phenotypes among lung cancer patients treated with immunotherapy: An early report.* Lung Cancer, 2019. 129: p. 75-79.

12. Gandhi, L., et al., *Pembrolizumab plus chemotherapy in metastatic non–small-cell lung cancer.* New England journal of medicine, 2018. 378(22): p. 2078-2092.

13. Paz-Ares, L., et al., *Pembrolizumab plus chemotherapy for squamous non–small-cell lung cancer.* New England Journal of Medicine, 2018. 379(21): p. 2040-2051.

14. Larkin, J., et al., *Combined nivolumab and ipilimumab or monotherapy in untreated melanoma.* New England journal of medicine, 2015. 373(1): p. 23-34.

15. Ge, X., et al., *Immunotherapy beyond progression in patients with advanced non-small cell lung cancer.* Translational Lung Cancer Research, 2020. 9(6): p. 2391.
16. Viñal, D., et al., Prognostic value of neutrophil-to-lymphocyte ratio in advanced cancer patients receiving immunotherapy. Clinical and Translational Oncology, 2021. 23(6): p. 1185-1192.

17. Bilen, M.A., et al., Combined effect of sarcopenia and systemic inflammation on survival in patients with advanced stage cancer treated with immunotherapy. The oncologist, 2020. 25(3): p. e528.

18. Guven, D., et al., PILE: a candidate prognostic score in cancer patients treated with immunotherapy. Clinical and Translational Oncology, 2021: p. 1-7.

19. Zeng, R., et al., PIV and PILE score at baseline predicts clinical outcome of anti-PD-1/PD-L1 inhibitor combined with chemotherapy in ES SCLC patients. Frontiers in Immunology: p. 4374.

Figures

Figure 1

Comparison of overall survival according to HPD or PD
Figure 2

Comparison of progression free survival according to HPD or PD