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The Impact of Age on Treatment Responses in Patients with Non-Small Cell Lung Cancer Treated with Immune Checkpoint Inhibitors

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Abstract

Objective: The correlation between age and the incidence and prevalence of cancer is well-established. Immunosenescence is thought to be underlying this condition. This retrospective research aimed to investigate the impact of aging on the responses to immune checkpoint inhibitor (ICIs) treatment responses in advanced non-small cell lung cancer (NSCLC) patients.

Methods: Data was retrospectively collected from one cancer center. The treatment responses of advanced NSCLC patients treated with ICIs were compared between 2 groups based on age 65.

Results: 30 patients were younger than 65 years old, and 20 patients were 65 years old or older.

While the median progression-free survival (PFS) under 65 years of age was 21.6 months (95% CI: 5.2-38.0), in patients ≥ 65 years of age it was 13.5 months (95% CI: 3.3-23.7) (Hazard Ratio (HR) 1.31, 95% CI: 0.67-2.57, P = .423). For the median overall survival (OS), it was 27.8 months (95% CI: 20.6-34.9) in patients under 65 years of age, and 20.2 months (95% CI: 1.7-38.7) in patients ≥ 65 years of age (HR 1.18, 95% CI: 0.56-2.46, P = .651). There was also no significant difference in the objective response rate (ORR) between patients under 65 and ≥ 65 years of age, with rates of 43.3% and 25%, respectively (P = .186).

Conclusion: Our study showed that age had no effect on ICIs responses in patients with advanced NSCLC. Prospective studies involving larger patient populations are required to evaluate the impact of age on ICIs responses.

Keywords: Age, immune checkpoint inhibitors, non small cell lung cancer

Introduction

The incidence and prevalence of numerous cancers increase with advancing age. Immunosenescence refers to the progressive decline in the immune system with age, playing a role in this situation.[1] Immunosenescence encompasses the loss of proliferation in B and T cells, quantitative changes in various cell subgroups, functional disorders, and qualitative alterations in antigen-presenting cells (APC).[2] Currently, immunosenescence is a topic of increasing interest, and it is interesting to consider how this phenomenon manifests itself in elderly patients treated with immune checkpoint inhibitors (ICIs).

Multiple studies have demonstrated that the use of ICIs in both the first and subsequent lines enhances survival and response rates among patients with advanced non-small cell lung cancer (NSCLC).[3-6] Although the incidence of NSCLC tends to rise with advancing age, the efficacy of ICIs in older individuals is still uncertain due to the small number of patients aged 65 and older in these studies. The effectiveness of ICIs in older patients has been assessed in several clinical studies as part of an exploratory analysis. The CheckMate 017 study demonstrated that nivolumab decreased mortality in patients aged 65-75 (HR 0.56, 95% CI, 0.32-0.82); however, no statistically significant HR for survival was observed in patients aged 75 and older (HR 1.85, 95%CI, 0.76-4.51). This situation is explained by the limited number of patients over 75 years of age in the study.[7] In another analysis of real-world data, the objective response rate (ORR), overall survival (OS), and progression-free survival (PFS) of elderly (≥ 75) NSCLC patients treated with nivolumab did not differ from younger patients.[8] When examining the safety of nivolumab in the elderly, it was observed that immune-related adverse events (irAEs) were comparable between the 2 age groups (< 70 years vs. ≥ 70 years).[9]

Here, we conducted a retrospective analysis to assess the treatment outcomes of patients under and over the age of 65 with NSCLC. Additionally, we analyzed the presence of irAEs between 2 age groups.

Methods

Patients

This was a retrospective study conducted at the Cerrahpaşa Medical Faculty. We evaluated the medical records of 50 patients with advanced-stage NSCLC who were treated with ICIs as monotherapy or in conjunction with chemotherapy (ChT). Anti-PD1 or anti-PD L1 monoclonal antibodies (mAb) were administered to all patients. The inclusion criteria for this study were limited to patients

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who had an Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1. None of the patients exhibited an EGFR-ALK-ROS1 mutation. Moreover, each patient exhibited a minimum PD-L1 expression rate of 1%. The study underwent assessment and approval by the İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine (Approval no 787574, Date: September 26, 2023). Due to the retrospective design of the study, informed consent was waived. The follow-up period concluded on April 12, 2023.

The definition of irAEs was based on the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. We compared PFS, OS, and ORR between the 2 groups, which consisted of patients under and over 65 years of age. In addition, the OS and PFS rates of patients aged 65-75 years and ≥ 75 years were compared to those of patients younger than 65 years.

Statistical Analysis

The Fisher's exact test and chi-square test were used for categorical data, and the *t*-test for continuous data to compare the patients' characteristics. The survival endpoints were OS and PFS. OS was defined as the time from starting the ICIs to death from any cause. PFS was defined as the time from starting ICIs to disease progression or death from any cause. Patients without events were censored at the time of the last follow-up. Survival curves were generated using the Kaplan–Meier method and compared using the log-rank test. Using Cox hazards regression models, the association between age categories and OS and PFS was analyzed and reported as hazard ratios (HR) with a 95% confidence interval (CI). For comparing ORR and the presence of irAEs, the chi-square test was used. Statistical tests were two-sided, and a *P*-value less than .05 was considered statistically significant. The statistical analyses were conducted using the Statistical Package for Social Sciences version 23.0 software (IBM Corp.; Armonk, NY, USA).

Results

There was an evaluation of 50 patients with advanced NSCLC. The median age was 61.5 (range: 38-79). There were 38 (76%) male patients and 12 (24%) female patients. Overall, ICIs with ChT were administered to 9 patients (18%), while 41 patients (82%) were treated with ICIs as single-agent PD-1 or PD-L1 inhibitors. 15 (30%) patients showed PD-L1 levels exceeding 50%, whereas 35 (70%) patients were identified as having PD-L1 levels of 1%-49%. 19 (38%) patients had at least 2 metastatic sites. 27 patients (54%) experienced irAEs of any grade, whereas 23 patients (46%) had no irAEs. 30 (60%) patients were < 65 years of age, while 20 (40%) patients were ≥ 65 years of age. Based on the 65-year age threshold, no statistically significant differences were observed in the initial clinicopathologic characteristics of the 2 groups. (Table 1).

IrAEs of any grade were observed in 17 (56.7%) patients under the age of 65, compared to 10 (50%) patients 65 years and older

Table 1. Baseline Characteristics of Patients According to the Age Cut-off of 65 Years

		Total (n = 50) No. (%)	< 65 years (n = 30) No. (%)	≥ 65 years (n = 20) No. (%)	*P*
Age	Range	38-79			
	Median	61.5			
Gender	Female	12 (24)	7 (23.3)	5 (25)	
	Male	38 (76)	23 (76.7)	15 (75)	.892
Smoking history	Nonsmoker	7 (14)	4 (13.3)	3 (15)	
	Current or former	43 (86)	26 (86.7)	17 (85)	.868
Histology	Squamous	12 (24)	7 (23.3)	5 (15)	
	Non-squamous	38 (76)	23 (76.7)	15 (75)	.892
PD-L1 expression	1%-49%	35 (70)	22 (73.3)	13 (65)	
	≥ 50 %	15 (30)	8 (26.7)	7 (35)	.529
Metastatic sites	≤ 2	31 (62)	20 (66.7)	11 (55)	
	> 2	19 (38)	10 (33.3)	9 (45)	.405
Brain metastases	No	36 (72)	22 (73.3)	14 (70)	
	Yes	14 (28)	8 (26.7)	6 (30)	.797
Liver metastases	No	46 (92)	28 (93.3)	18 (90)	
	Yes	4 (8)	2 (6.7)	2 (10)	.670
Treatment line	First	41 (82)	23 (76.7)	18 (90)	
	Second	9 (18)	7 (23.3)	2 (10)	.229
Treatment type	Anti-PD-(L)1 monotherapy	41 (82)	26 (86.7)	15 (75)	
	Anti-PD1+ ChT	9 (18)	4 (13.3)	5 (25)	.293

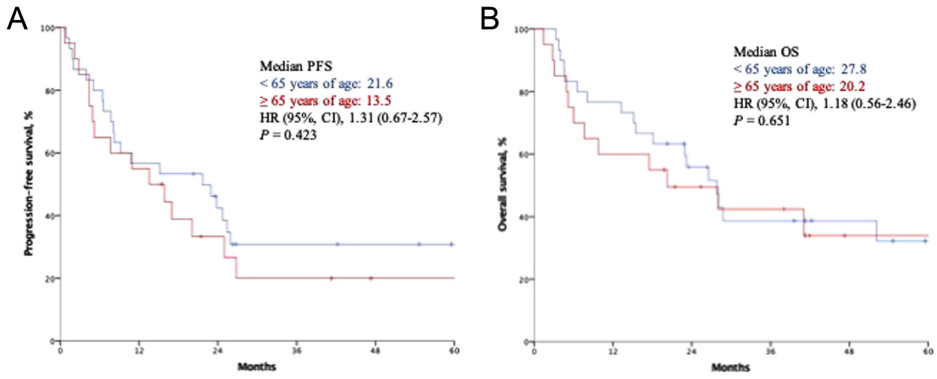

Figure 1. Progression-free survival (PFS) (A) and overall survival (OS) (B) in patients with < 65 years of age and ≥ 65 years of age.

(*P* = .643). The median PFS for patients under 65 years of age was 21.6 months (95% CI: 5.2-38.0), while it was 13.5 months (95% CI: 3.3-23.7) for patients 65 years and older (HR 1.31, 95% CI: 0.67-2.57, *P* = .423) (Figure 1A). In patients who were < 65 years of age, the median OS was 27.8 months (95% CI: 20.6-34.9) compared to 20.2 months (95% CI: 1.7-38.7) in patients who were ≥ 65 years of age (HR 1.18, 95% CI: 0.56-2.46, *P* = .651) (Figure 1B). When we compared the ORR between these age groups, the ORR was 43.3% in patients < 65 years of age and 25% in patients ≥ 65 years of age (*P* = .186).

A patient subgroup analysis was conducted on 3 distinct age groups: those younger than 65 years of age, those between 65 and 74 years of age, and those 75 years of age or older. The PFS and OS of these groups did not differ significantly (Table 2). The median PFS for patients aged 65-74 years was 15.8 months (95% CI: 8.7-22.9), while the median PFS for patients aged 75 years and older was 7.6 months (95% CI: 0.6-14.6) (*P* = .70). The median OS was 28.0 months (95% CI: 12.3-43.6) in patients 65-74 years old and 9.7 months (95% CI: 4.2-15.2) in patients ≥ 75 years old (*P* = .668). Kaplan–Meier curves for these 3 groups are shown in Figure 2A and B.

Discussion

Based on preclinical data, while the expression levels of most receptors in young and old dendritic cells, CD4+ and CD8+ T cells are comparable, the B7-H1 receptor, which negatively regulates immune responses, was significantly more prevalent in old CD8+ T cells compared to young CD8+ T cells.[10] Immune checkpoint proteins, including PD-1 and TIM-3, have been observed to increase in vivo models of immunosenescence; consequently, it has been hypothesized that elderly patients require novel ICIs.[11]

Table 2. Association Between Age Categories and PFS and OS

	HR (95% CI)	*P*
Progression-free survival		
< 65 years	Reference	
65-74 years	1.26 (0.58-2.70)	.550
≥ 75 years	1.43 (0.53-3.84)	.468
Overall survival		
< 65 years	Reference	
65-74 years	1.01 (0.42-2.43)	.976
≥ 75 years	1.55 (0.57-4.21)	.385

An examination of preclinical investigations concerning the safety of immunotherapy in the elderly reveals that chronic, low-grade inflammation, referred to as "inflammaging," progresses with age[12] and this process is thought to contribute to the fatal toxicities observed in aged mice receiving immunotherapy.[13]

Preclinical data in this context is not very compatible with clinical data. In the Keynote-010 trial, HR of death was similar between younger (< 65 years) and older (≥ 65 years) patients, favoring pembrolizumab in all groups.[14] In another study involving NSCLC patients with PD-L1 ≥ 50% and treated with ICIs, there was no difference in OS or PFS between age < 65 and ≥ 65 years group.[5] Nivolumab achieved a reduction of death by 49% in the 65-75 group, while no significant survival benefit was reported in patients ≥ 75 years.[7] A similar result was observed in a study involving nivolumab-treated patients with non-squamous NSCLC; while the risk of mortality decreased for patients aged 65 to 75, there was no statistically significant improvement in survival rate for patients aged 75 years and older.[3] The small sample size of patients aged ≥ 75 in these trials was shown to be the reason for the lack of survival advantage. In a real-world study, it was shown that elderly patients (≥ 75 years) responded similarly to nivolumab as younger patients, with no differences in ORR, PFS and ORR.[15,16] Our findings were mostly consistent with these studies. In our study, there was no correlation between age (< 65 years vs. ≥ 65 years) and PFS, OS, or ORR. Even after classifying patients into 3 categories, although numerically shortened PFS and OS were observed with increasing age, no statistical significance was observed. However, it has been considered that our patient population is relatively small.

In addition, recent research has demonstrated that irAEs are more prevalent in the elderly, and this is associated with an increase in autoantibodies with age.[17,18] Our findings did not support this either. There is a 56.7% prevalence irAEs rate in patients < 65 years of age while 50% prevalence irAEs rate in patients aged ≥ 65 years (*P* = .643). Additionally, another trial has demonstrated that the toxicity of ipilimumab for patients aged > 70 years is similar to that of younger patients.[19] It has also been also shown that patients aged ≥ 70 years presented higher grade irAEs than patients < 65 years.[20] Furthermore, it should be noted that in each of these studies including ours, patients aged 75 and older represented a minor proportion of the total cohort. Since the presence of irAEs correlates positively with the ICIs response, it is not remarkable that we did not observe a correlation between age and irAEs.

Although preclinical data indicate that the immune system declines with age, clinical and real-world data indicate that the efficacy outcomes of elderly patients are comparable to those of younger patients. In addition, the incidence of irAEs does not

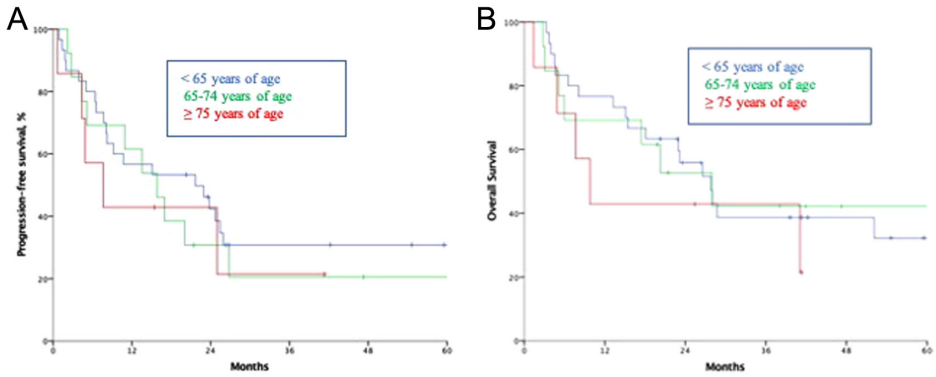

Figure 2. Progression-free survival (PFS) (A) and overall survival (OS) (B) in patients < 65 years of age, 65-74 years of age, and ≥ 75 years of age.

appear to be higher in older individuals. When recommending ICI treatments to patients, age should not be a distracting factor, especially for elderly patients in good health. In order to avoid age-related fragility or comorbidities, which are more prevalent in elderly patients, as a confounding variable, we limited our study to patients with an ECOG performance score of 0-1 only. It is well known that patients with poor performance display inferior ICI responses. The mechanism of action of ICIs in older individuals with poorer ECOG performance scores remains uncertain. There is a need for research to determine if it has the same efficacy and safety profile as in younger patients with an ECOG performance score of 2 or higher. Further investigation is warranted on comprehensive geriatric assessments and how they can be used to guide ICI initiation in elderly patients with low performance scores.

This study has several major limitations, mainly its retrospective design. Our sample size was very limited. An additional major limitation of this study is the heterogeneity of the population, with patients who received ICIs alone and in combination with ChT in both first-line and second-line settings. That is the reason we do not conclude with the results. Although it is known that the PD-L1 level in all patients is ≥ 1% and in some patients the PD-L1 expression level is ≥ 50%, another limitation of our study is that the PD-L1 level of all patients is not known exactly. Despite these limitations, our study revealed that in elderly patients with a good performance status, ICIs did not show a reduction in efficacy and had a favorable safety profile.

Although preclinical data emphasize immunosenescence, we did not observe a difference in treatment responses and toxicity rates, particularly in elderly patients with good clinical performance. Obviously, the fact that elderly patients comprised the smallest cohort in the studies could also be a factor. In addition, it is unknown to what extent biological age correlates to "immune age". There is a need to investigate markers that can detect the "immune age" of patients rather than their biological age in order to elucidate the impact of immunosenescence on ICIs responses.

Availability of Data and Materials: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine (Approval no 787574, Date: September 26, 2023).

Informed Consent: Due to the retrospective design of the study, informed consent was waived.

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Declaration of Interests: The authors have no conflict of interest to declare.

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