Original Article

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Nivolumab Efficacy and Safety in Cancer Patients with Renal Dysfunction

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Abstract

Aim: Immune checkpoint inhibitors have transformed cancer treatment; however, clinical trials often exclude patients with renal dysfunction. This study aimed to evaluate the efficacy and safety of nivolumab in this population, addressing the limited available data.

Methods: A retrospective cross-sectional study was conducted on patients with baseline renal dysfunction who received nivolumab between 2018 and 2023. The safety and efficacy endpoints, including immune-related adverse events (irAEs), treatment response, and progression-free survival.

Results: Fifty patients with various malignancies were included, with 30% experiencing manageable worsening of renal function. Approximately 51% of patients experienced no irAEs, whereas 8% experienced grade 3 or 4 adverse events. The treatment discontinuation rate due to adverse effects was 2%. Significantly, 68% of patients showed treatment benefits, with a median progression-free survival of 450 days.

Conclusion: Nivolumab is effective and safe for patients with renal dysfunction, with comparable outcomes to those without renal impairment. Despite the occurrence of IrAEs, they were manageable, and we observed benefits in long-term progression-free survival.

Keywords: Nivolumab, immune checkpoint inhibitors, kidney diseases, drug-related side effects and adverse reactions, progression-free survival

Introduction

In recent years, immune checkpoint inhibitors have greatly improved the outcomes of patients with malignancies. Many patients receive immunotherapy or a combination of chemotherapy and immunotherapy (1). However, most clinical trials on immunotherapies do not include patients with kidney problems, even though managing this specific group of patients presents practical challenges. Conventional chemotherapy often does not work well for patients with kidney problems, raising concerns about the effectiveness and safety of immunotherapies in this population.

Nivolumab is an approved anti-programmed cell death protein 1 monoclonal antibody used to treat various cancers, including non-small-cell lung cancer (NSCLC), renal cell carcinoma (RCC), melanoma, urothelial carcinoma, squamous cell carcinoma of the head and neck, colorectal cancer, and esophageal and gastric cancer (2). The effects of nivolumab in patients with existing kidney problems have not been thoroughly evaluated. Like other immunotherapies, nivolumab may cause immune-related adverse events (irAEs), such as joint pain, colitis, hepatitis, pneumonitis, rash, vitiligo, nephritis, and endocrinopathies (3,4). Notably, dose adjustments for nivolumab are not recommended for patients with kidney problems.

In this study, we hypothesized that, based on the mechanisms of immunotherapy, nivolumab treatment would not worsen kidney problems or lead to a higher incidence of irAEs in patients with kidney impairment. We aimed to retrospectively analyze the safety and efficacy of nivolumab in this specific patient population, focusing on relevant clinical endpoints.

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Methods

Compliance with Ethical Standards

The study protocol and subject matter were reviewed and approved by the University of Health Sciences Turkey, Bakirkoy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (approval no.: 2024/47, date: 04.03.2024). The research design was retrospective cross-sectional. The ethics committee anonymized and approved the database information without obtaining consent.

Study Design

Patients with baseline renal dysfunction treated with nivolumab between 2018 and 2023 were retrospectively screened (Figure 1). All patients had chronic renal failure. The additional inclusion criteria consisted of receiving at least one dose of either nivolumab or baseline renal dysfunction. Renal dysfunction was defined as an estimated glomerular filtration rate (eGFR) ≤60 mL/min/1.73 m^2. The eGFR was calculated using the creatinine equation published by The Chronic Kidney Disease Epidemiology Collaboration (5). Patients who received combination chemotherapy or immunotherapy with multiple agents (ipilimumab + nivolumab or chemotherapy + nivolumab) were excluded.

Statistical Analysis

The statistical analyses were conducted using SPSS (Statistical Package for the Social Sciences) version 22.0 for Windows. Intergroup comparisons of normally distributed data were performed using Student's t-test, while non-normally distributed data were analyzed using the Mann-Whitney U test. We used these tests to determine demographic and clinical characteristics, laboratory findings, and renal dysfunction in patients. Additionally, the Kaplan-Meier estimator was used to determine the progression-free survival (PFS) and overall survival (OS) functions.

Results

Patients

Table 1 presents patient demographic data and characteristics. Fifty patients with advanced malignancies and baseline eGFR 60 mL/min/1.73 m^2 received nivolumab. The median age was 67.5 years [interquartile range (IQR): 60.7-71.2]. Most had renal cell carcinoma (70%), were male (72%), and had an Eastern Cooperative Oncology Group performance score of 0-2. All patients received prior treatment, and those with RCC received prior tyrosine kinase inhibitor therapy. The median nivolumab dose was 10 (IQR: 6-28) cycles. Baseline creatinine values ranged between 1.2-4.7 mg/dL (median 1.34, IQR: 1.2-1.56), and baseline eGFR ranged between 58-21 mL/min/1.73 m^2 (median 54 IQR: 44-57, excluding patients on dialysis). Three patients had an eGFR of 30 mL/min/1.73 m^2, two of whom stage had 5 end-stage renal failure and were undergoing regular hemodialysis.

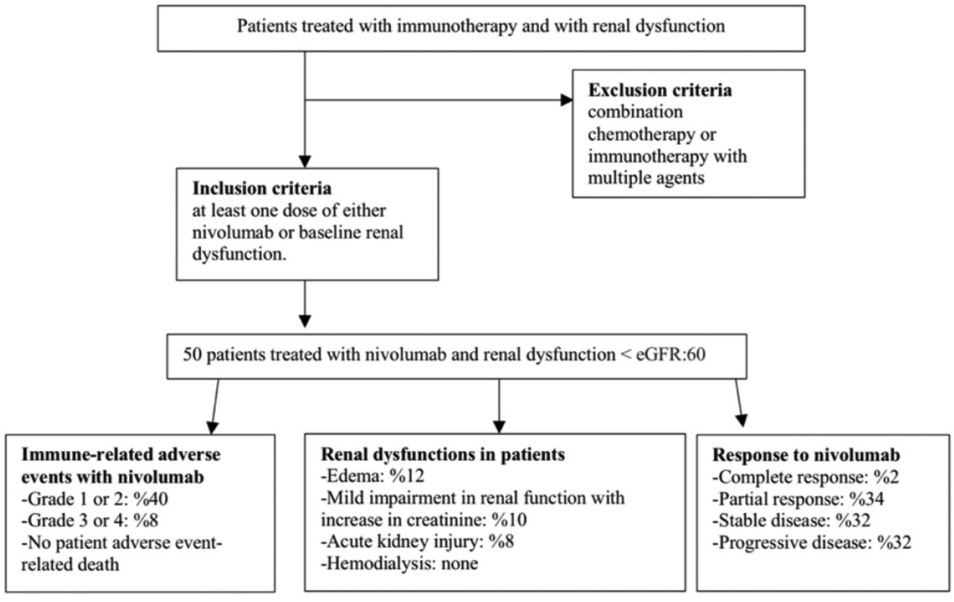

Figure 1. Flow chart of patient treatment

eGFR: Estimated glomerular filtration rate

Safety and Efficacy

Approximately half of the patients did not present with any grade (n=26, 51%). Grade 3 or 4 adverse events occurred in 8% of the patients who received nivolumab; the most common grade 3 or 4 adverse events were pneumonitis, hipofizitis, myocarditis, and nephrite. Grade 1 or 2 adverse events occurred in 40% of the patients; the most common grade 1 or 2 adverse events were thyroiditis and fatigue (Table 2).

One patient had metastatic RCC with a baseline eGFR of 40 mL/min/1.73 m^2 and concomitant brucellosis that occurred during treatment and experienced grade 3 nephritis that resolved with corticosteroids (prednisone 1 mg/kg). The other patient had NSCLC and cardiac dysfunction (ejection fraction 25-30%) and experienced grade 3 myocarditis that emerged concurrently and rapidly resolved with high-dose (1 mg/kg) prednisone. Another patient had grade 4 pneumonitis after nivolumab therapy and responded to high-dose prednisolone, but his imaging findings were consistent with hyper-progressive disease. Treatment was discontinued in these three patients.

We examined the effects of nivolumab on baseline renal dysfunction in patients. We examined renal worsening in 4 groups: development of edema with proteinuria, mild impairment in renal function with increased creatinine, development of acute kidney injury (AKI), and need for hemodialysis (Table 3). Worsening renal function occurred in 15 (30%) patients.

Thirty-four patients (68%) experienced treatment benefits (complete response, partial response, or stable disease). One (2%) patient had a complete response, 16 (32%) had stable disease as the best response, 17 (34%) had a partial response, and 16 patients (32%) had primary progressive disease. Sixteen patients (32%) had primary progressive disease (Table 4). The patient with a complete response received nivolumab for RCC and had a baseline eGFR: 42 mL/min/1.73 m^2. The patient is alive, and treatment is ongoing. Of the patients with partial responses, four had NSCLC and 13 had RCC. Among two patients on dialysis, one responded to therapy, and the other responded, although none of these patients experienced significant toxicities.

One patient experienced hyperprogression and death within 60 days of treatment initiation. This patient had grade 4 immune-related pneumonitis and was evaluated as having hyperprogression. The median PFS from initial treatment was 450 days with nivolumab (Figure 2), and the median OS was not reached.

Table 1. Baseline characteristics of the patients

Baseline characteristic (n=50)	n (%)
Median age (range)	67.5 (43-83)
Gender	
Male	36 (72%)
Female	14 (28%)
Disease state	
Renal cell carcinoma	35 (70%)
Nonsmall cell lung cancer	9 (18%)
Melanoma	4 (8%)
Urothelial cell carcinoma	1 (2%)
Mesothelioma	1 (2%)
ECOG	
0	14 (28%)
1	30 (60%)
2	6 (12%)
Comorbities	
Diabetes mellitus	14 (28%)
Hypertension	24 (48%)
Ischemic heart disease	13 (26%)
Chronic obstructive pulmonary disease	4 (8%)
Median nivolumab doses	10.5
Median creatinine level (range) mg/dL	1.34 (1-4.77)
Median eGFR mL/min/1.73 m^2	54

ECOG: Eastern Cooperative Oncology Group, eGFR: Estimated glomerular filtration rate

Table 2. Immune-releated adverse events with nivolumab

irAEs	Grade 1 or 2 (n)	Grade 3 or 4 (n)
Fatique	5	0
Hypophysitis	2	1
Thyroiditis	9	0
Myocarditis	0	1
Nephritis	1	1
Pneumonitis	3	1
Rash	3	0
Vitiligo	2	0

irAEs: Immune-related adverse events

Discussion

In this study, immunotherapy use in patients with cancer and baseline renal dysfunction resulted in irAE rates similar to those in previous clinical trials, including those in patients without renal dysfunction. Encouraging results were demonstrated in this heavily pretreated population with multiple comorbid illnesses. Clinical trials on nivolumab have included patients without renal dysfunction. In our study, the use of nivolumab therapy in patients with baseline renal dysfunction resulted in rates of irAEs and effectivity similar to those of clinical trials, including patients without renal dysfunction (6-8). Our patient group consisted of patients with multiple comorbid illnesses who received pretreatment. The 15-month PFS for the second treatment series and beyond was similar to that of other studies (9-11). This finding increased our confidence in using nivolumab for fragile patients with renal dysfunction.

Renal dysfunction was divided into four parameters and examined: development of edema with proteinuria, mild impairment of renal function with increased creatinine, development of AKI, and need for dialysis. None of the patients experienced worsening renal dysfunction until week 12. After the 12th week, peripheral edema was observed in six patients with proteinuria, but there was no increase in creatinine levels. Two of them were already on hemodialysis. This condition may be associated with inadequate hemodialysis. The volume of fluid administered with nivolumab may not have contributed to the progression of edema (100 cc). The patients responded to diuretic treatment, and they did not recur with the adjustment of oral diuretic dose. There was a moderate creatinine increase in 5 patients related to volume depletion. The oral intake of these patients needed to be improved. Response to intravenous isotonic liquid replacement. Four patients were diagnosed with acute renal injury according to the AKI criteria (12). Two of these cases involved immune-related nephritis, which was confirmed by renal biopsy.

Table 3. Renal dysfunction in patients	
No renal or clinic dysfunction	35 (70%)
Edema	6 (12%)
Increased creatinine in patients without AKI	5 (10%)
AKI	4 (8%)
Need for dialysis	0
AKI: Acute kidney injury	

Table 4. Response to nivolumab	
Response	**n (%)**
Complete response	1 (2%)
Partial response	17 (34%)
Stable disease	16 (32%)
Progressive disease	16 (32%)

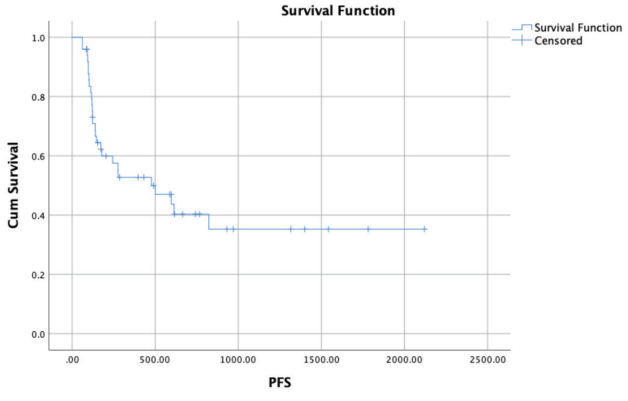

Figure 2. Progression-free survival
PFS: Progression-free survival

According to the American Society of Clinical Oncology guidelines (13), kidney biopsy should be considered in patients undergoing immunotherapy if they have proteinuria >3 g, oliguria, dysmorphic hematuria, or who do not respond well to initial treatment with corticosteroids. However, recent studies and case reviews have suggested that renal biopsy is important and should be performed even in patients who do not meet these criteria. In a recent case review, Rashidi et al. (14) recommended kidney biopsy when a clinical workup does not provide a clear explanation for AKI in the context of immune checkpoint inhibitor therapy, even in the absence of the traditional criteria for kidney biopsy, such as heavy proteinuria, hematuria, and pyuria (14).

Patients with immune-related nephritis responded to high-dose immunosuppressive therapy. One patient with grade 3 nephritis had concomitant brucellosis. Nivolumab could not be continued in this patient. However, nivolumab was continued in another patient after completion of immunosuppressive therapy. Compared with the literature, the risk of developing grade 3-4 immune side effects was the same in patients without renal dysfunction. No patient required additional hemodialysis with nivolumab therapy. Our two patients were already undergoing hemodialysis, and one patient on dialysis had previously undergone failed kidney transplantation.

Most clinical trials for cancer therapies usually exclude patients because they primarily focus on studying the effects and characteristics of these drugs, which is not feasible in dialysis patients (15). Although dose adjustment is not typically required in these patients, the risk of developing irAEs appears to be similar to that of the general population. This may be attributed to the fact that ICIs are not excreted through the kidneys, so it's logical that the frequency of adverse reactions is similar in both populations (16). Unfortunately, data are limited to the use of immunotherapy in patients undergoing kidney transplantation (17,18). The old allograft can be rejected upon initiating immunotherapy in patients undergoing hemodialysis (19,20). To prevent this, the dose regulation of immunosuppressive treatment can be performed before immunotherapy, and additional steroids can be administered if necessary (21). Hirsch et al. (22) described a case of acute rejection after immunotherapy in a patient undergoing dialysis who had previously undergone kidney transplantation. Mejia et al. (23) reported a case of a failed kidney allograft in a patient undergoing hemodialysis who received nivolumab and ipilimumab for metastatic papillary renal cancer. We can explain this situation using findings consistent with cell-mediated rejection induced by the blockade of the PD-1

pathway. This case series by Strohbehn et al. (24) discussed the effectiveness and safety of immunotherapy in 19 patients undergoing hemodialysis, with a high success rate. Four of these patients had previously undergone failed kidney transplantation. None of the patients showed any clinical signs or symptoms of rejection of the failed allograft when treated with immunotherapy, and none experienced abdominal pain (24). Similarly, the patient who underwent renal transplantation also did not experience renal rejection. They did not require additional immunosuppressive therapy. However, progressive disease was detected in scans obtained 3 months later.

Our study divided cancer outcomes in patients into four categories: complete remission, partial remission, stable disease, and progressive disease. Of all the patients studied, 65 had evidence of remission or stable disease. The response rate to treatment was similar to that reported in the literature for patients who did not experience renal function loss (25,26).

Study Limitations

The main limitations of our study are its retrospective and cross-sectional. Patient numbers overall were limited, limiting the ability to draw definitive conclusions. Most patients had stage 3 chronic kidney disease (eGFR between 30 and 60 mL/min/1.73 m^2). The number of patients with an eGFR 30 mL/min/1.73 m^2 was limited. This led to inadequate assessment in patients with significant renal damage. As a result, they might depict a relatively healthier cohort of patients with underlying renal dysfunction. However, conclusions regarding patients with end-stage renal failure cannot be reached. Despite these limitations, we believe this single-center experience is valuable because it will contribute to the literature by describing the side effects and efficacy in this fragile patient group. It is well known that data regarding patients with renal dysfunction are limited in the literature (27), highlighting the need for new research and treatments.

Conclusion

Although these patients can tolerate immunotherapy, which offers expectancy and moderate survival benefits, monitoring the side effects is crucial for safety. Nivolumab was shown to be efficacious and safe in these patients, with no increase in adverse events. Long-term studies are needed to confirm these findings.

Footnote

Ethics Committee Approval: The study protocol and subject matter were reviewed and approved by the University of Health Sciences Turkey, Bakirkoy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (approval no.: 2024/47, date: 04.03.2024).

Informed Consent: The research design was retrospective cross-sectional. The ethics committee anonymized and approved the database information without obtaining consent.

Authorship Contributions

Concept: E.D., Design: E.D., M.Y., D.T., Data Collection or Processing: G.S.E., A.G.S.D., Analysis or Interpretation: R.C., C.K., Literature Search: E.D., C.K., E.C.T., Writing: E.D.

Conflict of Interest: No conflicts of interest were declared by the authors.

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