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Research Article

Immunotherapy in Geriatric Patients With Advanced Cancer

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Abstract

Objectives: Successful responses have been obtained in treating many solid and hematological cancers using PD-1 and PDL-1 inhibitors as immunotherapy treatments. Although cancer is more common in elderly patients, this group is generally not included in clinical trials. Therefore, studies involving geriatric patients cannot reflect real-life data. The aim of our study is to share the real-life data of patients aged 65 years and older who had different cancer diagnoses and received immunotherapy treatments.

Methods: In our study, patients aged ≥65 years who received immunotherapy treatment at our center between 16.02.2016 and 31.12.2019 were evaluated retrospectively. The primary outcome was treatment tolerance and progression-free survival (PFS). The secondary outcomes were the overall survey immunotherapy (OS_{im}).

Results: The median age to start immunotherapy was 70 years (range 66–78). Comorbid diseases were present in 20 (74%) of the patients. The most common primary malignancy type was renal cell cancer (RCC) (n=9, 33.3%). The median PFS was 7.3 (range 1–49) months. After immunotherapy, 2 patients (7.4%) had complete response (CR), 13 patients (48.1%) partial response (PR), 5 patients (18.5%) stable response and 7 patients (25.9%) progression. The most common side effect was fatigue, occurring in 44.4% (n=12) of patients. Moreover, 66.7% (n=18) experienced an immunotherapy-related adverse event (irAE), among which rash (21%), thyroid dysfunction (13%), and pneumonitis (12%) were the most common. None of the patients died due to treatment-related side effects.

Conclusion: Although the efficacy of immunotherapy treatments was affected by comorbid diseases among cancer patients, it was observed that the elderly patients have efficacy and tolerability in accordance with the literature.

Keywords: Advanced Cancer, Geriatri, Immunotherapy

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After the widespread evaluation of cancer patients, it is now well-known that more than 50% of them are over the age of 65. 26.6% of the patients are in the 75-84 age range.[1, 2] Although there are many reasons why cancer is common in the elderly, it is the modifications in the immune system that are considered to have the greatest effect.[1]

Immunotherapy drugs, which were started to be used after the relationship between cancer and the immune system was established, was found to be effective in the treatment of many cancers.[3] Successful responses have been obtained in the treatment of many solid and hematological cancers using PD-1 and PDL-1 inhibitors as immunotherapy treatments.[4-10] Although cancer is more common in elderly patients, this group is generally not included in clinical trials. Participant patients are generally those who are in good general health, do not have comorbid diseases and have good organ functions. Therefore, studies involving geriatric patients cannot reflect real-life data.[11,12]

The aim of our study is to share the real-life data of patients aged 65 and over, who were diagnosed with different cancer and received immunotherapy treatments.

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Methods

In our study, patients aged ≥65 years who received immunotherapy treatment at our center between 16.02.2016 and 31.12.2019 were evaluated retrospectively. Patients with incomplete files and follow-up information were excluded from the study.

Patient data were retrieved from patient interview information, patient files, and electronic medical records. Demographic characteristics, primary diagnoses, comorbidities, baseline hemogram values, treatment step, treatment response and final status of the patients were noted.

The primary outcome was treatment tolerance and progression-free survival (PFS). The secondary outcomes were overall survey immunotherapy (OS_{im}). The first immunotherapy date was accepted as the start date for OS_{im} and PFS. The endpoint for OS_{im} was the last follow-up date for surviving patients and the date of death for patients who died. the exit date for ex-patients. The endpoint for PFS was the progression date for progressive patients, the last control date for living patients, and the date of death for patients who died.

Statistical Analysis

SPSS 24 was used in our study. The categorical demographic characteristics of the patients were calculated by Chi-square and Fisher's exact test. Spearman's rank correlation test was used for univariate correlation analysis. In the univariate survey analysis, Kaplan Meirer was used and compared with the log-rank test. In addition, Cox regression test was used in multivariate analyzes. The statistical significance limit was accepted as 0.05 and below. The receiver operating characteristic (ROC) curve (AUC) test was used for the predictive value of NLR and other hematological parameters. The hazard ratio (HR) and 95% confidence interval (CI) values of the significant results were noted. If HR >1, it is accepted that there is an increased relative risk with regard to the reference category.

Results

In our study, 27 patients aged ≥65 years who started immunotherapy between 16.02.2016 and 31.12.2019 were evaluated retrospectively. Their clinical and demographic characteristics are presented in Table 1. The median age of starting immunotherapy was 70 years (range 66–78). Of the 27 patients, 19 (70.4%) were male and 8 (29.6%) were female. Comorbid diseases were present in 20 (74%) of the patients.

The most common primary malignancy type was renal cell cancer (RCC) (n=9, 33.3%). 19 (70.4%) patients were at stage 4 at the time of diagnosis. Brain metastasis was observed in 3 (11.1%) patients; liver metastasis in 5 (18.5%); lung metastasis in 20 (74.1%); bone metastasis in 11 (40.7%); and metastases of other regions in 4 (14.8) (1 breast, 2 suprarenal, 1 spleen). Nine (33.3%) of the 27 patients underwent an op-

Table 1. Patients demographics and treatment details

Age	
Median	70 (66-78)
Sex	
Female	8 (29.7)
Male	19 (70.4)
Comorbidity	
None	7 (25.9)
Hypertension	11 (40.7)
Diabetes mellitus	3 (11.1)
Diabetes mellitus+hypertension	2 (7.4)
Hypothyroidism	2 (7.4)
Chronic obstructive pulmonary disease	1 (3.7)
Arrhythmia	1 (3.7)
Primary	
Small cell lung cancer	5 (18.5)
Non-small cell lung cancer	6 (22.2)
Malignant melanoma	5 (18.5)
Renal cell cancer	9 (33.3)
Bladder cancer	1 (3.7)
Hodgkin lymphoma	1 (3.7)
Diagnose stage	
Stage 2	2 (7.4)
Stage 3	6 (22.2)
Stage 4	19 (70.4)
Operation	
No	18 (66.7)
Yes	9 (33.3)
Radiotherapy	
No	20 (74.1)
Yes	7 (125.9)
Total Tx step	
1	3 (11.1)
2	20 (74.1)
3	3 (11.1)
4	1 (3.7)
Immunotherapy step number	
First	8 (29.6)
Second	17 (63)
Third	1 (3.7)
Fourth	1 (3.7)
Immunotherapy	
Atezolizumab	7 (25.9)
Nivolumab	14 (51.9)
Nivolumab+Ipilimumab	1 (3.7)
Pembrolizumab	5 (18.5)
Brain metastasis	
No	24 (88.9)
Yes	3 (11.1)

Table 1. Cont.

Liver metastasis	
No	22 (81.5)
Yes	5 (18.5)
Lung metastasis	
No	7 (25.9)
Yes	20 (74.1)
Bone metastasis	
No	16 (59.3)
Yes	11 (40.7)
Basale Neu	
Median	6800 (3800-9800)
Basale Lymph	
Median	1250 (800-1800)
Basale PLT	
Median	365000 (156000-478000)
Basale NLR	
Median	5.16 (3.17-9.75)
IT side effect	
No	26 (96.3)
Yes	1 (3.7)
Immunotherapy response	
CR	2 (7.4)
PR	13 (48.1)
Stable	5 (18.5)
Progression	7 (25.9)
Treatment after immunotherapy	
None	25 (92.6)
Tafinlar & Mekinist	1 (3.7)
Carboplatin paclitaxel	1 (3.7)
Last status	
Alive	17 (63)
Exitus	10 (37)

eration. Radiotherapy (RT) was administered to 7 (25.9%) patients. Immunotherapy was administered in 17 (63%) patients in the second step, most commonly with nivolumab (n=14; 51.9%).

After immunotherapy, 2 patients (7.4%) had complete response (CR), 13 patients (48.1%) partial response (PR), 5 patients (18.5%) stable response and 7 patients (25.9%) progression The most common side effect was fatigue, occurring in 44.4% (n=12) of patients. Moreover, 66.7% (n=18) experienced an immunotherapy-related adverse event (irAE), among which rash (21%), thyroid dysfunction (13%), and pneumonitis (12%) were the most common. Of the irAEs, 94.4% (n=17) were grade 1–2 in severity and the remaining (5.6%) was grade 3. None of the patients was died due to treatment-related side effects. Treatment was discontinued in 1 patient due to the development of grade 3 immunotherapeutic hepatotoxicity.

OS_{im} Detailed Analysis

During the follow-up period, 10 (37%) patients died. Median OS_{im} was 10 (range 2–49) months. The OS_{im} was 87.9% for 4 months, OS_{im} 83.5% for 6 months, OS_{im} 62.2% for 1 year, and OS_{im} 54.4% for 18 months.

Median OS_{im} in women was 6.6 (range 2–44) months, whereas in men, 10.8 (range 3–49) months, but the difference was not significant (p=0.064).

Median OS_{im} was 7.8 (range 6.5–12) months in small cell lung cancer patients, 3.8 (range 1–5) months in non–small cell lung cancer patients, 16 (range 4–49) months in malignant melanoma patients, 24 (range 4–49) months for patients with RCC, 44 months in the patient with Hodgkin lymphoma, and 3 months in the patient with bladder cancer.

A significant relationship was observed between the response to immunotherapy and OS_{im} (p=0.004). Median OS_{im}; 35 (range 20–49) months in patients observed CR; 14.5 (range 3–45) months in patients observed PR; it was 4.8 (range 3–7) months in patients with a stable response and 7.8 (range 2–14) months in patients who develop progression (Fig. 1).

The ROC curve analysis revealed no significant relationships between OS_{im} and the baseline neutrophil–lymphocyte ratio (NLR) (p=0.12) and baseline neutrophil (0.071), lymphocyte (p=0.48), and platelet (p=0.98) counts.

PFS Detailed Analysis

The median PFS was 7.3 (range 1–49) months. At 4 months, PFS was 84.4%; at 6 months, 74.5%; and at 1 year, 60%. The median PFS was 7.3 (range 5.8–11.9) months in small cell lung cancer patients, 3.3 (range 1.3–4.6) months in non–small cell lung cancer patients, 6 (range 2–16) months in malignant melanoma patients, 16 (range 4–49) months in patients with RCC, 44 months in the patient with Hodgkin

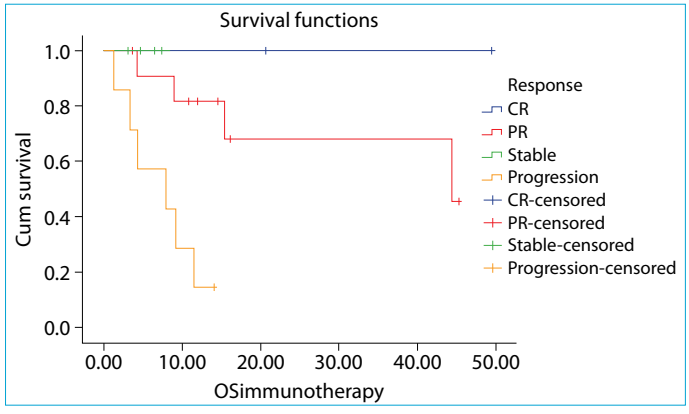

Figure 1. The relationship between the response to immunotherapy and OS_{im}.

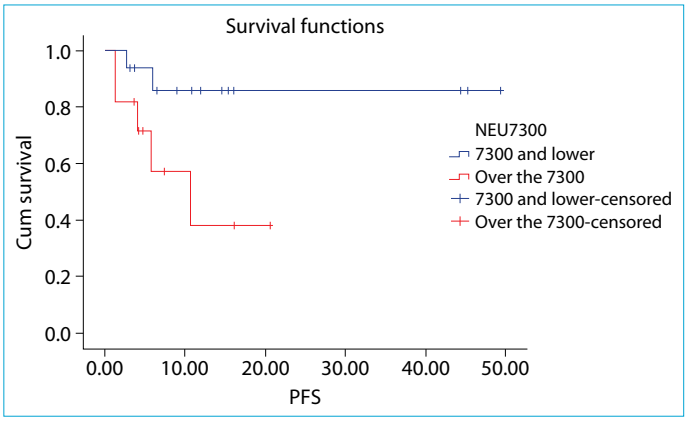

Figure 2. The relationship between the median PFS and baseline neutrophil count.

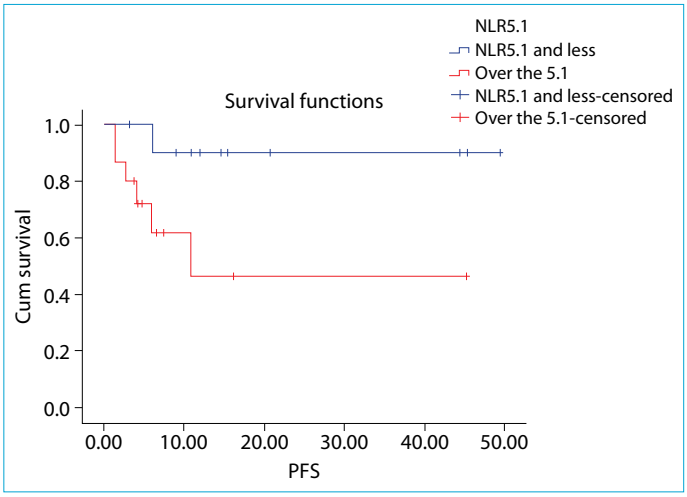

Figure 3. The relationship between the median PFS and baseline NLR.

lymphoma, and 3 months in the patient with bladder cancer.

Sex (p=0.20), comorbidity (p=0.58), history of surgery (p=0.85), primary malignancy (p=0.80), stage at diagnosis (p=0.79), total treatment steps (p=0.78), immunotherapy application step (p=0.88), and radiotherapy application (p=0.80) did not significantly affect PFS.

In addition, brain metastasis (p=0.85), lung metastasis (p=0.39), liver metastasis (p=0.31), bone metastasis (p=0.77), metastasis of other sites (p = 0.24), the type of immunotherapy (p=0.11), and immunotherapy initiation step (p=0.94) did not significantly affect PFS.

The ROC curve analysis revealed that the relationship between PFS and baseline lymphocyte (p=0.69) and baseline platelet (p=0.59) counts was not significant, but a significant relationship was observed between PFS and baseline neutrophil count. The threshold value for neutrophil=7300 was 71.4%, and the specificity was 30.0% (p=0.027; AUC 0.78; 95% confidence interval: 0.591–0.980).

The median PFS value of 16 patients with baseline neutrophil count ≤7300 was 11.3 (range 2–49) months and that of 11 patients with baseline neutrophil count >7300 was 4.6 (range 1–20) months (p=0.033, HR 2.5, 95% confidence interval: 0.40–16) (Fig. 2).

The ROC curve analysis revealed a significant relationship between baseline NLR and PFS. The threshold value for NLR=5.1 was 85.7%, and the specificity was 40.0% (p=0.007; AUC 0.85; 95% confidence interval: 0.696–0.980).

The median PFS value of 12 patients with baseline NLR of ≤5.1 was 13.2 (range 3–49) and that of 15 patients with NLR >5.1 was 4.6 (range 1–45) (p=0.034, HR: 4.3, 95% confidence interval: 0.40–47) (Fig. 3).

Discussion

Immunotherapies, especially PD-1 and PD-L1 checkpoint inhibitors, have revolutionized the treatment of advanced cancers. These agents, which we prefer to use rather than cytotoxic chemotherapy in many cancer treatments, show increased effectiveness in treating cancers when given either as monotherapy or in combination with other anticancer treatments chemotherapy, radiotherapy, or other immunotherapy agents). Immunotherapies are used in different steps in the treatment of different tumors in the metastatic period. However, although these therapies have proven to be very effective, the data regarding the safety and efficacy of immunotherapies in older adults with cancer are limited. When the results of our study were evaluated, it was found that the data on the efficacy and tolerability of the treatment in our geriatric patients with metastatic cancers were consistent with the literature.

In a study by Herbst et al. reported that patients with PD-L1-positive, advanced non-small-cell lung cancer had the median overall survival (OS) of 11.8 months in KEYNOTE-010,[13] and the median progression-free survival (PFS) of 3.7 months for those who had previously been treated. In our study, the median PFS was reported as 3.3 months in patients with advanced non-small-cell lung cancer, and our median PFS result is consistent with the literature.

In the CheckMate 067[14] study by Wolchok et al., which included patients with advanced melanoma, the median OS of patients who received nivolumab was 37.6 months, and the median PFS was 6.9 months. In the group that received nivolumab, 118 (37.3%) patients were 65 years and older. In advanced melanoma patients in our study, the median OS_{im} was 16 months, and the median PFS was 6 months. Our median PFS results are consistent with the literature, although all of our patients were 65 years or older.

In the study of IMpower133 [15] by Horn et al., which included 201 patients with metastatic small-cell cancers who

were treated with first-line atezolizumab treatment combined with carboplatin and etoposide, the median OS Was 12.3 months for the atezolizumab group and the median PFS Was 5.2 months. Among the patients who participated in the study, 44.8% Were aged 65 and over and the median OS of these patients was 12.5 months. The median OS_{im} was 7.8 months, and the median PFS was 7.3 months in our study, which included patients with advanced stage small-cell lung cancers who received primary immunotherapy treatment. The median PFS is compatible with the literature, and the reason for the finding of a lower median OS has been attributed to the fact that the average age of patients with small cell lung cancer was 71 and they had comorbid diseases.

The efficacy of immunotherapy (IL-2 and IFN) in the treatment of patients with metastatic renal cell carcinoma (RCC) was first shown in 1990. The efficacy among patients using IL-2 and IFN has been shown to be age-independent.[16] The CheckMate025 study was carried out by Motzer et al. to demonstrate the efficacy and safety of immunotherapy in the secondary step in patients with metastatic RCC. In this study, the median OS was 25 months, and the median PFS was 4.6 months. The study included 153 patients (37.3%) aged 65 years and over, and found that their health was improved significantly in HR 0.64, especially in the group aged 65-75 years who received the nivolumab treatment.[6] The median OS_{im} was 24 months and the median PFS was 16 months in patients with metastatic RCC in our study. Our results are consistent with the literature.

The most common side effect found in our study was fatigue, with immune-related adverse events (irAE) were observed as the greatest severity at 95% grade 1-2. Treatment was discontinued in one patient due to the development of grade 3 immunotherapeutic hepatotoxicity. IrAE control was achieved in all of our patients, and none died due to irAE.

The negative aspects of our study are that it is a retrospective study, it was performed in a heterogeneous disease group, and the number of patients was limited. The positive aspects of our study are that it is one of the first in which the efficacy and tolerability experiences of different immunotherapies are shared in a single center in a group of patients aged 65 years and older.

Conclusion

In conclusion, although the efficacy of immunotherapy treatments was affected by comorbid diseases among cancer patients, it was observed that the elderly patients have efficacy and tolerability in accordance with the literature and they should be evaluated in prospective studies on different patient groups and large patient populations.

Disclosures

Ethics Committee Approval: The study was approved by the Ethics Committee of Gülhane Training and Research Hospital with the decision number 19/28 (12.02.2019).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – B.Y., R.A.; Design – B.Y.; Supervision – B.Y.; Materials – R.A.; Data collection &/or processing – R.A.; Analysis and/or interpretation – R.A., B.Y.; Literature search – B.Y., R.A.; Writing – B.Y.; Critical review – B.Y., R.A.

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