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Prognostic Value of Lactate Dehydrogenase in Patients with Melanoma Treated with Pembrolizumab

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ABSTRACT

Introduction: Elevated LDH levels have been extensively reported as a biomarker of poorer outcome in patients with melanoma during the chemotherapeutic era. The role of LDH level as a prognostic factor for treatment outcomes in patients with metastatic melanoma treated with immunooncological therapy has also been reported but requires further analysis.

Objectives: In this study, we aimed to evaluate the prognostic value of lactate dehydrogenase (LDH) among patients with metastatic and unresectable melanoma treated with pembrolizumab in terms of progression-free survival (PFS).

Methods: The study included 59 patients with unresectable and metastatic melanoma treated with pembrolizumab. A comparison was performed between patients with normal and elevated levels of LDH in terms of PFS, with subgroup analysis.

Results: There was a significant reduction in PFS among patients with elevated levels of LDH compared with patients with normal levels of LDH (NR vs. 5 months; *P*=0.02). Patients with elevated LDH levels were older (*P*=0.01), with liver metastasis (*P*=0.004), and with less frequent CNS deposits (*P*=0.028).

Conclusion: Although novel agents improved outcomes in patients with melanoma, high levels of LDH persist as an independent prognostic biomarker of poor prognosis.

KEY WORDS: melanoma, pembrolizumab, lactate dehydrogenase

INTRODUCTION

Melanoma is a type of cancer that originates from melanocytes, with its cutaneous form being the most common (1). The disease represents a significant socioeconomic burden due to the increasing incidence, especially in less developed countries, in which primary and secondary prevention measures have not been adequately implemented. In Serbia, cutaneous melanoma is the eleventh most common cancer, with an incidence of 5.1/100000 and mortality among both genders (2.1/100000) (2).

In the last 10 years, new systemic treatment options for metastatic melanoma have immensely impacted outcomes in patients with melanoma by significantly improving progression-free survival (PFS) and overall survival (OS), replacing chemotherapeutic agents such as dacarbazine (3). Immune checkpoint inhibitors (PD-1 and CTLA-4) in both BRAF mutant and wild-type melanoma and BRAF and MEK inhibitors in BRAF mutant melanomas have become the standard of care based on the current guidelines (ESMO, NCCN, EADO) (4,5).

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The tumor microenvironment (TME) is characterized by aberrant metabolic properties. Due to increased energy requirement, malignant cells tend to amplify metabolic interactions, thus exploiting opportunistic methods for nutrient acquisition. This leads to the flourishing of an otherwise unwholesome microenvironment. Lactate dehydrogenase represents one of the main metabolic enzymes in TME, which, through conversion of pyruvate to lactate and the reverse, has a role in the proliferation and dissemination of malignant cells through catalyzation of aerobic glycolysis (Warburg effect) (6). This has led to the incorporation of LDH into several staging and prognostic scores (7-9). This was also acknowledged in patients with melanoma through its addition into the 7th edition of the American Joint Committee on Cancer (AJCC) staging, and into every M1 (metastatic) subgroup in the 8th edition (10).

Elevated LDH levels have been extensively reported as a biomarker of poorer outcome in patients with melanoma during the chemotherapeutic era (12-20). The role of LDH level as a prognostic factor for treatment outcomes in patients with metastatic melanoma treated with immunooncological therapy has also been reported but requires further analysis.

Table 1. Patient characteristics

	n (%)
Age (years, mean ± SD)	61.86±13.084
Sex	
male	42 (71.2)
female	17 (28.8)
ECOG PS	
0	31 (52.5)
1	28 (47.5)
LDH levels	
normal	25 (42.4)
elevated	34 (57.6)
Number of metastatic sites	
1	13 (21.0)
2	15 (25.4)
3	17 (28.8)
≥4	14 (23.8)
BRAF mutation status	
Negative	46 (78.0)
Positive	13 (22.0)

SD: standard deviation; ECOG PS: Eastern Cooperative Oncology Group performance status; LDH: lactate dehydrogenase

PATIENTS AND METHODS

Patients

We conducted a retrospective analysis among 59 patients with unresectable and metastatic melanoma treated with pembrolizumab at the University Clinical Center Nis from February 2017 to March 2021. Eligibility criteria included unresectable stage III and stage IV (metastatic) melanoma with Eastern Cooperative Oncology Group performance status (ECOG PS) 0-1, treated with at least one dose of pembrolizumab in the first-line treatment. Exclusion criteria were previous targeted treatment, ECOG 2 or higher, and noncutaneous melanoma. Clinical staging was based on the 8th edition AJCC.

Treatment and response evaluation

Pembrolizumab was administered in the standardized dose of 200 mg every three weeks, or 400 mg every six weeks, intravenously for 30 minutes until disease progression or intolerable toxicity. Efficacy was assessed every 4 cycles by multi-slice computed tomography and according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1). A comparison was performed between patients with normal and elevated levels of LDH.

Statistics

Chi-square test or Fisher's exact test were used to evaluate the categorical variables, as appropriate for the category size.

Progression-free survival (PFS) was estimated using the Kaplan-Meier method. The CI was set to 95%, and a *P*-value of <0.05 was considered statistically significant. Progression-free survival was defined as the time from the first dose of pembrolizumab until the first evidence of disease progression or death. As for patients without progression, survivors were censored at the last follow-up. Survival was compared between the patients with or without elevated LDH using a log rank, with $P<0.05$ as the determinator of significance. Survival analyses were performed in SPSS v 26 (Chicago, IL, USA).

Table 2. The best overall response to pembrolizumab

Response	n (%)
Complete response	8 (13.6)
Partial response	9 (15.3)
Stable disease	19 (32.2)
Progressive disease	23(38.9)

RESULTS

Patient characteristics

A total of 59 patients, 42 men and 17 women, were included. The median age was 65 years (range 27-81 years). According to 8th edition AJCC, almost half of the patients were at the M1c clinical stage (49.1%), followed by M1d (27.1%), M1b (11.9%), and M1a (10.2%), with only one patient had CS III (1.7%). Elevated LDH level was observed in 57% of patients.

The majority of patients with elevated LDH levels were at the M1c clinical stage (68.8%) with 3 or more metastatic sites (67.6%), which can be considered a high tumor burden. Patient characteristics are summarized in Table 1.

Tumor response

The total number of administered cycles was 729, with an average of 11.5 cycles per patient. Among all 59 treated patients, 8 achieved complete response (CR; 13.6%), 9 achieved partial remissions (PR; 15.3%), and 19 achieved stable disease (SD; 32.2%), with a disease control rate (DCR) of 51.1%. The overall response rate was 28.9%, and a median PFS of 33 months (CI 95%) was achieved. The median time to response was 6 months (range 2-8 months). At data cut off, 29 patients (49%) were still receiving treatment, while 30 patients (51%) had discontinued treatment. Reasons for discontinuation were disease progression (PD) (n=23; 38.9%), adverse events (n=2; 3.39%), patient withdrawal (n=3; 5.1%), or being lost to follow-up (n=2; 3.39%). Treatment response is summarized in Table 2.

Table 3. Patient characteristics and LDH levels

	LDH normal (n=) n (%)	LDH elevated (n=) n (%)	*P* value
Age (years, mean ± SD)	56.8 ± 11.75	65.6 ± 12.91	0.010
Sex			0.490
Male	19	23	
female	6	11	
ECOG PS			0.135
0	16	15	
1	9	19	
Presence of CNS metastases			0.028
	10	5	
Presence of liver metastases			0.004
	3	16	
BRAF mutation present			0.957
	6	7	
PD as a response to treatment			0.01
	5	18	

Patient characteristics and LDH levels

LDH levels among different subgroups are summarized in Table 3. There were no gender differences in the rate of elevated LDH levels (*P*=0.49), while the mean age of the patients with elevated LDH levels was significantly higher (*P*=0.01). Elevated levels of LDH were more often observed in patients with liver metastasis (*P*=004), as opposed to CNS deposits (*P*=0.028). As for ECOG performance status, BRAF mutational status, and irAEs, no statistically significant difference was observed. Among the patients with disease progression, almost 80% had elevated levels of LDH (*P*=0.01).

LDH levels and PFS

The association between LDH and survival is shown in Figure 1. There was a significant shortening of PFS among the patients with elevated levels of LDH compared with patients with normal levels of LDH (NR vs. 5 months; *P*=0.02).

DISCUSSION

LDH is a biomarker widely used for several malignancies due to its wide availability and prognostic qualities (7,9). Increased levels of LDH are often observed in highly invasive hypoxic malignancies characterized by resistance to chemotherapy and radiotherapy (11).

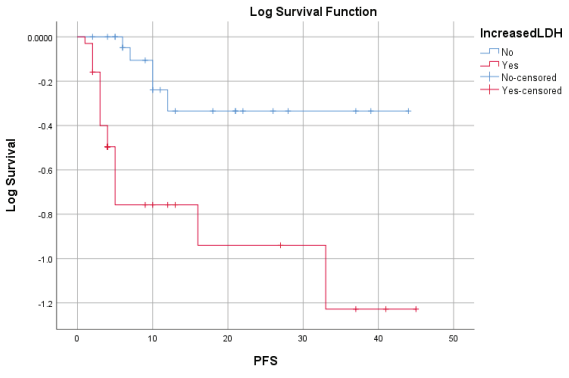

Figure 1. Progression-free survival curves.

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In the chemotherapeutic era, a vast number of studies focused on the prognostic values of elevated LDH in patients with melanoma (12-20). These studies identified elevated LDH levels as a factor of worse prognosis. LDH levels were also included as a prognostic factor in the 7th edition of the AJCC staging system.

Advancements in treatment metastatic melanoma completely transformed the management and prognosis of patients with melanoma (3). Although the effects of targeted therapy and immunotherapy immensely improved PFS and OS, there is still a large proportion of patients (40-60%) with primary and secondary resistance to available treatment options. Additionally, the question of sequencing treatment in BRAF mutant metastatic melanoma is an unresolved issue, and there is a need for establishing prognostic and predictive biomarkers in a novel agent era. The first subgroup analysis involving LDH levels in patients treated with PD-1 was conducted in phase 2 of the Keynote 002 study. Results were discouraging in terms of the prognostic value of LDH, with no difference in PFS between patients with normal and elevated LDH (21).

In the present study, we identified a prognostic value of increased levels of LDH in terms of poorer outcomes. Similar results were reported in a metanalysis conducted by Petrelli *et al.* They evaluated the prognostic value of elevated LDH in 52 studies on patients with cutaneous metastatic melanoma treated with novel agents, with a total of 7960 patients (11). This study included both patients treated with ICIs and targeted agents. Generally, increased LDH levels were associated with an HR for OS of 1.72 (95% CI: 1.6-1.85; $P<0.0001$). HR for PFS was 1.83 (95% CI: 1.53-2.20; $P<0.0001$). Out of 52 studies, 35 included patients solely treated with ICIs, which was the key focus of our study. This subgroup was associated with HR for OS of 1.84 (95% CI: 1.60-1.85; $P<0.001$) (11).

A recent metanalysis by Xu *et al.* included 22 studies and involved 2745 patients receiving PD-1/PD-L1. This study also confirmed the association of elevated levels of LDH with an HR for OS of 2.44 (95% CI: 1.95-3.04, $P<0.001$). Among the 22 studies included, 13 reported PFS, which was used as a parameter of the efficacy of our study. Analysis of those studies correlated increased baseline LDH with a significantly shorter PFS, with an HR of 1.61 (95% CI: 1.34-1.92; $P<0.001$) (22).

The mechanism which may lead to poorer outcomes in patients with advanced melanoma with elevated LDH was a focus of different *in vitro* and *in vivo* studies. There are indications that high levels of lactate favor the immunosuppressive microenvironment, leading to a decreased influx of natural killer cells (NK cells) and cytotoxic CD8+ T-lymphocytes (23). Several studies showed that an increased level of LDH-A correlates with tumor growth, metastatic potential, and local recurrence (24,25). As for the predictive aspect of LDH in patients receiving immune checkpoint inhibitors, it has been reported that the expression of PD-1 and PD-L1 is regulated by lactate which is present in the microenvironment of the tumor, with LDH-A being a key enzyme in its conversion. It has been shown in a mice model that blockade of LDH-A enhances the effect of the PD-1 antibody, which could hypothetically be a therapeutic target and potentially improve the prognosis of patients with poor prognostic parameters (26). The necessity of finding a predictive biomarker of ICIs treatment has emerged. Unfortunately, neither PD-1 expression nor BRAF mutation status showed a clinically meaningful predictive role in patients with melanoma treated with ICIs (27,28). Several new biomarkers have emerged in recent years, such as tumor mutation burden (TMB), microsatellite instability-high (MSI-H) phenotype, circulating tumor DNA (ctDNA), and tumor microenvironment (TME), with promising results and potential clinical usage (29-38). Although our study included a small number of patients, we believe it is a worthwhile addition to real-world data in our patient population.

CONCLUSION

Although novel agents improved outcomes in patients with melanoma, high levels of LDH persist as an independent prognostic biomarker of poor prognosis. As for the predictive role of increased LDH, there is no strong evidence supporting it. New potential predictive biomarkers are emerging, but further studies are needed to establish their role in the management of metastatic melanoma.

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