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Outcomes of Immunotherapy in Elderly Patients with Non Small Cell Lung Cancer: A Retrospective Analysis

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ABSTRACT
Immunotherapy with ICIs is a promising treatment for elderly NSCLC patients, offering a balance of efficacy and safety. This methodology provides a comprehensive framework for assessing the outcomes of immunotherapy in elderly NSCLC patients, focusing on survival rates, response rates and treatment-related toxicity. The use of retrospective data and statistical analyses allows for the evaluation of real-world effectiveness and safety of immunotherapy in this population. First-line treatment comprised chemotherapy in 70.4%), IO immunotherapy in (18.7%) and targeted therapy in 13.5%. Among chemotherapy-treated patients, 674 (96.6%) received platinum-based chemotherapy and carboplatin-based doublet or triplet chemotherapy was the most commonly administered regimen 72.4% of chemotherapy-treated patients]. In the overall population, patients (29.5%) received 2 L therapy, which was chemotherapy in (37.1%), IO monotherapy in (52.5%) and targeted therapy in (13.1%). Immunotherapy remains a viable and effective treatment option for elderly NSCLC patients, with age alone not being a limiting factor. The decision to use ICIs should consider the patient's overall health and performance status rather than age alone, and further research is needed to optimize treatment strategies for this growing patient population.

INTRODUCTION

Immunotherapy, particularly using immune checkpoint inhibitors (ICIs), has become a significant treatment option for elderly patients with non-small cell lung cancer (NSCLC). While it offers a favorable safety profile compared to traditional chemotherapy, its effectiveness can vary due to age-related factors. ICIs have shown comparable efficacy and safety in elderly patients (≥65 years) as in younger populations, with no significant increase in toxicity[1-3]. However, patients over 75 may experience reduced benefits, potentially due to immunosenescence, which is the age-related decline in immune function[1,4,5]. Elderly patients often have comorbidities and reduced organ function, which can complicate treatment. Despite these challenges, ICIs are generally better tolerated than chemotherapy, making them an attractive option for this demographic[1,4,5]. Combining ICIs with chemotherapy or radiotherapy is being explored, but the safety and efficacy of these combinations in the elderly remain less clear. More data from dedicated clinical trials are needed to fully understand the impact of these combinations[6,7,8]. Biomarkers and Patient Selection: Identifying reliable biomarkers to predict which elderly patients will benefit most from ICIs is crucial. This can help tailor treatments to individual needs and improve outcomes[7-9]. The treatment of non-small cell lung cancer (NSCLC) in elderly patients presents unique challenges, particularly with the advent of immunotherapy. NSCLC is the most prevalent form of lung cancer, accounting for approximately 80% of cases and is often diagnosed at an advanced stage in older adults[1]. Immunotherapy, specifically immune checkpoint inhibitors (ICIs), has revolutionized the treatment landscape for NSCLC by offering a more favorable toxicity profile compared to traditional chemotherapy, making it an attractive option for elderly patients who may have comorbidities and reduced organ function[1,7]. Despite the potential benefits, the efficacy of ICIs in older patients remains a subject of debate. Studies have shown that while ICIs can be effective, the response may vary with age, and patients over 75 years may experience diminished benefits due to immunosenescence, a decline in immune function associated with aging[1,5]. Further more, elderly patients are often underrepresented in clinical trials, leading to a lack of robust data on the safety and efficacy of these treatments in this demographic[1,7]. Real-world data suggest that advanced age does not necessarily correlate with reduced efficacy or increased toxicity of immunotherapy, provided that patients maintain a good performance status[3,10]. However, the presence of multiple chronic conditions and the potential for drug interactions in older patients necessitate careful consideration and personalized treatment approaches[2]. As the population ages, understanding the outcomes of immunotherapy in elderly NSCLC patients is crucial for optimizing treatment strategies and improving survival and quality of life in this growing patient population.

MATERIALS AND METHODS

Study Design: A retrospective analysis was conducted to evaluate the outcomes of immunotherapy in elderly patients with non-small cell lung cancer (NSCLC). The study included patients aged 65 years and older who received immune checkpoint inhibitors (ICIs) as monotherapy or in combination with other treatments.

Patient Selection: Patients were stratified into age groups: <70 years, 70-79 years and ≥80 years. This stratification allowed for the assessment of age-related differences in treatment outcomes. Inclusion criteria required patients to have advanced NSCLC and to have received immunotherapy at the institution between specified dates.

Data Collection: Data were collected retrospectively from medical records, including demographic information, clinical characteristics, treatment regimens and outcomes. Key variables included performance status (PS), number of metastatic sites, and line of immunotherapy treatment.

Outcome Measures: Response Rate Assessed using radiographic evaluations to determine the proportion of patients achieving partial or complete response to treatment. Progression-Free Survival (PFS) Time from the start of immunotherapy to disease progression or death, estimated using the Kaplan-Meier method. Overall Survival (OS) Time from the start of immunotherapy to death from any cause, also estimated using the Kaplan-Meier method. Toxicity Monitored and recorded based on adverse events reported in patient records, with a focus on immune -related adverse events.

Statistical Analysis:

Comparative Analysis: Chi-square tests were used to compare qualitative variables across age groups.

Survival Analysis: Kaplan-Meier method was used to estimate survival curves and the log-rank test was applied to compare these curves across different age groups. Cox proportional hazards model was employed

to identify factors influencing PFS and OS, adjusting for potential confounders such as performance status and number of metastatic sites. This methodology provides a comprehensive framework for assessing the outcomes of immunotherapy in elderly NSCLC patients, focusing on survival rates, response rates and treatment-related toxicity. The use of retrospective data and statistical analyses allows for the evaluation of real-world effectiveness and safety of immunotherapy in this population.

Ethical Considerations: The study was conducted in accordance with ethical standards and received approval from the institutional review board. Patient consent was obtained where applicable and data confidentiality was maintained throughout the study.

RESULTS AND DISCUSSIONS

Patient data were not obtained from 1 of 10 planned sites because of capacity is- sues., 2 sites (Nottingham University Hospitals NHS Trust and the Clatterbridge Cancer Centre NHS Foun-dation Trust) contributed 56.9% of patients. In the study population, the median age was 68 years (range, 28-93 years), 54.7% were male, Eastern Cooperative Oncology Group performance status score was 0-1 in 76.5% and ≥2 in 25.2% and tumor histology was non-squamous in 64.8%, squamous in 25.1% and unknown in 12.8% (Table 1). All patients had metastatic disease at diagnosis. First-line treatment comprised chemotherapy in 70.4%), IO monotherapy in (18.7%), and targeted therapy in 13.5%. Among chemotherapy -treated patients, 674 (96.6%) received platinum-based chemotherapy and carboplatin-based doublet or triplet chemotherapy was the most commonly administered regimen 72.4% of chemotherapy- treated patients]., Table 2). In the overall population, patients (29.5%) received 2 L therapy, which was chemotherapy in (37.1%), IO monotherapy in (52.5%) and targeted therapy in (13.1%., Table 2).

The efficacy of immune checkpoint inhibitors (ICIs) in elderly patients with non-small cell lung cancer (NSCLC) has been a subject of extensive research. Studies indicate that advanced age does not significantly reduce the efficacy of immunotherapy. For instance, a retrospective analysis found that response rates and survival outcomes were similar across different age groups, suggesting that ICIs can be effective irrespective of age, provided the patients have an optimal performance status at baseline[3]. However, it is noted that patients older than 75 years may benefit less from ICIs, potentially due to immunosenescence, which refers to the reduced activity of the immune system with age[1,5]. The safety profile of ICIs in elderly patients is generally favorable compared to traditional chemotherapy. Immunotherapy is associated with reduced toxicity, making it an attractive option for older patients who often have comorbidities and reduced organ function. Studies have shown that the incidence of severe adverse events is comparable between younger and older patients and no significant increase in toxicity was observed in the elderly population.

Despite the promising outcomes, there are challenges in treating elderly NSCLC patients with immunotherapy. The phenomenon of immunosenescence may contribute to primary resistance to ICIs in older patients, necessitating further research to understand the molecular mechanisms involved. Additionally, elderly patients are often under-represented in clinical trials, which limits the generalizability of trial results to this population. There is a need for prospective studies specifically targeting older and frail patients to optimize treatment strategies. Given the current evidence, ICIs should be considered for elderly NSCLC patients, especially those with a good performance status. The combination of immunotherapy with other modalities like radiotherapy may offer additional benefits and should be explored further. It is crucial to develop reliable biomarkers to predict which elderly patients will benefit most from immunotherapy, allowing for more personalized treatment approaches. Immunotherapy, particularly immune checkpoint inhibitors (ICIs), has become a pivotal treatment for non-small cell lung cancer (NSCLC). Studies indicate that advanced age does not significantly reduce the efficacy of immunotherapy. For instance, a retrospective analysis showed that response rates and survival outcomes were similar across different age groups, including those aged 70 and above[1]. However, some studies suggest that patients older than 75 may experience less benefit, potentially due to immunosenescence, which is the gradual decline of the immune system with age[3]. The safety profile of ICIs in elderly patients is generally favourable compared to traditional chemotherapy. Toxicity levels were found to be comparable across age groups, with no significant increase in adverse events among older patients[3,6]. This makes immunotherapy a viable option for elderly patients who may not tolerate chemotherapy well due to comorbidities and reduced organ function[1,2]. Despite the promising outcomes, elderly patients are often underrepresented in clinical trials, leading to a lack of robust data specific to this demographic[7]. The phenomenon of immunosenescence poses a challenge,

Table 1: Patient Demographics in the Overall Population and in Subgroups Defined by 1 L Drug Class Received

	All patients (n=1063)	1 L chemotherapy (n=718)	1 L IO monotherapy (n=199)	1 L targeted therapy (n=146)
Proportion of study population, %	100	67.5	18.7	13.7
Median follow-up (range), months	8.1 (0.0-43.6)	8.7 (0.0-43.6)	13.6 (0.2-38.2)	17.2 (0.1-38.1)
Median age at diagnosis (range), years	70 (29-94)	70 (29-89)	68 (49-91)	72 (33-94)
Sex, n (%)				
Male	571 (53.7)	405 (56.4)	104 (52.2)	62 (42.4)
Female	492 (46.2)	313 (43.5)	95 (47.7)	84 (57.3)
Tumor histology, n (%)				
Adenocarcinoma	653 (61.4)	393 (54.7)	137 (68.8)	132 (90.4)
Squamous cell carcinoma	261 (24.5)	208 (28.9)	44 (22.1)	5 (3.4)
Large cell carcinoma	12 (1.1)	6 (0.8)	4 (2.0)	0
Not specified	137 (12.8)	111 (15.4)	14 (7.0)	9 (6.1)
TNM stage at diagnosis, n (%) T				
T X-4	968 (91.0)	657 (91.5)	180 (90.4)	131 (89.7)
N/A	95 (8.9)	61 (8.4)	19 (9.5)	15 (10.2)
N X-3	969 (91.1)	658 (91.6)	180 (90.4)	131 (89.7)
N/A	94 (8.8)	60 (8.3)	19 (9.5)	15 (10.2)
M				
M1a	542 (50.9)	357 (49.7)	121 (60.8)	66 (45.2)
M1a	184 (17.3)	126 (17.5)	28 (14.0)	30 (20.5)
M1b	328 (30.8)	230 (32.0)	50 (25.0)	50 (34.2)
M1c	9 (0.8)	5 (0.6)	0	0
ECOG PS score at diagnosis, n (%)				
0–1	789 (74.2)	523 (72.8)	167 (83.9)	99 (67.8)
2+				
EGFR+ status, n (%)b	274 (25.7)	195 (27.1)	32 (16.0)	47 (32.1)
Documented	20 (1.8)	1 (0.1)	0	18 (14.3)
Assumed				
ALK+ status, n (%)b	90 (9.7)	0	0	89 (70.6)
Documented	3 (0.3)	0	0	3 (1.5)
Assumed				
PD-L1+ status, n (%)b	18 (1.6)	0	0	18 (14.4)
Documented	12 (1.1)	4 (0.6)	8 (2.8)	0
Assumed	174 (18.2)	0	174 (97.1)	0

Table 2: First-Line and Second-Line Treatment Regimens

Regimen	Patients, n (%)	
	1 L therapy (n=1063)	2 L therapy (n=317)
Chemotherapy		
Carboplatin-based doublet or triplet therapy[a]	50.7	20.8
Carboplatin	0.4	0
Cisplatin-based doublet or triplet therapy[a]	18.3	3.2
Docetaxel	0.6	6.8
Docetaxel + nintedanib	0.6	6.4
Gemcitabine	0.4	0.4
Nintedanib	0	0.2
Paclitaxel	0	2.2
Pemetrexed	0.8	0
Vinorelbine	0.4	0.2
Immuno-oncology therapy		
Atezolizumab	0	12.2
Nivolumab	0.6	8.1
Pembrolizumab	18.2	34.3
Targeted therapy[b]		
Afatinib	7.8	2.8
Alectinib	0.3	0.8
Ceritinib	0.7	2.1
Crizotinib	2.1	2.3
Erlotinib	2.1	2.6
Gefitinib	3.5	2.1
Osimertinib	0.5	5.4

as it may affect the immune response to ICIs, potentially leading to primary resistance in older patients[5]. Therefore, there is a need for more targeted research to understand the molecular mechanisms and to identify biomarkers that can predict which elderly patients will benefit most from immunotherapy[5].

CONCLUSION

In summary, immunotherapy offers a promising treatment option for elderly patients with NSCLC, with efficacy and safety profiles comparable to those in younger populations. However, the impact of immunosenescence and the need for more inclusive clinical trials remain critical areas for future research.

Addressing these challenges will help optimize treatment strategies and improve outcomes for elderly patients with NSCLC. In summary, while immunotherapy presents a viable treatment option for elderly NSCLC patients, ongoing research is essential to address the unique challenges posed by aging and to refine treatment protocols for this growing patient demographic.

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