Blood based biomarkers as predictive factors for hyperprogression

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Abstract

Purpose With the widespread use of immunotherapy agents, we encounter treatment responses such as hyperprogression disease (HPD) that we have not seen with previous standard chemotherapy and targeted therapies. It is known that survival in patients with HPD is shorter than in patients without HPD. Therefore, it is important to know the factors that will predict HPD. We aimed to determine the factors that would predict HPD. **Methods** A total of 121 adult metastatic cancer patients treated with immunotherapy for any cancer between were included. Baseline demographics, ECOG performance status, type of tumors, and baseline blood count parameters were recorded. Possible predisposing factors were evaluated with univariate and multivariate analyses. **Results** The median age was 62.28 (interquartile range (IQR) 54.02-67.63) years, and the median follow-up was 12.26 (IQR 5.6-24.36) months. Renal cell carcinoma (33%) and melanoma (33.8%) were most common diagnoses. Twenty patients (16.5%) had a HPD. High LDH level ($p:0.001$), hypoalbuminemia ($p:0.016$), $NLR>5$ ($p:0.007$) and NSCLC diagnosis (0.026) are at high risk for HPD. Sex (female vs. male, $p:0.114$), age (>65 vs <65 , $p:0.772$), ECOG (0 vs 1-4, $p:0.480$), PNI (>45 vs <45 , $p:0.055$), presence of liver metastases (present vs. absent, $p:0.752$), the line of treatment (1-5, $p:0.112$) were not found to be associated with hyperprogression. **Conclusions** In this study, we observed HPD in 16.5% of immunotherapy-treated patients and increased HPD risk in patients with high LDH level ($p:0.001$), hypoalbuminemia ($p:0.016$), $NLR>5$ ($p:0.007$) and NSCLC diagnosis (0.026).

Introduction

Immunotherapy is a promising treatment option that has changed the treatment algorithms, especially in advanced cancer patients. It is widely used in melanoma [1], squamous and non-squamous non-small-cell lung cancer (NSCLC) [2], renal cell carcinoma [3], breast cancer [4], head and neck squamous cell carcinoma (HNSCC) [5], urothelial carcinoma [6] and Hodgkin lymphomas [7]. Response rates of 10%-30% are observed with ICI's [1, 8]. However, some patients treated with these agents experience rapid treatment unresponsiveness and progression that cannot be defined by the RECIST criteria. This situation is considered as hyperprogression. There is no universally accepted definition of hyperprogression at this time. For this reason, it's also difficult to determine the exact incidence of the phenomenon since this can vary with the definition used. Studies have shown that the survival time is short in patients with hyperprogression [9]. Therefore, it is important to identify factors that predict hyperprogression. In many different studies, predictive evaluations of hyperprogression have been made, but different results have been obtained. In our study, we aimed to determine the predictive factors of hyperprogression.

Method

In our retrospective cohort study, 175 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. Patients treated in the context of clinical trials and patients without an

available baseline (n=18) or follow-up (n=36) cross-sectional image with contrast were excluded from the study.

Baseline patient demographics, patient weight and height, ECOG performance status, tumor histology, ICI types, comorbidities, regularly used drugs, baseline lactate dehydrogenase (LDH), neutrophil levels, thrombocyte levels and were recorded together with survival data.

Patients with HP 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 ≥ 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. Multivariate analyses for clinical and laboratory parameters related to hyperprogression risk were conducted with backward binary logistic regression analysis with a model including the clinical parameters with a p-value of 0.50 or lower in the univariate analyses. 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. The multivariate analyses results were expressed with hazard ratios (HR) and 95% confidence intervals (CI). 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

After the exclusion of patients without baseline or follow-up images (n=54), a total of 121 patients were included in the study. The median age was 62.28 (interquartile range (IQR) 54.02-67.63) years, and the median follow-up was 12.26 (IQR 5.6-24.36) months. 70% of the patients were male and 83% were over 65 years of age. Before treatment, 63% of the patients had an ECOG score of 0. 40% of the patients had high LDH levels and 61% had low albumin. Of the patients, 33.9% were diagnosed with malignant melanoma, 33% with RCC and 17% with NSCLC. 19 patients had other cancers. 33% of the patients had liver metastases and 13% had metastases to more than two organs. Approximately 30% of patients had NLR scores above 5 and 45% of patients had PNI scores above 45.

Twenty patients (16.5%) had hyperprogression. The baseline characteristics of patients with and without hyperprogression are shown in Table 1. High LDH level ($p:0.001$), hypoalbuminemia ($p:0.016$), $\text{NLR}>5$ ($p:0.007$) and NSCLC diagnosis (0.026) are at high risk for hyperprogression.

Sex (female vs. male, $p:0.114$), age (>65 vs <65 , $p:0.772$), ECOG (0 vs 1-4, $p:0.480$), PNI (>45 vs <45 , $p:0.055$), presence of liver metastases (present vs. absent, $p:0.752$), the line of treatment (1-5, $p:0.112$) were not found to be associated with hyperprogression.

In the binary logistic regression analyses including LDH levels, hypoalbuminemia and NLR levels as dependent variables, LDH level was the only factor that had a significant association with hyperprogression risk (HR: 5.491 95% CI: 1.809–916.672, $p=0.003$) (Table 2).

Patients with hyperprogression had a shorter median progression-free survival time (1.8 months vs 6.7 months, $p:0.000$) and overall survival (4 months vs 16.3 months, $p:0.000$) compared to patients without hyperprogression (figure 1 and figure 2).

Discussion

In this study, 16.5% of patients treated with immunotherapy had hyperprogression. Patients with hyperprogression had a shorter median progression-free survival time (1.8 months vs 6.7 months, $p<0.001$) and overall survival (4 months vs 16.3 months, $p<0.001$) compared to patients without hyperprogression. Therefore, it is important to know the predictive factors of hyperprogression.

HPD has been observed between 4% and 29% in previous studies.[11, 12] The reason why it is detected in such a wide range is that there is no common definition of hyperprogression. Due to the inclusion of patients participating in clinical trials in the first studies, parameters such as tumor growth rate and tumor growth kinetics that required at least two imaging checks before immunotherapy was used in the definition of hyperprogression. However, with the widespread use of immunotherapy agents in first-line treatment, it is not possible to perform two imaging controls before treatment. Therefore, in our study where we presented real-life data, we defined hyperprogression according to the criteria defined in Russo's study. [10]

In the study of Russo et al. in which patients with NSCLC diagnosis were included, the incidence of hyperprogression was found to be 25.7%, while in our study it was found to be 33.3% in the NSCLC group. 102 patients with renal cell carcinoma (RCC) and 101 patients with urothelial cell carcinoma (UCC) were included.[13] HPD was observed in 5.7% of patients. In this trial, we detected HPD in 7.5% of patients with RCC. Champiat et al. report an incidence of hyperprogression of 9% (4/45 patients) during the treatment of melanoma with anti-PD1 in phase 1 trials. [14] In our trial, 9/41 (21.9%) patients had HPD.

Many studies have been conducted to identify predictive factors of hyperprogression. Many studies have produced different results, and many do not support each other. This may be caused by the different definitions of hyperprogression and the differences in the patient groups included in the study. Being over

65 years old in Champiat's study [14], female gender in Kanjanapan's study [15], presence of EGFR, MDM2/4 and DNMT3A alterations in Kato's study [11], more than 2 metastatic sites in Ferrara's study [16], density of myeloperoxidase myeloid cells within the tumor and low PD-L1 expression in tumor cells in Russo's study [10], high LDH level, liver metastasis, presence of more than 2 metastatic sites in Kim's study [17], ECOG>1 and presence of liver metastases in Sasaki's study [18], high NLR level in Petrova's study [19], hypoalbuminemia in Hwang study [13] were found to be associated with hyperprogression. As can be seen, the results are not consistent with each other. In our study, high LDH level, hypoalbuminemia and NLR>5 were found to be associated with hyperprogression.

Like many other studies, we did not find a relationship between the presence of more than two organ metastases, liver metastases, ECOG>1 or the line of treatment at which he received immunotherapy and hyperprogression. This situation supports that there is no relationship between hyperprogression and high disease burden. The mechanism of hyperprogression has not been fully elucidated and it is thought to be immunologically based.

The limitations of our study are that it was a retrospective cohort study, different cancer subtypes were evaluated together, the number of our patients was insufficient, and there were many different subtypes in the diagnosis of cancer categorized as other.

Conclusion

In this study, 20 (16.5%) patients treated with ICIs developed HPD. Care should be taken in terms of hyper progression in patients with NLR>5, hypoalbuminemia and high LDH levels.

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.

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Tables

Table 1. Baseline clinical and laboratory features of patients with or without hyperprogression

		HPD present	HPD absent	p score
Median age		61.6 (47.2-67.0)	62.28 (55.3-67.6)	
Sex	Female	3 (15%)	33 (32.7%)	0.091
	Male	17 (85%)	68 (67.3%)	
Age	>65	7 (35%)	32 (31.7%)	0.772
	<65	13 (65%)	69 (68.3%)	
LDH	Normal	5 (25%)	67 (66.3%)	0.001
	>ULN	15 (75%)	34 (33.7%)	
Albumin	>4	3 (15%)	43 (42.6%)	0.016
	<4	17 (85%)	58 (57.4%)	
ECOG score	0	11 (61.1%)	66 (69.5%)	0.485
	1-4	7 (38.9%)	29 (30.5%)	
PNI	>45	13 (65%)	42 (41.6%)	0.055
	<45	7 (35%)	59 (58.4%)	
KC metastasis	Present	6 (30%)	34 (33.7%)	0.750
	Absent	14 (70%)	67 (66.3%)	
>2 metastaz	Present	3 (15%)	13 (12.9%)	0.517
	Absent	17 (85%)	88 (87.1%)	
Immunotherapy plus CT	Present	6 (30%)	22 (21.8%)	0.426
	Absent	14 (70%)	79 (78.2%)	
NLR	>5	11 (55%)	25 (24.7%)	0.007
	<5	9 (45%)	76 (75.7%)	
Diagnosis	Melanom	9 (45%)	32 (31.6%)	0.026
	RCC	3 (15%)	37 (36.6%)	
	NSCLC	7 (35%)	14 (13.8%)	
	Other	1 (5%)	18 (17.8%)	
Line of treatment	1	2 (10%)	13 (12.9%)	0.112
	2	12 (60%)	34 (33.7%)	
	3	3 (15%)	24 (23.8%)	

4	1 (5%)	25 (24.7%)
5	2 (10%)	5 (4.9%)

Table 2: Multivariate analysis of factors associated with hyperprogression

Clinical Factor	Risk of hyperprogression	
	HR (95 %)	p score
LDH (high-normal)	5.491(1.809-16.672)	0.003
Albumin (low-normal)	3.743(0.992-14.118)	0.051
NLR (>5 - <5)	2.191(0.743-6.457)	0.155

Figures

Figure 1

Comparison of progression free survival according to the presence or absence of hyperprogression

Figure 2

Comparison of overall survival according to the presence or absence of hyperprogression