Immunotherapy Outcomes in Advanced Melanoma in Relation to Age

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Editor's note

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ABSTRACT

Introduction: Older age is a melanoma risk factor. Elderly individuals are likelier to have immunosenescence, which could help melanoma cells escape immune surveillance. Hence, it is believed that elderly people cannot mount a potent immune response to checkpoint inhibitors to eliminate melanoma.

Objectives: To investigate age-related differences in the time to progression, overall survival, and immunotherapy-related adverse events among patients with metastatic melanoma who received checkpoint inhibitors.

Methods: We retrospectively identified patients at our institution between January 2012 and December 2016 with stage IV melanoma who received at least 1 dose of ipilimumab, pembrolizumab, nivolumab, or combined ipilimumab and nivolumab. Demographic, pathologic, and clinical characteristics were obtained. Immune-related response criteria were used to define responses.

Results: Twenty-nine patients were younger than age 65 years and 31 were age 65 years or older. Time to progression was comparable between the age groups (hazard ratio = 0.79, 95% confidence interval = 0.37-1.70, p = 0.46). Overall survival was not significantly different after immunotherapy between groups (hazard ratio = 0.75, 95% confidence interval = 0.31-1.82, p = 0.491). Overall, immunotherapy-related adverse events were comparable between groups, with 62% in younger patients (18/29) and 45% in older patients (14/31 p = 0.19). Of 60 patients, 30 responded to immunotherapy. Nonresponders were more likely than responders to have *BRAF*-mutated melanomas (16 [53.3%] vs 8 [27.6%]; p = 0.04) and less likely to have immunotherapy-related adverse events (12 [40%] vs 20 [66.7%]; p = 0.04).

Conclusion: Aging does not seem to affect response to checkpoint inhibitors. Elderly patients with metastatic melanoma should be treated similarly to younger patients.

INTRODUCTION

The incidence of cutaneous melanoma is increasing faster than any other potentially preventable cancer in the US.[1] An estimated 96,480 new cases of cutaneous melanoma were diagnosed in the US in 2019.[2] High-dose interleukin-2 has been the agent of choice to treat metastatic melanoma since 1985.[3] With high-dose interleukin-2, long-term survivals are observed in 5% to 10% of patients. However, because of the severe toxicity profile, its use is restricted to a minority of patients who are physically fit enough to withstand such therapy.[3]

The advent of immunotherapy with checkpoint inhibitors has revolutionized the management of metastatic melanoma. It is known now that the cytotoxic T-lymphocyte antigen-4 (CTLA-4) imposes a negative feedback on T cells, leading to inactivation of their cytotoxic function. Targeting CTLA-4 with ipilimumab helps restore T-cell activity against melanoma.[4] The programmed death-1 protein (PD-1) is an immune checkpoint receptor expressed by activated T cells. The PD-1 binds to its ligands PDL1 and PDL2, on melanoma cells, which deactivate the T cell, allowing melanoma cells to escape immune surveillance. The CTLA-4 inhibitor, ipilimumab, and the PD-1 inhibitors, pembrolizumab and nivolumab, are approved by the US Food and Drug Administration to treat metastatic melanoma.[5]

Checkpoint inhibitors help activate T cells but also can give rise to immunotherapy-related adverse events (irAEs) such as immune-mediated colitis, rash, autoimmune pneumonitis, pruritus, nausea, anemia, arthralgia, vomiting, constipation, immune-mediated hepatitis, immune-mediated nephritis and renal dysfunction, autoimmune endocrine deficiencies (hypothyroidism, hypophysitis, and adrenal insufficiency), autoimmune encephalitis, and fatigue.[6]

Age is an important prognostic factor in cutaneous melanoma. Melanoma has an aggressive biology, and, with advancing age, carries a worse prognosis.[7-9] Differences in the natural history of melanoma between younger and older patients are believed to be partially the result of immunosenescence that helps melanoma cells escape an effective immune surveillance.[8] All immune cells originate from the hematopoietic stem cells in the bone marrow, and as we age, there is a 2-fold to 4-fold decline in the proliferative capacity of these stem cells compared with younger people.[10] Although, production of pro-B cells decreases markedly with aging, T-cell precursors seem to be less affected.[11] Aging results in decreased Toll-like receptor function. Toll-like receptors have been found to induce the protective adaptive immune responses in antitumor immunity,[12] reduced cytokine production,[13] and decreased production of nitric oxide and reactive oxygen species by macrophages.[14] Likewise, the ability of NK (natural killer) cells to produce interferron-γ becomes modestly impaired in older individuals, thus impairing the ability to destroy melanoma cells.[15] Moreover, aging results in a decline in the number and function of T cells and dendritic cells (the most potent antigen-presenting cells).[10] It also reduces

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the costimulatory molecule CD28, which impairs the ability of T cells to proliferate and secrete interleukin-2.[16]

Our basic understanding of immunosenescence has broadened, giving rise to the myth among some physicians that checkpoint inhibitors may not be as effective in treating the elderly patients with metastatic melanoma as it is in treating the younger ones. This study was conducted to investigate age-related differences in outcomes among patients with metastatic melanoma who received immunotherapy with checkpoint inhibitors.

METHODS

Patients

All patients with metastatic melanoma (M1a, b, or c), regardless of pathologic type (cutaneous, mucosal, and ocular), who received immunotherapy with checkpoint inhibitors at our institute between January 2012 and December 2016, were included in this retrospective study. Evaluable patients received at least 1 dose of ipilimumab, pembrolizumab, nivolumab, or combined ipilimumab and nivolumab.

Baseline characteristics included age, sex, melanoma pathologic type, *BRAF* mutation status, prior melanoma-directed therapies, Eastern Cooperative Oncology Group (ECOG) performance status, baseline serum lactate dehydrogenase levels, and presence of brain metastases. The Charlson Comorbidity Index, which predicts the 1-year mortality for a patient who may have a range of comorbid conditions, such as heart disease, AIDS, or cancer (a total of 22 conditions), was calculated. Each condition was assigned a score of 1, 2, 3 or 6, depending on the risk of dying associated with each one the score was calculated and reported for every patient. IrAEs including fever, fatigue, diarrhea and biopsy-confirmed colitis, hypothyroidism, adrenal insufficiency, rash, itching, vitiligo, central nervous system adverse events, and other adverse events believed to be caused by immune therapy, were noted. The date of death and/or the date of melanoma recurrences were recorded.

End Points and Assessment

The primary objective of this study was to evaluate the baseline demographic, clinical, and pathologic characteristics between responders and nonresponders to immune checkpoint inhibitors among patients with metastatic melanoma, then to investigate the age-related differences (< 65 years vs ≥ 65 years) in the time to progression, overall survival, and irAEs. Responses to checkpoint inhibitors were defined as complete response, partial response, or stable disease observed on positron emission tomography or total-body computed tomography scans obtained 6 months after the initiation of immunotherapy. Any evidence of radiologic progression (an increase in tumor burden of at least 25% compared with baseline) at 6 months was considered progressive disease. Because of lack of documentation, irAEs were not graded but were recorded as all irAEs of any severity.

The study protocol was approved by the institutional review board at the University of Arkansas for Medical Sciences, Little Rock, AR.

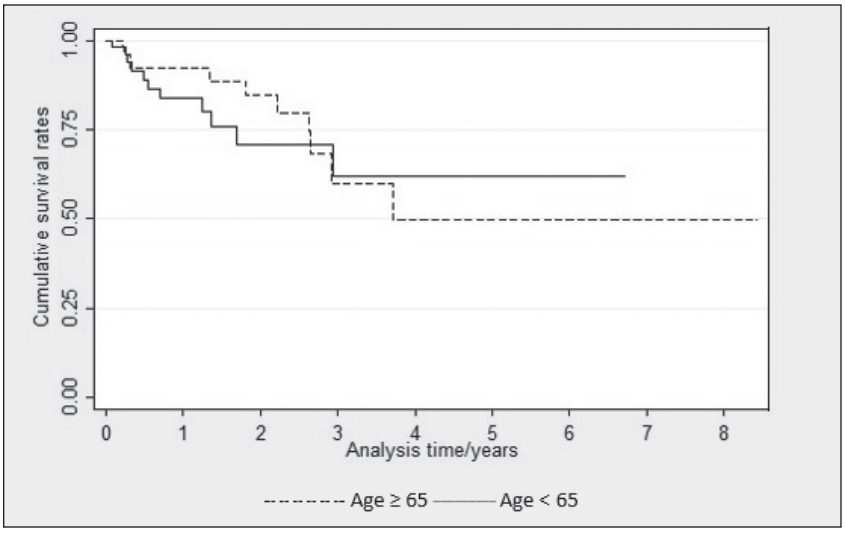

Figure 1. Kaplan-Meier survival plot for overall survival among patients with stage IV melanoma[a]

[a] Adjusted for sex, melanoma type, and brain metastasis (p = 0.491) in patients younger than age 65 years or age 65 years and older.

Statistical Analysis

We used bivariate analyses to describe the distribution of response to immunotherapy by demographics and pathologic characteristics. Study participants enrolled in the study at the time of immunotherapy initiation. Participation in the study ended because of disease progress, termination of immunotherapy, death, or the end of our study (February 1, 2017). The Cox proportional hazards regression model was used to assess the response to immunotherapy and the overall survival by age group. Because our eligible participants were all non-Hispanic whites and had stage IV melanoma, we did not need to adjust for race and disease stage to control confounding in our Cox proportional hazards models. All analyses were conducted using Stata 14.0 software (StataCorp, College Station, TX).

RESULTS

Responders versus Nonresponders

Of 96 patients with metastatic melanoma diagnosed at the University of Arkansas for Medical Sciences, 36 patients were excluded from the study because they received treatment elsewhere. Thus, 60 patients were available for this retrospective review. As shown in Table 1, 36 (60%) of 60 patients were men. Cutaneous melanoma was the predominant type. Forty percent of patients (n = 24) harbored the *BRAF* mutation. Prior treatment before starting immunotherapy was documented in 22 (36.6%) of 60 patients. Adverse events to immunotherapy were found in 32 (53.3%) of 60 patients.

Patients who did not respond to immunotherapy were more likely to have a *BRAF* mutation, a higher Charlson index, and a lower irAE profile. No difference

between responders and nonresponders was noted regarding the type of immunotherapy used (Table 1). Overall irAEs were present in 20 (66.7%) of responders compared with 12 (40%) of nonresponders (p = 0.03). Endocrinopathies, hepatitis, pneumonitis, dermatitis, and central nervous system adverse effects were similar in both responders and nonresponders. Thirty percent of patients (n = 10) who responded to immunotherapy had colitis compared with 7% (n = 2) in nonresponders (p = 0.03). Similarly, rheumatologic adverse effects were more common in responders (p = 0.007). There was no statistical difference between responders and nonresponders regarding the presence or absence of brain metastasis (p = 0.78).

Table 1. Demographic and pathologic characteristics among patients with stage IV melanoma, by response to immunotherapy[a]

Characteristic	Responders (n = 30)	Nonresponders (n = 30)	p value
Age at initiation of immunotherapy, y median, (IQR)	66.9 (54.3-73.3)	62.7 (54.3-69.1)	0.48
Sex			0.6
Men	19 (63.3)	17 (56.7)	
Women	11 (36.7)	13 (43.3)	
Melanoma type			0.06
Cutaneous	28 (93.3)	26 (86.7)	
Mucosal	0 (0.0)	4 (13.3)	
Ocular	2 (6.7)	0 (0.0)	
BRAF mutation			0.04
No	21 (70.0)	14 (46.7)	
Yes	8 (26.7)	16 (53.3)	
Missing	1 (3.3)	0 (0.0)	
Previous treatment			0.59
None	18 (60.0)	20 (66.7)	
Yes	12 (40.0)	10 (33.3)	
Charlson Comorbidity Index, median, (IQR)	6 (6,8)	9 (6,10)	0.003
ECOG score, median, (IQR)	0 (0,1)	0 (0,1)	0.51
Brain metastasis			0.78
No	21 (70.0)	20 (66.7)	
Yes	9 (30.0)	10 (33.3)	
Elevated baseline serum LDH level			0.28
No	27 (90.0)	24 (80.0)	
Yes	3 (10.0)	6 (20.0)	

[a] Data are presented as number (percentage) unless indicated otherwise.
ECOG = Eastern Cooperative Oncology Group; IQR = interquartile range; LDH = lactate dehydrogenase.

Table 2. Cox regression for overall survival among patients with stage IV melanoma

Age group, y	Survival status after immunotherapy initiation		Hazard ratio (95% confidence interval)		Median survival, y
	Alive, no. (%)	Dead, no. (%)	Crude	Adjusted[a]	
< 65	18(46.2)	11 (52.4)	1.0	1.0	4.14
≥ 65	21 (53.8)	10 (47.6)	0.81 (0.34-1.92)	0.75 (0.31-1.82)	5.00

[a] Adjusted for sex, melanoma type, and brain metastatis.

Table 3. Cox regression for disease progression in patient with stage IV melanoma

Age group, y	Disease progression		Hazard ratio (95% confidence interval)		Median time to progression, y
	No, no. (%)	Yes, no. (%)	Crude	Adjusted[a]	
< 65	13 (43.3)	16 (53.3)	1.0	1.0	0.33
≥ 65	17 (56.7)	14 (46.7)	0.78 (0.38-1.61)	0.79 (0.37-1.70)	0.99

[a] Adjusted for sex and melanoma type.

Time to Progression and Overall Survival by Age Group

Twenty-nine patients were younger than age 65 years and 31 were age 65 years and older. After adjustment for sex, melanoma type, and presence of brain metastasis, there was no significant difference in survival after immunotherapy between the 2 age groups (hazard ratio [HR] = 0.75, 95% confidence interval [CI] = 0.31-1.82, p = 0.491; Table 2 and Figure 1). Similarly, the time to progression was compared between groups, and after adjustment for sex and melanoma type, the time to progression was found to be comparable with no statistically significant difference (HR = 0.79, 95% CI = 0.37-1.70, p = 0.46; Table 3).

Age-Related Differences in Immunotherapy-Related Adverse Events

Overall irAEs in the 2 age groups were comparable, with 62% in the younger patients (18/29) and 45% in the older patients (14/31; p = 0.19). The irAEs, including endocrinopathies, colitis, hepatitis, pneumonitis, dermatitis, and central nervous system adverse effects, were similar in both age groups. Interestingly, rheumatologic adverse effects were more common in younger patients (p = 0.035; Table 4).

DISCUSSION

Aging is accompanied by functional decline in both innate and adaptive immunity.[17] We found no significant differences, when adjusted for sex, type of melanoma, and presence of brain metastasis, in the time to progression and the overall survival between the younger than age 65 and age 65 years and older groups who received checkpoint inhibitors for treatment of metastatic melanoma. Our results were similar to those of other studies.[18] In one study, 855 patients with unresectable stage III or stage IV melanoma received ipilimumab after failure to respond or intolerance to at least 1 prior systemic treatment. There were no statistically significant

Table 4. Immune-related adverse events (AEs; number of patients)

	Age < 65 years (n = 29)		Age ≥ 65 years (n = 31)		
Adverse event	AEs	No AEs	AEs	No AEs	p value
Overall adverse events	18	11	14	17	0.190
Endocrinopathies	8	21	4	27	0.155
Colitis	8	21	4	27	0.833
Hepatitis	1	28	1	30	0.962
Pneumonitis	3	26	0	31	0.066
Dermatitis	4	25	6	25	0.563
Rheumatologic disease	6	23	1	30	**0.035**[a]
CNS adverse effects	1	28	1	30	0.962

[a] Boldface indicates significant.
CNS = central nervous system.

differences in the median progression-free survival and overall survival between the older (> 70 years) and the younger (≤ age 70 years) group.[19] In the US Expanded Access Program, the 1-year survival rate in patients with metastatic melanoma treated with ipilimumab was not different among age 65 years and younger compared with age 65 years and older, which was 38% and 37%, respectively.[20] Another study of 95 patients, treated with immunotherapy for metastatic melanoma, showed that the survival and response rates, to checkpoint inhibitors, in patients older than age 80 years were very similar to those for younger patients.[21]

Immunotoxicity is an indirect marker of the efficacy of immunotherapy. Our results revealed that responders, regardless of age, had a higher rate of irAEs (66.7%) than did nonresponders (40%; p = 0.04). Immune-mediated colitis, in particular, was higher in responders compared with nonresponders (approximately 30% [n = 10] vs 7% [n = 2], p = 0.03). One prior study showed significantly improved response rates in patients in whom immune-mediated enterocolitis developed because of ipilimumab.[22] Other studies showed a strong correlation between the treatment response rate and irAEs,[23-25] but these studies pertain to patients who received anti-CTLA-4; the data are conflicting regarding anti-PD-1 immunotherapy. The results of recently concluded multicenter randomized controlled trials, including CheckMate 037[26] and KEYNOTE-006,[27] showed significantly improved progression-free survival and decreased rates of adverse effects in patients receiving anti-PD-1 immunotherapy compared with those receiving anti-CTLA-4. Our study findings lend support to the correlation between response rate and irAEs irrespective of the type of immunotherapy administered.

There is also a strong correlation between the development of vitiligo and the tumor response in patients receiving immunotherapy.[28-30] In our study, vitiligo developed in only 2 patients (3.3%) and both had complete response to immunotherapy. A systematic review was conducted of 137 studies comprising 139 treatment arms (11 general immune stimulation, 84 vaccine trials, 28 antibody-based trials, and 16 adoptive T-cell transfer studies) and including a total of 5737 patients.[30] The overall cumulative incidence of vitiligo was 3.4% (95% CI = 2.5%-4.5%). Vitiligo development was significantly associated with better progression-free survival (HR = 0.51; 95% CI = 0.32-0.82; p < 0.005) and overall survival (HR = 0.25; 95% CI = 0.10-0.61; p < 0.003), indicating that these patients have 2 to 4 times less risk of disease progression and death, respectively, compared with patients without vitiligo development.[30]

In our study, 7 (11.7%) of the patients treated with checkpoint inhibitors had immune-related rheumatologic adverse effects. Interestingly, this was particularly common in younger patients (p = 0.03). Another study showed that 1.3% of the total patients treated with nivolumab and ipilimumab experienced rheumatologic adverse events.[31]

A *BRAF* mutation has been associated with earlier age of onset, more aggressive clinical course, and decreased survival in patients who did not receive BRAF inhibitor therapy.[32] Our study showed increased rates of the BRAF mutation in patients who failed to respond compared with the ones who responded to the immunotherapy (53% vs 27%, p = 0.04). However, BRAF inhibitors have improved survival in these patients with gene mutations.[33] Sequential treatment with BRAF inhibitors and checkpoint inhibitors has emerged as a new strategy in the treatment of *BRAF*-mutated melanoma, but data remain conflicting regarding the preferred sequence.[34-36] Nonetheless our study touches on the interaction between the *BRAF* mutation and the response to immunotherapy, and the data regarding this interaction per se are still lacking. A *BRAF* mutation contributes to immune escape. Boni et al[37] showed that BRAF inhibition increases the expression of melanocyte differentiation antigens, which is associated with increased antigen-specific T-cell recognition; MEK inhibition, on the other hand, impairs T-lymphocyte function. It is not fully understood whether patients with a *BRAF* mutation should be treated with BRAF inhibitors first or immunotherapy first. Clinical trials are being conducted to clarify the appropriate sequence. In a retrospective study, progression-free survival and response rates were found to be similar irrespective of the timing of BRAF inhibitor therapy (before or after immunotherapy).[35] In another study, a longer overall survival was found if ipilimumab was given before a BRAF inhibitor compared with a BRAF inhibitor followed by ipilimumab, or with either agent alone.[38] The results of that study support the use of immunotherapy as first line in patients with *BRAF* mutations.[38]

Other studies have shown that immunotherapy in elderly patients may respond better in melanoma because of fewer regulatory T cells relative to CD8+ T cells in tumor deposits.[39] Another study by Li et al[40] showed that immune checkpoint inhibitors significantly prolonged the survival in both younger and older groups with melanoma. Anti-PD-1 agents were more efficient in older compared with younger patients with melanoma.

Although our study discussed all the checkpoint inhibitors as 1 group, further research will be necessary to identify differences, if any, between these agents. In

addition, because our study is a retrospective study with a small sample size, it is likely to have practitioner bias because of the lack of randomization. It is a single-institution study in the Southern US. Further randomized multicenter studies with larger sample sizes will be useful to better evaluate the differences between these 2 age groups in terms of response to treatment, survival, and adverse effect profile.

CONCLUSION

Aging does not seem to affect the response to checkpoint inhibitors. Time to progression, overall survival, and immune-mediated adverse events were similar in younger and older patients with metastatic melanoma receiving checkpoint inhibitors. Autoimmunity owing to checkpoint inhibitors, especially immune-mediated colitis and vitiligo, are markers of better response. Elderly patients with metastatic melanoma should be treated similarly to younger patients, even with combination therapy such as ipilimumab and nivolumab. Future studies should investigate better biomarkers, such as PDL1, to predict response to checkpoint inhibitors. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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Kathleen Louden, ELS, of Louden Health Communications performed a primary copy edit.

Authors' Contributions

Dinesh Atwal, MD; Fade Mahmoud, MD; Krishna Joshi, MD; and Rahul Ravilla, MD, did protocol writing, data collection, and data analysis. Issam Makhoul, MD; Laura Hutchins, MD; Naveen Yarlagadda, MD; Sunil Kakadia, MD; and Yadav Pandey, MD, helped with the literature review, discussion, and writing the manuscript.

All authors vouch for the accuracy and completeness of the data and analyses, and all have given final approval to the manuscript.

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