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Efficacy of nivolumab as second-line treatment for elderly patients with metastatic malign melanoma

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Abstract

Aim: This study aimed to analyse the clinical characteristics, effectiveness and safety of nivolumab monotherapy in patients aged≥ 65 years with metastatic melanoma.

Materials and Methods: This study involved patients aged ≥65 years who were diagnosed with metastatic cutaneous or mucosal melanoma. Patients with BRAF wild type, ECOG performance status 0-1, and who had previously received one line of chemotherapy were included, irrespective of PD-L1 expression. The study analyzed PFS, OS, and adverse event profiles.

Results: Twenty-one patients, with a median age of 70, were analysed in the study. The median PFS for nivolumab as second-line therapy in elderly patients was 3.5 months (95% CI, 1.5 to 5.6 months), while the median OS was 14.5 months (95% CI, 10.3 to 18.6 months). The most common grade 1-2 adverse events were anemia (66.7%) and serum creatinine increase (23.8%). Additionally, the rate of grade 3-4 adverse events due to all causes was 28.6%. There was no grade 5 adverse event.

Conclusion: Nivolumab is effective and safe as second-line therapy in patients aged ≥65 years with metastatic melanoma. It is a tolerable and effective treatment choice for elderly patients who cannot received nivolumab in first line therapy.

Introduction

Melanoma originates from melanocytes in the skin, and less frequently in the mucous membranes. The incidence of melanoma is increasing, with a median age of diagnosis at 63 years [1, 2]. Mortality in melanoma patients is predominantly observed in individuals aged 75-84 years, highlighting the importance of planning safe treatment methods for this specific population within the field of oncology [1]. Correct the ther reference number like this.

In elderly patients, prognosis can be worse compared to other age groups due to various factors, including age-related immune weakening and the presence of concurrent diseases [3]. Immunosenescence, characterized by thymic involution associated with aging, results in decreased functionality of T cells and secretion of proinflammatory cytokines [4, 5]. This phenomenon can also impede effective checkpoint inhibition, which is a key aspect of melanoma treatment [6]. Additionally, elderly patients often have comorbidities that can lead to decreased functional reserves, and they commonly require multiple concomitant medications [7]. Difficulties in accessing medical care, cognitive impairment, and depression may further contribute to a poorer prognosis in the elderly patient population [8].

The advancement of immunotherapy and targeted treatment modalities has resulted in long-term survival among elderly patients. Checkpoint inhibition as a treatment strategy is increasingly being employed across various malignancies diagnosed in advanced age [9]. Nivolumab, a promising immunotherapeutic agent, is utilized in the treatment of melanoma [10]. Nivolumab is a human monoclonal antibody with an immune suppression mechanism against programmed death receptor-1 (PD-1) [11, 12]. The CheckMate 066 trial showed significantly improved overall survival (OS) in the nivolumab group compared to dacarbazine, as well as superior progression-free survival (PFS) in the nivolumab arm (median: 5.1 versus 2.2 months) [13-15]. The management of metastatic melanoma in elderly patients with is generally similar to that of younger patients [16]. Luca et al. demonstrated the efficacy and safety of nivolumab as a first-line treatment in patients aged 75 years and older [17].

This study aims to present our clinical experience with nivolumab monotherapy as a second-line treatment in elderly patients with melanoma.

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We analysed the clinical features, efficacy, and safety of nivolumab in this specific patient population.

Materials and Methods

In Turkey, current legislation stipulates that reimbursement for nivolumab treatment in BRAF wild metastatic melanoma is contingent upon receiving one line of chemotherapy. Therefore, in our study, we evaluated the efficacy of nivolumab as a second-line therapy in elderly melanoma patients. The study was approved by Gazi University Ethics Committee.The report was conducted in accordance with the provisions of the Declaration of Helsinki.

Study design

In this study, medical data of elderly patients with metastatic melanoma was evaluated retrospectively. While the primary end point was progression-free survival, secondary end points were overall survival and adverse event profile. The OS was identified as the time between the initiation of nivolumab therapy and either patient death or the last follow-up visit. PFS was stated as the time between the initiation of therapy and either disease progression, patient death, or the last follow-up visit, whichever occurred first.

Patient selection

Patients aged 65 and over, diagnosed with metastatic cutaneous or mucosal melanoma in our hospital's department of Medical Oncology constituted the sample size. Patients with BRAF wild type, ECOG performance status of 0-1, and patients who had previously received first line chemotherapy were included in the study regardless of PD-L1 expression. BRAF mutant patients, those with a diagnosis of ocular or uveal melanoma, and those who received anti-PD-L1, anti-PD 1, or anti-CTLA 4 treatment in the first line were not included in the study. Additionally, patients diagnosed and treated for other malignancies were excluded. Patients who had received adjuvant or neoadjuvant therapy in the past were eligible for inclusion.

Nivolumab administration

Nivolumab was infused intravenously at a dose of 3 mg/kg every 2 weeks over a 60-minute period. In case of withdrawal of consent, disease progression, unacceptable toxicity, or death, treatment was stopped. Depending on the severity of adverse events, nivolumab was discontinued, and corticosteroids were given for at least 1 month, followed by a gradual tapering. Grading of adverse events severity was done using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [18].

Statistical analysis

The Statistical Package for the Social Sciences software version 23 (SPSS) was used during analysing the data. We used the non-probability consecutive sampling technique. Nonnormally distributed quantitative variables were expressed as median values (range). Qualitative variables were expressed as proportions such as gender, ECOG PS, tumour site, serum LDH level, BRAF status, prior adjuvant therapy, prior systemic therapy, presence of comorbidity and adverse events. For the purpose of testing the OS and PFS with nivolumab usage, Kaplan-Meier method was used.

Results

Twenty-one patients were enrolled in the analysis of OS and PFS. The most of the patients were male (85.7%), and the median age was 70 years (range: 65-84) (Table 1). Fourteen point three persent of the included patients were 75 years and older. Cutaneous melanoma was the most common type of primary melanoma, accounting for 90.5% of patients. Of the patients, 42.9% had received adjuvant treatment, with all of them having received interferon alfa for one year. All patients were BRAF wild type and had received first line of chemotherapy. Temozolomide was the most commonly used chemotherapeutic agent in the first line (71.4%). The other drugs used in first-line therapy for

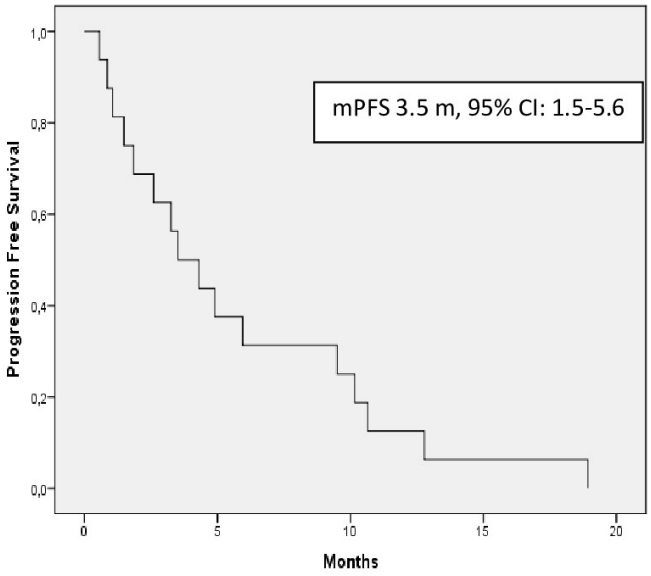

Figure 1. PFS of study population.

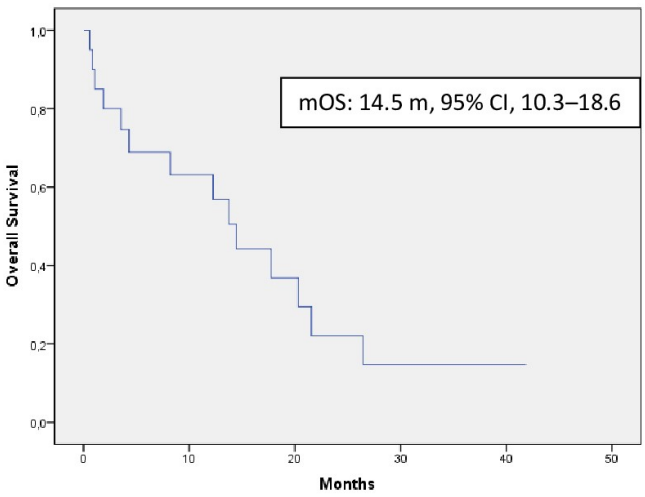

Figure 2. OS of study population.

Table 1. Patient baseline characteristics.

Number of patients		21
Age (years) Median (range)		70 (65-84)
Gender, (n/%)	Male	18 (%85.7)
	Female	3 (%14.3)
Presence of comorbidity	0-1	13 (%61.9)
	≥2	8 (%38.1)
ECOG PS	0	11 (%52.4)
	1	10 (%47.6)
Tumour site	Cutaneous	19 (%90.5)
	Mucosal	2 (%9.5)
Serum LDH level, (n/%) (At the initation of nivolumab therapy)	Normal (0-248 U/L)	12 (%57.1)
	High (> 248 U/L)	9 (%42.9)
BRAF status (n/%)	Wild-type	21 (%100)
	Mutant	0 (%0)
Prior adjuvant therapy, n (%) *	Yes	9 (%42.9)
	No	12 (%57.1)
Prior systemic therapy, n (%)	Temozolamide	15 (%71.4)
	Temozolamide plus Cisplatin	2 (%9.5)
	Carboplatin plus Paclitaxel	3 (%14.3)
	Dacarbazine	1 (%4.8)

* The patients received interferon alpha. ECOG PS: Eastern Cooperative Oncology Group performance status LDH: = Lactate dehydrogenase.

Table 2. Adverse events[a] in 21 elderly patients.

Event Patients			(n)
Fatigue (Grade 1)			2
Nausea (Grade 1)			2
Vomiting (Grade 1)			2
Diarrhea (Grade 2)			1
Rash (Grade 1-2)			3
Pruritus (Grade 1-2)			3
Hypothyroidism (Grade 1-2)			2
Increased creatinine (Grade 1-2)			5
Esophagitis (Grade 2)			1
Encephalitis (Grade 3)			1
Hematologic toxicity	Anemia	Grade 1-2	14
		Grade 3-4	2
	Neutrophil count decreased	Grade 1-2	2
		Grade 3-4	2
	Thrombocytopenia	Grade 1-2	6
		Grade 3-4	1

a: Graded according to the Common Terminology Criteria for Adverse Events, version 4.0.

elderly patients with metastatic melanoma are provided in Table 1.

The median PFS for second-line nivolumab therapy in elderly patients was 3.5 months (95% CI, 1.5 to 5.6 months; Figure 1). The median OS was 14.5 months (95% CI, 10.3 to 18.6 months; Figure 2). All the patients who experienced disease progression during follow-up, they received subsequent-line chemotherapy.

At the initiation of nivolumab treatment, the median LDH value was 202 U/L (127-1540). Patients with LDH in the normal range at the start of nivolumab therapy had a numerically longer PFS compared to those with high LDH levels but this was not statistically significant (respectively: 4.9 months, 3.5 months, p: 0.21). The median OS was 14.5 months for patients with normal LDH values at initiation, while it was 4.3 months for patients with high LDH values. Although a numerical superiority was observed in terms of OS for patients with LDH in the normal range, the difference was not found to be statistically significant (p: 0.11).

The PFS of patients who received adjuvant therapy before was numerically higher than those who did not (respectively; 4.9 m, 2.6 m, p:0.39). Compared with ECOG performance status, patients with ECOG 0 had a numerically higher PFS than patients with ECOG 1 (respectively; 9.5m, 3.5m, p:0.37).

Nivolumab was usually well tolerated, and treatment-related adverse events were evaluated and reported after each treatment course according to the CTCAE, version 4.0. Patient population continued treatment until disease progression or unacceptable toxicity, and no treatment-related deaths occurred. Most adverse events were grade 1-2. Among the hematological adverse events, anemia was the most common (Table 2). Grade 1-2 thrombocytopenia (28.6%) and grade 1-2 increased creatinine levels were among other common adverse events (23.8%). At the start of nivolumab treatment, the median level of the creatinine was found as 0.8 mg/dL (0.38-1.29). At the last visit of the patients, the median serum creatinine level was calculated as 0.95 mg/dL (0.51-1.55). Among the patients with increased creatinine, acute kidney injury was considered in 4 patients and acute interstitial nephritis (AIN) was considered in 1 patient. Biopsy could not be performed because the patient who was thought to have AIN refused. However, there was a response to corticosteroid therapy. The patients did not need dialysis in the follow-up, and it did not occur again in the following cures.

Most immune-related adverse reactions were managed according to national guidelines. When immune-related toxicities were seen, nivolumab treatment was stopped and cortisone was administered in gradually increasing doses. One patient with grade 2 thyroid dysfunction, an immune-related endocrine toxicity, received treatment with levothyroxine from an endocrinologist. In one patient who developed grade 3 encephalitis after the 8th cycle of nivolumab treatment, the drug was discontinued and not reintroduced.

Discussion

The present report aimed to analyse the clinical characteristics, effectiveness, and safety of nivolumab as a second-line treatment in elderly patients with advanced melanoma. The study included BRAF wild-type patients with a median age of 70 years, an ECOG PS of 0 or 1, and prior treatment experience. The analysis showed a median PFS of 3.5 months and a median OS of 14.5 months in the elderly patients. Grade 3-4 adverse events were seen in 28.6% of the patient population.

In a retrospective study involving patients of various age groups with a median age of 66 years, nivolumab treatment reported an mPFS of 3.3 months and an mOS of 14.1 months. Most patients in that study received nivolumab as a second- or later-line treatment, with an mPFS of 3.2 months for second or subsequent lines [19]. The CheckMate 037 study, focusing on objective response, reported secondary endpoints of mOS: 15.7 months and mPFS: 3.1 months. The study included patients who had previously received ipilimumab or ipilimumab with a BRAF inhibitor, with a median age of 59 years [20,21]. Our study yielded similar results in terms of both PFS and OS, indicating that age did not affect OS in nivolumab treatment.

Luca et al. demonstrated in their report that the first-line efficacy of nivolumab in 55 patients aged 75 years and older, reporting an mPFS of 5.1 months. The study demonstrated the effectiveness and safety of nivolumab in this patient population [17]. Additionally, the study of Luca et al. indicated that the efficacy and safety findings with nivolumab were similar regardless of BRAF mutation status. Our study specifically included patients with BRAF wild type.

Baseline LDH level is a known prognostic factor for OS and PFS in metastatic melanoma patients [22,23]. In our study, patients with baseline LDH values within the normal range showed numerical superiority in both OS and PFS, although not statistically significant. This observation may be due to the small sample size.

In previous studies of nivolumab, common adverse reactions associated with any grade of treatment included pruritus, fatigue, rash, and diarrhea [13,24,25]. In current study, the most frequently observed grade 1-2 adverse events, irrespective of cause, were anemia (66.7%) and increased serum creatinine levels (23.8%). Renal adverse events of nivolumab therapy are rare [19,26]. Cases of AIN due to nivolumab have been reported [27]. Compared to other studies, the increase in creatinine levels was more frequent in our study. All of them were grade 1-2 patients and did not require drug dose reduction or drug discontinuation. Additionally, the rate of grade 3-4 adverse events for all causes in our study was 28.6%. In the CheckMate 066 study, all-cause grade 3-4 adverse events were reported as 34% [13,24]. No grade 5 adverse events were observed. The safety profile of nivolumab in our study was found like in previous studies, demonstrating manageable adverse events.

Small smalple size is among limitations of this report. Furthermore, as this report was retrospective, there were instances of missing patient data.

The results of our retrospective analysis demonstrate the efficacy and safety of nivolumab as a second-line therapy in elderly patients with wild-type BRAF. Our findings support the effectiveness and safety of nivolumab in second-line treatment for elderly patients who are unable to receive it as a first-line therapy.

Conclusion

Nivolumab presents a promising therapeutic option for patients aged ≥ 65 years. It may serve as a viable choice for second-line treatment in elderly patients who are unable to receive nivolumab in the initial treatment or have progressed after starting chemotherapy.

Authorship contribution statement

Conceptualization, Methodology, Software: OÜ, OY
Data curation, Writing- Original draft preparation: OÜ, OY, NÖ, AÖ
Visualization, Investigation: OÜ, OY
Supervision: NÖ, AÖ
Software, Validation: OY, AÖ
Writing- Reviewing and Editing: OÜ, OY, AÖ

Ethical approval

The study protocol received approval from the ethics committee of our university (Gazi University Ethics Committee, 2023-763).

Conflict of interest

The authors have no conflicts of interest to declare.

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