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ORIGINAL ARTICLE

VITILIGO-LIKE DEPIGMENTATION AS A PREDICTOR OF PROLONGED RESPONSE TO IMMUNE CHECKPOINT INHIBITORS IN PATIENTS WITH ADVANCED MELANOMA: A SINGLE-CENTER EXPERIENCE

Aleksandar Popović[1] **Ana Stojković**[1] **Ana Cvetanović**[1,2] **Andrija Jović**[3] **Milica Radić**[1,2] **Irena Conić**[1,2] **Ivan Petković**[1,2]

[1]Clinic of Oncology, University Clinical Center Niš, Niš, Serbia [2]Department of Oncology, University of Niš Faculty of Medicine, Niš, Serbia [3]Clinic of Dermatovenerology, University Clinical Center Niš, Niš, Serbia

Immune checkpoint inhibitors (ICIs) have significantly improved outcomes in melanoma patients. Vitiligo-like depigmentation (VLD) is a well-documented adverse event of ICIs, which is generally well-tolerated and often associated with prolonged response to treatment. The aim of this study was to assess the effect of VLD occurrence on survival in melanoma patients treated with ICIs.

We conducted a retrospective analysis of unresectable stage III and stage IV melanoma patients treated with pembrolizumab or nivolumab at the University Clinical Center Niš from May 2017 to February 2024. The Chi-square or Fisher's exact test was used to evaluate categorical variables. Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan–Meier method (95% CI; $p < 0.05$). Survival rates between patients with and without VLD were compared using a log-rank test ($p < 0.05$).

A total of 109 patients were included, of whom 22 patients developed VLD (20.2%). Median follow-up in the VLD group was 39.4 months, with 59% still alive and progression-free three years after treatment initiation. The overall response rate (ORR) was 72.7% vs. 29.9%, with 31.8% vs. 13.8% of complete responses in favor of the VLD subgroup. The occurrence of VLD was associated with significantly longer median PFS (8.148 vs. 52.862 months; $p = 0.0001$) and median OS (12.715 vs. not reached (NR) months; $p = 0.0001$).

Prediction of VLD occurrence is not currently possible; therefore, it cannot be considered a predictive parameter per se, but it can be associated with prolonged response to ICI treatment in patients who develop this adverse event.

Keywords: melanoma, vitiligo-like dermatitis, survival, immunotherapy

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Correspondence to:
Aleksandar Popović
Clinic of Oncology
University Clinical Center Niš
Bulevar dr Zorana Đinđića 48, Niš, Serbia
E-mail: popovic992@yahoo.com

INTRODUCTION

Metastatic melanoma is the most aggressive form of skin cancer with a poor prognosis, and its overall incidence is increasing rapidly, with the highest rates in northern countries in Europe, such as the Netherlands and Ireland (1). During the last 20 years, multiple approaches have resulted in a better understanding of tumor immunology and the genomic characteristics of melanoma. With the introduction of immune checkpoint inhibitors (ICIs) as new therapeutic options, survival for melanoma patients has immensely improved (2). Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) are the most widely used ICIs (3). They both regulate the T-cell response. Although CTLA-4 muffles T-lymphocyte activation in the early phase of the immune response, PD1-mediated immune response plays a role in the later effector phase (4). Their T cell-mediated antitumor effect can also trigger a series of immune-related adverse events (irAEs), with skin toxicity being the most frequent. Cutaneous irAEs are heterogeneous and tend to be low-grade and well-tolerated. Vitiligo-like dermatitis (VLD) is a site-specific, well-tolerated irAE that affects melanoma patients predominantly treated with anti-PD-1 antibodies.

Despite a clear benefit for patients with advanced melanoma and the existence of long responders, a vast number of them (30-50%) fail to respond or develop resistance to treatment. Potential biomarkers associated with response to ICIs therapy in melanoma are widely researched, but only LDH has been introduced into everyday clinical practice (5-7).

Several irAEs have been associated with prolonged response to ICS, with VLD being one of them. The aim of this study was to assess the effect of VLD occurrence on progression-free survival (PFS) and overall survival (OS) in advanced melanoma patients treated with ICIs.

METHODS

We conducted a retrospective analysis among 109 unresectable stage III and stage IV melanoma patients treated with pembrolizumab or nivolumab at the University Clinical Center Niš from May 2017 to February 2024. The included patients had unresectable stage III and stage IV (metastatic) melanoma with Eastern Cooperative Oncology Group performance status (ECOG PS) 0-1 and at least one radiological assessment by Response Evaluation Criteria in Solid Tumors (RECIST 1.1) after treatment initiation. The Chi-square or Fisher's exact test were used to evaluate the categorical variables, as appropriate for the category size. PFS and OS were estimated using the Kaplan–Meier method (CI 95%; $p < 0.05$). Survival between the patients with or without VLD was compared using a log-rank ($p < 0.05$). Survival analyses were performed in SPSS v 26 (Chicago, IL, USA). Ethical approval for this study was obtained from the Institutional Ethics Committee (approval no. 13826, May 29, 2020).

RESULTS

A total of 109 patients were included, comprising 22 patients who developed VLD (20.2%). The median time of VLD onset was 10.44 months (range 3.94-31.15). There was no statistically significant difference in the occurrence of VLD based on gender ($p = 0.192$), mean age ($p = 0.99$), BRAF mutation status ($p = 0.206$), elevated LDH ($p = 0.582$), or ECOG PS ($p = 0.166$). Median follow-up in the VLD group was 39.4 months, with 59% still alive and progression-free three years after treatment initiation.

The overall response rate (ORR) was 72.7% vs 29.9%, with 31.8% vs. 13.8% of complete responses in favor of the VLD subgroup. Patient characteristics and VLD occurrence are summarized in Table 1. The occurrence of VLD was associated with significantly longer median PFS (8.148 vs. 52.862 months; $p = 0.0001$) (Figure 1), and median OS (12.715 vs. NR months; $p = 0.0001$) (Figure 2).

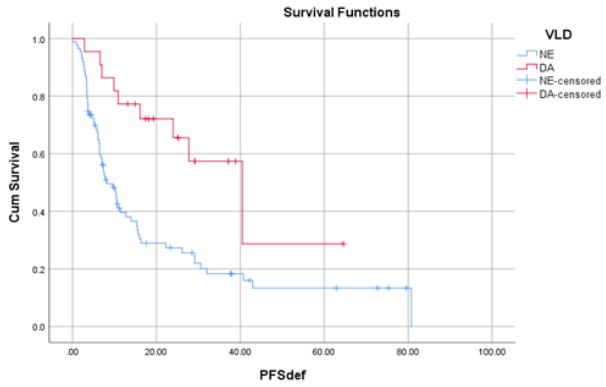
DISCUSSION

Immune checkpoint pathways keep the immune system in balance through the inhibition of T-cells. They adjust the duration and level of the immune response through downregulation of T cell response, therefore reducing unnecessary tissue damage (8). These pathways are used

Table 1. *Patient characteristics and VLD occurrence*

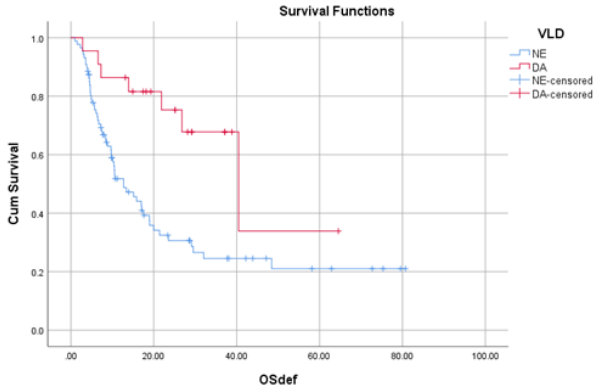
	VLD (n=22) n (%)	Non-VLD (n=87) n (%)	P value
Age (years, mean ± SD)	63.18 ± 12.316	65.6 ± 12.294	0.99
Sex			0.498
Male	16	52	
female	6	34	
ECOG PS			0.568
0	16	51	
1	6	36	
Elevated LDH			0.568
	31	8	
BRAF mutation status			0.206
BRAF mutant	26	4	
BRAF wild type	61	18	

VLD: Vitiligo-like dermatitis; SD: standard deviation; ECOG PS: Eastern Cooperative Oncology Group performance status; LDH: lactate dehydrogenase



VLD: Vitiligo-like dermatitis; PFS: Progression-free survival;

Figure 1. *Progression-free survival and VLD occurrence*



VLD: Vitiligo-like dermatitis; OS: Overall survival;

Figure 2. *Overall survival and VLD occurrence*

by malignant cells to evade normal immune responses by expressing ligands that overactivate them (9). Immune checkpoint inhibitors (ICIs) overcome this tumour-induced inhibition, creating a proinflammatory microenvironment potentially leading to an antitumor effect.

Initially, they were introduced in the treatment of advanced melanoma, and later in adjuvant and perioperative settings. Their mechanism of action led to the usage of nine, currently FDA-approved ICIs, in eighty-five treatment settings in many different cancers (10).

Currently, the most widely used ICIs in melanoma treatment are PD-1 antibodies pembrolizumab and nivolumab, CTLA-4 antibody ipilimumab, and lately, LAG-3 inhibitor relatlimab.

Due to their unique mechanism of action, new immune-related adverse events were observed, which differed from well-known and dose-dependent adverse events of conventional chemotherapeutic agents. Also, patients with preexisting autoimmune disorders should be approached in a precautionary manner (11). This is likely due to prolonged T-cell activation mostly, which can affect many organs. IrAEs involving skin can develop in 30–50% of the patients treated with ICIs, therefore making them the most frequent adverse event (12).

They can manifest a plethora of dermatological conditions ranging from mild, such as psoriasis, vitiligo, lichenoid dermatitis, and maculopapular rash, but also severe and life-threatening, such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), Stevens-Johnson and Acute generalised exanthematous pustulosis (AGEP) (13). An abundance of lymphocytes in the skin may be the reason why irAEs occur so often on the skin and can develop so early. Even though the median time to onset of skin toxicity is 4-6 weeks, they can occur more than a year after treatment initiation (14).

Although similar to vitiligo, which affects the general population, ICI-induced VLD shows different clinical and biological patterns (15). VLD has a progressive nature and tends to occur at an older age with bilateral distribution and confetti-like presentation (16).

Although VLD may have a certain psychosocial effect on patients, it is considered a benign adverse event of ICI treatment that is well tolerated. Prevalence of vitiligo in the general population ranges from 0.5-2%. On the other hand, VLD can occur in 2-25 % of melanoma patients treated with ICIs and is rarely described in other solid cancers (17). In addition, the occurrence of VLD is more often observed in patients treated with anti-PD-1 compared with CTLA-4 antibodies (13,18). In our analysis, VLD was observed in 20.2% of the patients treated with ICIs. The high percentage among our patients may be due to the inclusion of patients solely treated with anti-PD-1 agents and the fact that our analysis included only patients who had at least one RECIST evaluation and were, therefore, on treatment for at least three months.

Compared with other skin irAEs, VLD tends to develop later with a median time to onset of 6-9 months, which is sooner than reported in our paper (10.44 months), although this may be due to less frequent dermatological assessment and consequently later reporting of adverse events (19,20).

The occurrence of dermatological irAEs was more often observed in older populations treated with anti-PD-1 drugs. Still, in our case, there was no statistically significant difference in age when VLD and non-VLD groups were compared (21,22). Also, skin toxicity tends to be less

observed in the female population (23,24). In our study, there was a numerical but not a statistical significance, which is most likely due to a small number of patients included. As for ECOG PS, no impact was observed regarding the occurrence of irAEs, which is in correlation with our results (25). Regarding the BRAF mutational status, opposing results were observed. One analysis showed less frequent occurrence of VLD in patients bearing BRAF mutation, while no significant difference was observed in others (24,25). In our analysis, no difference in the occurrence of VLD regarding the BRAF mutational status was observed.

It is assumed that VLD develops due to CD8+ activations which target both melanoma cells and melanocytes due to their shared expression of melanocyte differentiation antigens. Therefore, it is hypothesized that VLD development can be a sign of immunogenic response and may predict response to ICI treatment.

The VLD occurrence was associated with better response in melanoma patients treated with anti-PD-1treatment (19). This was also observed in our analysis with almost two-and-a-half-fold higher ORR and a doubling of the number of complete responses to treatment.

Significant prolongation of PFS and OS was observed in several meta-analyses, which was also observed in our analysis with a very high statistical significance (26). This indicates that vitiligo, a relatively benign adverse event, can be a good clinical sign of a prolonged response to ICI treatment.

Interestingly, regression of ICI-induced VLD may be associated with disease progression; therefore regular dermatological assessments are of utmost importance (20).

Potential biomarkers for the prediction and early detection of irAEs are currently under investigation, and they can be both site-specific and non-specific. As for the skin-specific adverse events, there are few promising biomarkers. High levels of rheumatoid factor (RF) before treatment initiation showed a higher possibility of developing skin-specific irAEs (27). Also, circulating blood cell counts represent a potential and easily accessible biomarker for both adverse event prediction and response to treatment, but further studies are needed (23).

Although being an adverse event, VLD also presents a potential sign of a favorable outcome. Certain vitiligo-specific soluble biomarkers, such as CD25 and CXCL9 levels, and also the levels of regulatory T cells, were being assessed before and during ICI treatment, showing their possible usage in predicting the response. However, furthers studies are needed (28).

Although our study included a modest number of patients, it still presents an addition to real-world data regarding the ICI-treated patients.

The usage of ICI in everyday practice is growing each day, with their inclusion in the treatment of numerous malignancies, making them one of the most exploited and explored medicaments. Even though there is still a large proportion of patients who have an inadequate response to treatment, predictive biomarkers for treatment response are widely explored, with several of them showing promising results. Aside from predictive biomarkers of response, prediction of the duration of response is also clinically significant and could help us tailor treatment to the individual; therefore, avoiding overexposure to treatment and potential late toxicity. The occurrence of VLD is an easily observed adverse event and is associated with a favorable outcome in melanoma patients treated with ICIs, making it a very convenient surrogate biomarker of prolonged response to ICI treatment.

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Statement of Ethics

Ethical approval for this study was obtained from the Institutional Ethics Committee (approval no. 13826, May 29, 2020).

Competing Interest

The authors declare no relevant conflicts of interest.

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