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Research Article

QTc Interval Prolongation, Decreased Total Atrial Conduction Time, and Increased Pro-BNP Levels Associated with Immune Checkpoint Inhibitors: An Observational, Prospective, Surveillance Study

Canan Karan,[1] İpek Büber,[2] Cihan İlyas Sevgican,[2] Arzu Yaren,[3] İsmail Doğu Kılıç[2]

[1]Department of Oncology, Gaziantep Liv Hospital, Gaziantep, Türkiye
[2]Department of Cardiology, Pamukkale University Faculty of Medicine, Denizli, Türkiye
[3]Department of Oncology, Pamukkale University Faculty of Medicine, Denizli, Türkiye

Abstract

Objectives: We aimed to investigate potential cardiotoxic effects in patients with cancer treated with PD-1/PD-L1 inhibitors.

Methods: In this prospective observational cohort study, 52 cancer patients received immunotherapy in a tertiary care hospital. After elimination, 33 patients underwent at least two evaluations, and their examinations were analyzed. The electrocardiographic and echocardiographic assessment was performed on the first visit before ICI administration and three months after treatment.

Results: The mean age was 62 years. Thirty patients were at the metastatic stage. Most patients had non-small cell lung cancer, and 84% of patients had received anti-cancer treatment previously. Pro-BNP levels were higher in the post-treatment period (273.13±56.15 pg/mL vs. 812.32±419.1pg/mL; p=0.034; pre- and post-treatment, respectively). For Left ventricular stroke volume (LVSV) and cardiac output (CO) were lower in the post-treatment period (for LVSV: 61.19±13.72 mL vs. 57.80±10.15 mL; p=0.049; for CO: 5.00±1.14 L/min vs. 4.69±0.85 L/min, p=0.048). QTc interval was prolonged post-treatment period (433.57±26.19 msec vs. 451.86±39.41 msec; p=0.029; pre- and post-treatment, respectively). Total atrial conduction time was shorter in the post-treatment period (106.87±17.76 msec vs. 101.19±14.74 msec; p = 0.009; pre- and post-treatment, respectively).

Conclusion: Increased pro-BNP levels, prolonged QTc interval, and decreased total atrial conduction time were observed at short-term follow-up after ICI treatment.

Keywords: Diastolic function, elevated pro-BNP, immune checkpoint inhibitors, systolic function, QTc prolongation

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Antineoplastics are associated with serious cardiovascular adverse events such as supraventricular and ventricular arrhythmias, systolic and diastolic cardiac dysfunction, and coronary artery disease.[1] Emerging cancer therapies require better assessment of cardiotoxic effects. Cancer development is fundamentally driven by the fight against the host immune system, which leads to uncontrolled cell growth and metastasis. In recent years, vital drugs have

Address for correspondence: Canan Karan, MD. Department of Oncology, Gaziantep Liv Hospital, Gaziantep, Türkiye
Phone: +90 505 965 34 93 **E-mail:** karancanan16@gmail.com

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been researched and approved for the treatment of various cancers. Cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) and programmed death-1 (PD-1) receptors on the surface of T cells and programmed death-ligand 1 (PD-L1) pathways on tumor cells prevent immune response by inhibiting T cell activation.[2] Immune checkpoint inhibitors (ICIs) have prevented cancer development to progression and spread by targeting these immune system inhibitory pathways. ICIs have shown significant benefits for specific malignancies and their frequency of use is increasing. PD-1 inhibitors (pembrolizumab, nivolumab, cemiplimab), CTLA-4 inhibitors (ipilimumab, tremelimumab) and PD-L1 inhibitors (atezolizumab, durvalumab, avelumab) developed as drugs against these inhibitory pathways have been approved by the U.S. Food and Drug Administration (FDA) and Europan Medicines Agency (EMA) for various cancer types.[3] Boosting the immune system with ICIs through T-cell activation, which induces cancer response but may cause autoimmune toxicities.[4] Immune-related side effects are more likely to occur when dual ICIs, such as ipilimumab + nivolumab, or single-agent ICIs in combination with other agents (e.g. chemotherapy or targeted therapies) are used for cancer treatment. The most common immune-related toxicities are fatigue, rash, thyroid disorders, diarrhea, colitis, and elevated transaminases.[5] Cardiovascular toxicity associated with ICIs is rare but potentially fatal, and the true incidence of these events is unknown.[6] Although the most known cardiotoxic effect is fatal fulminant myocarditis, ventricular arrhythmias, conduction disorders, atrial fibrillation, non-inflammatory left ventricular dysfunction, pericarditis, and coronary artery disease would be observed.[7–11] There are no data on diastolic and atrial function that may affect morbidity in patients treated with ICIs.

Therefore, detecting immune-related cardiotoxicity is crucial. More prospective studies on immune-related cardiotoxicity in patients receiving ICIs are needed. In this prospective observational cohort study, we aimed to investigate the potential cardiac toxic effects on systolic, diastolic, and atrial function of patients treated with ICIs for different types of cancer.

Methods

Study Population

In this prospective observational cohort study, 52 patients who received immunotherapy as anti-cancer treatment in the medical oncology department of a tertiary care hospital between March 2021 and September 2021 were followed and observed for 159.44±66.46 days. Among the 52 patients planned for treatment, a total of 31 patients underwent at least two evaluations and their examinations were analyzed. Patients with acute or chronic infections, autoimmune and/or hematologic diseases and/or chronic liver and kidney diseases who are not suitable for immunotherapy were excluded from this study. Patients with pulmonary hypertension, severe valvular pathology, cardiac conduction disturbances, atrial fibrillation and/or low left ventricular ejection fraction (LVEF) before the first ICI administration were excluded. Four patients did not attend their appointments, and one patient was excluded from the control group due to acute anterior myocardial infarction after the first dose. As a result, the study was completed with data from 31 patients.

The study protocol was approved by the local institutional review board and conducted according to the Declaration of Helsinki (Approval no: 02/03/2021-05). Participants were informed about the study protocol, and their informed consent was obtained before the first echocardiographic evaluation.

Clinical data collection. Demographic and clinicopathologic characteristics of the patients were recorded before the first ICI application. Laboratory values, height, weight, blood pressure measurements, electrocardiogram (ECG) and echocardiographic evaluations were analyzed before the first dose and at the control visit. Follow-up visits were performed three months after immunotherapy.

Oncological status and treatment protocol of the study population. The entire cohort consisted of patients with pathologically confirmed locally advanced or metastatic cancer of any type who were treated with immunotherapy (nivolumab, atezolizumab, pembrolizumab) as a single agent until progression, death, or unacceptable side effects. In the study, ICIs doses were administered according to a specific routine for three months: (1) nivolumab 240 mg every two weeks, (2) atezolizumab 1200 mg every three weeks and (3) pembrolizumab 200 mg every three weeks. As mentioned above, follow-up visits were conducted three months after the initiation of immunotherapy for the early detection of cardiotoxicity.

Echocardiographic evaluation. Two-dimensional, M-mode, pulse wave doppler and pulse tissue doppler imaging (TDI) were used for echocardiographic evaluations. All cardiac chamber measurements were performed in appropriate echocardiographic windows according to current guidelines.[7] LVEF and left ventricular (LV) end-systolic volume were calculated by Simpson's method.[8] LV mass, relative wall thickness (RWT), LV stroke volumes and left atrial (LA) volumes were calculated using various formulas:

Cardiac output (CO) was calculated by multiplying LV Stroke volume (SV) and heart rate: (HR x CO=SV*HR/1000). Cardiac indices (CI) were calculated by dividing cardiac output (CO) by body surface area (BSA) according to the following formula: CI = CO/BSA. Left atrial volume indices (LAVI) were calculated as left atrial volume (LAV) divided by BSA: LAVI = LAV/BSA.

LA maximum and minimum volumes were estimated with the appropriate LA diameters using the formula above. Pre-contraction time refers to surface ECG measurements taken during the onset of the p-wave. LA volume estimates were made according to various formulas: (1) LA total stroke volume = LA maximum volume - LA minimum volume; (2) LA active stroke volume = LA pre-contraction volume - LA minimum volume; and (3) LA passive stroke volume = LA maximum volume - LA pre-contraction volume). Left atrial ejection fractions (LAEF) were calculated by dividing the LA total stroke volume by the LA maximum volume.

Electrocardiographic evaluation. QTc intervals were calculated with the Bazett formula.[9] Total atrial conduction times were defined as the time interval from the onset of the p wave on surface ECG to the peak of the A wave on TDI echocardiography. PA was defined as the time interval from the onset of the P wave on the surface electrocardiogram to the onset of the A wave obtained by the area defined in the TDI (septal, lateral, and tricuspid valve walls). Inter- and intra-atrium electromechanical delays were calculated by the formulas: (1) Inter-atrial electromechanical delay = PA lateral - PA tricuspid and (2) intra-atrial electromechanical delay = PA septum - PA tricuspid.

Statistical Analysis

Data were analyzed using SPSS software for Windows (IBM SPSS 25, IBM Corp., Armonk, NY). Shapiro-Wilk test was used to evaluate distribution. Continuous variables were expressed as mean±standard deviation, and categorical variables were summarized as numbers and percentages (n, %). Paired t- and Wilcoxon signed-rank tests were used depending on the distribution. P-value <0.05 was considered statistically significant.

Results

A total of 52 individuals were assessed at baseline, 33 of whom received at least two assessments, and their examinations were reviewed in detail. Therefore, the 31 patients who received immunotherapy monotherapy were included in our prospective observational study. The mean age of the patients was 62 years. Twenty-seven patients (81.8%) were male. Twenty-four patients (72.7%) had a history of smoking. All patients were receiving immunotherapy for locally advanced or metastatic disease.

The most common type of cancer in our study population was non-small cell lung cancer (NSCLC) with 13 patients (42.4%), including seven adenocarcinomas, three squamous cell carcinomas and one each of adenosquamous, large cell carcinoma and sarcomatoid. Only two patients with small cell lung cancer (SCLC) have been reported. Other types of cancer are divided into several types: renal cell carcinoma (n=7), bladder cancer (n=3), squamous esophageal cancer (n=2), cutaneous melanoma (n=2), hepatocellular carcinoma (n=1), malignant pleural mesothelioma (n=1), thymic carcinoma (n=1) and breast cancer (n=1) (Table 1). Twelve patients diagnosed with NSCLC received first-line platinum-based chemotherapy followed by nivolumab monotherapy, and one patient with 50% PD-L1 positivity received pembrolizumab monotherapy (Table 1). Patients diagnosed with SCLC who received first-line treatment with atezolizumab in combination with platinum-based chemotherapy were excluded from the statistical analysis. Patients diagnosed with renal cell carcinoma (RCC) received nivolumab monotherapy as second-line treatment after TKI (sunitinib or pazopanib) (Table 1). Malignant melanoma patients received immunotherapy after first line temozolomide treatment (Table 1). Other patients have achieved immunotherapy for salvage therapy, mostly after second-line chemotherapy or TKI therapy. Only one patient with NSCLC did not receive systemic therapy before ICI administration (Table 1). There were no patients receiving IO-IO combination therapy (Table 1). Eight patients received mediastinal radiotherapy (Table 1). The demographic data of the patients are summarized in Table 1.

Table 1. Demographic data of patients

	n	%
Gender, male	27	81.8
Age, years (mean)	62.76±9.74	
Stage of disease		
Locally advanced	3	9.0
Metastatic	30	90.9
Cerebral metastases	9	27.2
Comorbidities		
Diabetes mellitus	8	24.2
Hypertension	6	18.1
Coronary artery disease	5	15.1
History of Coronary artery bypass surgery	2	6.0
Patient's habits		
Smoking	24	72.7
Alcohol consuming	10	30.3
Patients who received radiotherapy		
Palliative radiotherapy	12	36.3
Mediastinal radiotherapy	8	24.2
Drug of choice		
Nivolumab	26	78.7
Atezolizumab	5	15.1
Pembrolizumab	2	6.0
Prior treatment		
Absent	4	12.1
Chemotherapy	13	39.3
Chemotherapy + Radiotherapy	6	15.1
Tyrosine kinase inhibitor	8	24.2

Table 2. Laboratory findings, weight and BSA of patients

Laboratory findings	Pre-treatment	Post-treatment	p
Weight, kg	70.10±12.66	69.68±13.25	0.31
BSA, kg/m^2	1.81±0.18	1.80±0.19	0.23
Troponin (ng/L)*	36.86±16.71	67.82±35.2	0.18
Creatinine (mg/dl) *	1.04±0.55	1.07±0.87	0.51
ALT (IU/L)*	31.23±11.69	19.87±3.22	0.78
TSH (mU/L)*	2.05±0.4	14.15±7.79	0.22
CRP (mg/L)*	32.38±6.31	47.32±12.05	0.31
NT-pro BNP (ng/L)*	273.12±56.15	812.32±419.1	0.034**

*: p value was calculated with Wilcoxon signed-rank test due to abnormal distribution of data, **: p<0.05. BSA: Body surface area, ALT: Alanine amino transferase, TSH: Thyroid stimulant hormone, CRP: C-reactive protein, NT-pro BNP: n terminal brain natriuretic peptide.

Table 3. Echocardiographic data of the patients

	Pre-treatment	Post-treatment	p
Diastolic diameter of LV, mm	46.62±4.00	46.84±4.17	0.55
Systolic diameter of LV, mm	30.16±3.17	30.25±3.03	0.79
RWT	0.41±0.06	0.41±0.04	0.20
LV Mass, gr	159.81±34.40	158.66±41.97	0.73
LV stroke volume, mL	61.19±13.72	57.80±10.15	0.049**
Cardiac output, L/min	5.00±1.14	4.69±0.85	0.048**
Cardiac index, L/min/m^2	2.76±0.66	2.61±0.50	0.08
LV end-systolic volume, mL	22.69±7.86	22.41±7.25	0.78
LV septum thickness, mm*	10.06±1.19	9.84±1.42	0.12
LV posterior wall thickness, mm*	9.59±1.10	9.50±0.95	0.40
LVEF*	61.40±2.51	61.07±2.98	0.33
MPI*	0.58±0.26	0.59±0.18	0.81
DT, msec*	139.72±46.48	135.29±39.09	0.24
TAS, cm/s*	13.32±2.52	12.84±1.97	0.20
TAPSE, mm	19.39±2.72	19.55±2.78	0.62
e/e' ratio	8.65±3.15	9.24±3.18	0.11

*: p value was calculated with Wilcoxon signed-rank test due to abnormal distribution of data, **: p<0.05. LV: Left ventricle, RWT: Relative wall thickness, LVEF: Left ventricle ejection fraction, MPI: myocardial performance index, DT: Deceleration time, TAS: Myocardial systolic velocity, TAPSE: Tricuspid annular plane systolic excursion.

Patients were followed for 159.44±66.46 days (minimum: 89 days, maximum: 323 days) after immunotherapy. Brain natriuretic peptide (NT-proBNP) levels were significantly higher in the post-treatment period (812.32±419.1 pg/mL and 273.13±56.15 pg/mL, p=0.034) (Table 2).

The LV echocardiographic evaluations of the patients before and after treatment are shown in Table 3. Left ventricular stroke volume (LVSV) and cardiac output (CO) values were statistically lower in the post-treatment control (for LVSV: 61.19±13.72 mL and 57.80±10.15 mL, p=0.049; for CO: 5.00±1.14 L/min and 4.69±0.85 L/min, p=0.048; respectively). CI measurements were lower in the post-treatment control, but it was not statistically significant (2.76±0.66 L/min/m^2 and 2.61±0.50 L/min/m^2, p=0.085).

Atrial measurements of the patients are shown in Table 4. LAEF was detected higher in the post-treatment period (68.26±13.75 and 70.17±11.98, p=0.036).

ECG measurements and electromechanical delays of the patients are presented in Table 5. The QTc interval was prolonged in the posttreatment period (433.57±26.19 msec and 451.86±39.41 msec, p=0.029). Total atrial conduction time was shorter in the post-treatment period (106.87±17.76 msec and 101.19±14.74 msec, p=0.009).

One patient was excluded from the analyses due to receiving a chemo-immunotherapy combination. His first-line treatment regimen consisted of a combination of carboplatin, etoposide, and atezolizumab. This patient developed an acute anterior myocardial infarction following the first

Table 4. Atrial measurements of the patients (echocardiographic data)

	Pre-treatment	Post-treatment	p
LA vertical diameter, mm	49.06±7.08	48.78±6.40	0.70
LA horizontal diameter, mm*	37.31±3.14	37.06±3.85	0.36
LA maximum volume, mL*	42.80±14.80	39.48±13.30	0.04**
LA pre-contraction volume, mL	24.22±9.65	22.20±8.14	0.12
LA minimum volume, mL	13.52±7.17	11.73±6.21	0.06
LA total stroke volume, mL*	29.27±12.40	27.75±11.41	0.95
LA active stroke volume*	10.70±6.56	10.47±5.59	0.45
LA passive stroke volume*	18.58±12.41	17.28±10.24	0.98
LAEF*	68.26±13.75	70.17±11.98	0.036**
LAVI*	23.66±7.67	21.92±6.40	0.08
RA vertical diameter, mm*	28.61±4.95	27.70±3.96	0.043**
RA horizontal diameter, mm*	41.22±5.07	40.48±4.96	0.049**

*: p value was calculated with Wilcoxon signed-rank test due to abnormal distribution of data, **: p<0.05. LA: Left atrium, LAEF: Left atrium ejection fraction, LAVI: Left atrium volume index, RA: Right atrium.

Table 5. Electrocardiographic measurements and electromechanical delays of the patients

Measurements	Pre-treatment	Post-treatment	p
PR interval, msec	148.50±20.29	139.50±19.32	0.05
QRS duration, msec	85.69±15.38	88.46±17.25	0.16
QTC interval, msec	433.57±26.19	451.86±39.41	0.029**
Heart rate, bpm	79.64±14.01	87.43±19.28	0.10
Total atrial conduction time, msec*	106.87±17.76	101.19±14.74	0.009**
PA septal, msec*	41.65±12.25	40.84±12.64	0.67
PA lateral, msec*	55.23±16.70	53.19±14.93	0.40
PA tricuspid, msec*	28.03±11.84	26.26±9.44	0.35
Intra-atrial electromechanical delay, msec*	13.61±8.89	14.58±8.83	0.11
Inter-atrial electromechanical delay, msec	27.19±13.38	26.94±12.40	0.84

*: p value was calculated with Wilcoxon signed-rank test due to abnormal distribution of data, **: p<0.05. PA: The time interval from the onset of the P wave on surface electrocardiogram to the beginning of A wave obtained by tissue Doppler imaging.

administration of therapy and subsequently underwent revascularization of the proximal left anterior descending artery. He was a 59-year-old man with advanced-stage small cell lung cancer (SCLC) and had two chronic comorbidities: diabetes mellitus and chronic obstructive pulmonary disease (COPD). He also had a 40 pack-year smoking history.

Discussion

This study was conducted using clinical, electrocardiographic, and echocardiographic follow-up data of patients treated with ICI. The most relevant findings are described below. No deaths from cardiac toxicity occurred during the follow-up period. No cases of myocarditis were observed during the study period. Unlike NT-pro BNP values, there was no significant increase in the patients' troponin values. While cardiac output and LV stroke volume decreased, no significant change was observed in diastolic parameters and LVEF. While a decrease in right atrium LA maximum volume was observed, LAVI did not change. Additionally, the decrease in total atrial conduction time and the prolongation of the QTc interval are interesting.

Cancer treatment-related cardiotoxicity refers to damage to the heart and cardiovascular system during or after cancer treatment. It is commonly defined as a decrease in left ventricular ejection fraction (LVEF) by 10% to below 50%, with or without symptoms of congestive heart failure (CHF).[12] Newer treatments, including chemotherapy, radiotherapy, and immunotherapies, can exacerbate cardiovascular side effects such as myocardial dysfunction, heart failure, myocarditis, coronary artery disease, arrhythmias, and myocardial infarction.[1–3,5,13] Well-known cardiotoxic agents include anthracyclines (e.g., doxorubicin), HER2-targeted therapies (e.g., trastuzumab), tyrosine kinase inhibitors (TKIs), and immunotherapies (e.g., nivolumab, ipilimum-

ab).[2,5,13–15] These agents may cause cardiotoxicity through distinct mechanisms, such as irreversible damage (type 1) or reversible myocardial dysfunction (type 2).[15,16] Surveillance for cardiotoxicity is crucial as it may necessitate treatment modifications, potentially reducing cancer treatment efficacy, impairing quality of life, and in rare cases, causing cardiac-related mortality. Immune-related cardiotoxicity, however, is not yet clearly defined, and ICI therapy may increase cardiotoxic risks, particularly in patients with prior or concurrent chemotherapy-related cardiac damage.

Although myocarditis was not detected in our study, it remains a rare but potentially fatal complication of immune checkpoint inhibitor (ICI) therapy, necessitating vigilant monitoring. Both preclinical and clinical evidence indicate that ICIs can induce T cell–mediated myocarditis through loss of immune tolerance to cardiac antigens.[17–19] PD-L1 may have a cardioprotective role, while dual ICI therapies, such as ipilimumab and nivolumab, may increase the risk of 'on-target' cardiac effects.[18–20] The incidence of myocarditis ranges from 0.04% to 1.14%, with a high mortality rate of 25% to 50%.[21,22] Given the variability in onset (2 to 454 days),[23] we planned to assess cardiac outcomes 3 months after ICI initiation.

In this present study, elevated BNP levels in the absence of a corresponding rise in troponin suggest the presence of functional, non-inflammatory cardiotoxicity following immune checkpoint inhibitor (ICI) therapy. Although no clinical arrhythmias were documented, the observed QTc interval prolongation is of potential concern, as QTc values exceeding 500 ms or increases of more than 50 ms from baseline are associated with a heightened risk of torsades de pointes (TdP).[24] While BNP elevation and QTc prolongation reflect distinct aspects of cardiac physiology—myocardial wall stress and ventricular repolarization, respectively—they may share common underlying mechanisms, including myocardial strain, subclinical inflammation, or autonomic dysfunction.[25,26] Notably, a recent meta-analysis of 32 clinical trials demonstrated a significantly increased risk of both all-grade and grade 3–5 arrhythmias with PD-1/PD-L1 inhibitors combined with chemotherapy, compared to chemotherapy alone.[27] These findings underscore the importance of routine QTc monitoring and proactive management of modifiable risk factors, such as concomitant QT-prolonging medications and electrolyte imbalances, during ICI therapy. However, the clinical implications of these findings remain to be fully elucidated, particularly in the context of small observational studies lacking longitudinal outcome data.

Cardiac dysfunction related to cancer treatment is typically defined by a decline in left ventricular ejection fraction (LVEF);[28] however, the role of diastolic dysfunction remains less well established, with conflicting evidence regarding its timing, association with treatment, and prognostic implications.[29] In our study, no deterioration in LVEF was observed. While some studies have reported that changes in diastolic parameters during anthracycline- or trastuzumab-based therapies may predict future systolic dysfunction,[30–32] others have not confirmed this relationship.[33] To date, the impact of immune checkpoint inhibitors (ICIs) on diastolic and left atrial (LA) function has not been well investigated. In this cohort, no evidence of diastolic dysfunction was identified; left atrial volume index (LAVI) remained unchanged, and LA contractile function improved following treatment. Furthermore, total atrial conduction time, a surrogate marker for atrial remodeling and a known predictor of atrial fibrillation (AF), was significantly reduced post-treatment, and no AF episodes were recorded. Although not statistically significant, a trend toward reduction in LA diameter may have contributed to these findings. Collectively, these results suggest that ICI therapy does not adversely affect diastolic or atrial function, at least over the short term.

In our study, cardiac systolic and diastolic functions remained preserved; however, a significant prolongation of the QTc interval, a reduction in total atrial conduction time, and an elevation in proBNP levels were observed at the three-month follow-up following ICI therapy. These alterations may indicate an increased risk for cardiac arrhythmias, including Torsades de Pointes. Currently, standardized diagnostic criteria and uniform biomarker monitoring protocols for immune-related cardiotoxicity are lacking. The NCCN guidelines recommend cardiology consultation and a range of diagnostic evaluations (e.g., ECG, echocardiography, cardiac biomarkers, inflammatory markers, cardiac MRI, catheterization, or myocardial biopsy) when myocarditis, pericarditis, or vasculitis is clinically suspected.[34] Based on our findings, we propose that cardiac monitoring is essential during ICI therapy. A comprehensive assessment of pre-existing cardiac disease, comorbidities, and polypharmacy should be undertaken prior to treatment initiation, with subsequent monitoring—including ECG, echocardiography, and cardiac biomarkers—at regular intervals (every 2 to 3 months) or in the event of new cardiovascular symptoms to facilitate early detection and management of immune-related cardiotoxicity.

This study has several limitations. First, it is a single-center study with a small sample size and short-term follow-up, which may limit the generalizability and long-term clinical implications of the findings. Second, cardiac magnetic resonance imaging (MRI) and myocardial strain imaging—both valuable tools for detecting subclinical cardiotoxicity—were not utilized. Third, no patients received combination immune checkpoint inhibitor therapy, which is known to increase the risk of immune-related adverse events and

may have altered cardiac outcomes. Lastly, all echocardiographic assessments were performed by a single operator, which, while reducing inter-observer variability, may introduce measurement bias.

Conclusion

Our study demonstrated that, during short-term follow-up after immune checkpoint inhibitor (ICI) therapy, cardiac systolic and diastolic functions remained stable, while QTc interval prolongation and a reduction in total atrial conduction time were observed. These electrophysiological changes may reflect early subclinical alterations in cardiac function. However, the clinical relevance of these findings remains uncertain. Therefore, long-term prospective studies with larger patient cohorts are warranted to better define the cardiovascular effects of ICI therapy and to determine their prognostic implications.

Disclosures

Ethics Committee Approval: The study was approved by the Pamukkale University Ethics Committee (date: 02.03.2021, no: 05).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Consept – C.K., İ.B., A.Y., İ.D.K.; Design – C.K., İ.B.; Supervision – İ.D.K., C.İ.S.; Materials – C.İ.S., C.K., İ.B.; Data collection-processing – C.K., İ.B.; Analysis and/or interpretation – C.İ.S.; Literature search – C.K., İ.B., C.İ.S.; Writing – C.K., İ.B.; Critical review – İ.D.K., A.Y., C.İ.S.

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