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Analysis of Vascular Endothelial Growth Factor Receptor Tyrosine Kinase Inhibitor-Induced Left Ventricular Dysfunction

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Abstract

Vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitor (VEGFR-TKI), an oral molecular targeted drug, reportedly causes serious adverse cardiovascular events such as hypertension and left ventricular failure. The association between VEGFR-TKI-induced hypertension and heart failure with preserved left ventricular ejection fraction (LVEF) (HFpEF) has been previously studied. Therefore, we investigated the relationship between hypertension onset and associated cardiac diastolic dysfunction due to VEGFR-TKI use. Patients who used VEGFR-TKIs (target drugs: sunitinib, axitinib, sorafenib, pazopanib, and cabozantinib) at the Department of Urology, Hokkaido Cancer Center were recruited between May 2009 and October 2021 and were divided into two groups based on whether their blood pressure was elevated during VEGFR-TKI use. The markers of left ventricular diastolic function (E/A, Dct (ms), mean E/e, septal e') and left ventricular systolic function (LVEF, LVDd, and LVDs) were evaluated. LVEF and mean E/e in the elevated blood pressure group (n = 41) showed significant changes before and after treatment. LVEF values (contractile function markers) in the TKI-HT (+) group significantly decreased from 70.7% ± 6.8% before treatment to 68.3% ± 7.8% after treatment (p = 0.03). Conversely, no significant difference was observed for any ventricular systolic function marker in the TKI-HT (−) group. E/e (diastolic function marker) in the TKI-HT (+) group significantly decreased from 11.9% ± 3.6% before treatment to 10.3% ± 3.0% after treatment (p = 0.02). However, no change was observed in any ventricular diastolic function marker in the TKI-HT (−) group. The results of this study suggest that cardiac function may be affected in patients using VEGFR-TKI. Furthermore, appropriate an-

tihypertensive treatment and early monitoring with regular echocardiography, even in asymptomatic patients, may help prevent VEGFR-TKI-induced deterioration of systolic and diastolic function.

Keywords

VEGFR-TKI, Left Ventricular Dysfunction, Cardio-Oncology, HFrEF, HFpEF, CTRCD

1. Introduction

Renal cell carcinoma is a cancerous transformation of cells in the renal parenchyma, and the condition often progresses undetected without characteristic symptoms. Though renal cell carcinoma is difficult to diagnose in its early stages because it progresses asymptomatically, the widespread use of ultra-sound scans and CT scans during routine examinations has made its detection possible [1]. Moreover, they are often inoperable, and drug therapy is the treatment of choice. To date, the mainstay of drug therapy has been cytokines (using interferon-α (IFN-α) and interleukin-2); however, owing to their insufficient therapeutic effects, the development of new therapeutic agents was desired [2]. In 2008, the vascular endothelial growth factor receptor tyrosine kinase inhibitor (VEGFR-TKI) sorafenib was introduced, and thereafter, various VEGFR-TKIs have become available for renal cell carcinoma.

VEGFR-TKIs are broadly classified into antibody drugs against vascular endothelial growth factor (VEGF), vascular endothelial growth factor receptor (VEGFR), multi-kinase inhibitors against VEGFR, fibroblast growth factor receptors (FGFRs), and platelet-derived growth factor receptor (PDGFR) kinases. More than 10 different drugs are used in various types of cancer. VEGFR-TKIs have shown beneficial effects for the treatment of a wide range of solid malignancies [3].

In recent years, the emergence of novel therapies such as molecular-targeted drugs and immune checkpoint inhibitors has improved the outcome of cancer treatment; however, an increasing number of cancer patients experience cancer treatment-related cardiovascular disease (CTRCD), which hinders the continuation of cancer treatment. This has led to a call for onco-cardiology, which has the completion of cancer treatment and the improvement of prognosis as its common goal [4]. CTRCD is the most alarming cardiovascular complication of cancer therapy, and is characterized by a decreased left ventricular ejection fraction (LVEF) of at least 10% and a lower limit of normal (typically 53%), with or without symptoms of heart failure [5]. Therefore, the necessity for monitoring and safety of therapeutic interventions for cardiovascular complications has been emphasized in advancing cancer treatment appropriately. Anthracycline and other drugs induce adverse events of cardiovascular toxicity; though such events have been sufficiently managed, they warrant further attention in the medical field. Con-

versely, VEGFR-TKIs cause serious cardiovascular adverse events through mechanisms that differ from those of conventional anthracyclines, such as hypertension, myocardial infarction, and aortic dissection [4] [6] [7]. Previous, experimental studies on the adverse effects of the VEGFR-TKI sunitinib on mouse cardiomyocytes have reported a 7-fold higher incidence of cardiomyocyte apoptosis in hypertensive mice compared to normotensive mice [7]. In this regard, hypertension may induce VEGFR-TKI-derived cardiac dysfunction. The frequency of hypertension is high in the TKI group in general, and left ventricular systolic dysfunction induced by TKI-derived hypertension can trigger severe heart failure in some cases [6] [8]. Therefore, elevated blood pressure may result in a dose reduction or withdrawal of VEGFR-TKI.

Heart failure, in about 40% of cases, may be caused by left ventricular diastolic dysfunction [9]. Diastolic dysfunction is associated with comorbidities, such as hypertension, and it is possible that hypertension, which is also an adverse event of VEGFR-TKIs, affects the diastolic function of the left ventricle. However, a system for monitoring blood pressure and cardiac function after VEGFR-TKI administration by pharmacists has not been established, and the effects of VEGFR-TKI administration on blood pressure and cardiac function in renal cell carcinoma have not been reported in actual clinical practice.

In this study, we investigated the effect of VEGFR-TKI-induced hypertension on left ventricular function in renal cell carcinoma to establish a monitoring system for CTRCD.

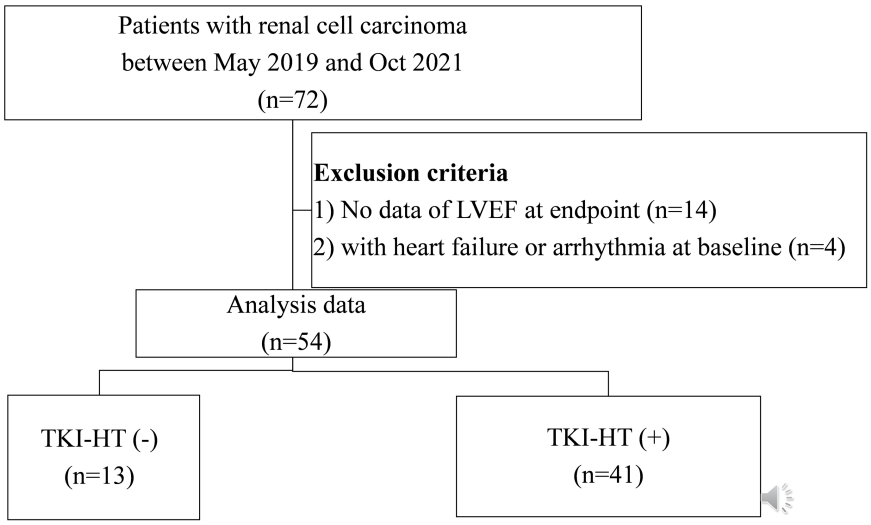
2. Materials and Methods

2.1. Study Design

The study included patients who visited the Department of Urology at the Hokkaido Cancer Center between May 1, 2009, and October 31, 2021, and 1) who received monotherapy with VEGFR-TKIs (sunitinib, axitinib, sorafenib, pazopanib, cabozantinib), 2) underwent an echocardiographic examination before and after VEGFR-TKI treatment, and 3) had an EF ≥ 50% before starting treatment. Exclusion criteria were: 1) patients with atrial fibrillation, 2) patients with tumor infiltration into cardiac tissue, and 3) patients who changed to anticancer agents other than VEGFR-TKI during the echocardiography period (**Figure 1**).

2.2. Survey Items

Data were collected retrospectively from the medical records. The surveyed patient background items were age, sex, body mass index complications (hypertension, diabetes, coronary artery disease, and presence or absence of dyslipidemia), and the type of VEGFR-TKI administered. To evaluate cardiac function markers, markers of diastolic dysfunction [E/A (ratio of E-wave velocity ÷ A-wave velocity), Dct (ms) (E-wave decay time of mitral valve orifice blood velocity waveform), Mean E/e (ratio of E-wave velocity ÷ e-wave velocity), septal e' (migration velocity waveform of mitral valve annulus)], and markers of systolic



Study cohort. Study subjects were selected from 72 patients treated with vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR-TKIs), such as sunitinib, sorafenib, pazopanib, and axitinib, according to inclusion and exclusion criteria. LVEF indicates left ventricular ejection fraction; and AF, atrial fibrillation.

Figure 1. Flow chart.

dysfunction [LVEF, left ventricular end-diastolic diameter (LVDd), and left ventricular end-systolic diameter)] were measured. In addition, side effects other than hypertension were also investigated.

The study participants were classified into two groups: those who developed hypertension during VEGFR-TKI administration [TKI-HT (+)] and those who did not develop hypertension while on the therapy [TKI-HT (−)]. Changes in cardiac function markers before and after VEGFR-TKI use in each group were investigated according to the guidelines for the diagnosis and treatment of acute and chronic heart failure (JCS 2017/JHFS 2017).

2.3. Statistical Analysis

The number of patients (%) is shown when the data are on a nominal scale and the mean ± standard deviation when it is on a continuous scale. Statistical analysis was performed using Excel Statistics 2015 ver. 4.0 (Social Survey Research Information Co., Ltd., Tokyo, Japan) and JMP® Pro ver. 16 (SAS Institute Inc., Cary, NC, USA). Differences were considered statistically significant at $p < 0.05$, using Fisher's exact test or t-test to compare patient demographics and cardiac function markers, and paired t-test for paired data.

2.4. Ethical Considerations

The study protocol and informed consent forms were conducted in accordance with the Declaration of Helsinki and its amendments and ethical guidelines for medical and health research involving human subjects. Ethical approval was obtained from the Hokkaido University of Science Research Ethics Committee (approval no. 22-12).

As this was a retrospective study, no written or verbal consent was obtained from the research participants. However, they were provided with information regarding this study and were guaranteed the opportunity to refuse its implementation. Data were anonymized before handling to ensure patient confidentiality.

The echocardiographic examination was conducted twice, once before the initiation of VEGFR-TKI administration and once after the end of its use; furthermore, echocardiographic examinations were performed during the period of use if a patient developed subjective symptoms specific to heart failure such as palpitations and shortness of breath.

3. Results

3.1. Patient Population

Seventy-two patients met the inclusion criteria for this study. Of these, 54 patients were included in the analysis after excluding patients with no echocardiographic data after VEGFR-TKI administration (n = 14) and those with atrial fibrillation or cardiac dysfunction before VEGFR-TKI administration (n = 4). Thirteen patients (24.0%) did not develop hypertension after VEGFR-TKI administration [TKI-HT (−)], and 41 patients (75.9%) developed hypertension [TKI-HT (+)] (**Figure 1**).

3.2. Patient Background

The patient background included an average age of 67 years, 13 males (24.0%) and 41 females (75.9%), and a history of hypertension in 18 patients, diabetes in 8 patients, and dyslipidemia in 5 patients. None of the patients had a history of coronary artery disease. Additionally, none of the patients had a history of cancer treatment (administration of anthracyclines or radiation (sternum)). The VEGFR-TKIs administered were sunitinib (29), axitinib (8), sorafenib (6), pazopanib (6), and cabozantinib (6). No significant differences were observed between the TKI-HT (−) and TKI-HT (+) groups (**Table 1**).

3.3. Changes in Ventricular Systolic Function Markers

In the TKI-HT (+) group, LVEF decreased significantly from 70.7% ± 6.8% to 68.3% ± 7.8% ($p = 0.03$). However, no changes were observed in the LVDd and LVDs (**Table 2**). In contrast, no significant difference was observed for any item in the TKI-HT (−) group. When the change in ventricular systolic function markers before and after VEGFR-TKI administration was compared between the two groups, no significant difference was observed in any of the items (**Table 3**).

3.4. Changes in Ventricular Diastolic Function Markers

E/e' was significantly decreased in the TKI-HT (+) group ($p = 0.02$), but no changes were observed in the other items. Conversely, no change was observed in any ventricular diastolic function marker in the TKI-HT (−) group (**Table 4**).

Table 1. Background of analysis data.

	ALL (n = 54)	TKI-HT (−) (n = 13)	TKI-HT (+) (n = 41)	*P*-value
Age, mean (SD)	67.0	60.3 (13.0)	68.1 (8.4)	0.06
≥ 65, n (%)	35 (64.8)	6 (46.2)	29 (70.7)	0.08
Sex (male/female), n (%)	13/41 (24.0/75.9)	2/11 (15.3/84.6)	11/30 (26.8/73.1)	0.48
BMI (kg/m^2), mean (SD)	21.5	21.8 (3.5)	21.2 (3.8)	0.58
BMI ≥ 25, n (%)	9 (16.7)	1 (7.7)	8 (19.5)	0.43
Medical history				
Hypertension, n (%)	18 (33.3)	2 (15.4)	16 (39.0)	0.18
Diabetic mellites, n (%)	8 (14.8)	2 (15.4)	6 (14.6)	1.00
Hyperlipidemia, n (%)	5 (9.3)	1 (7.7)	4 (9.8)	1.00
VEGFR-TKIs				
Sunitinib, n (%)	29 (53.7)	4 (50.0)	25 (61.0)	1.00
Axitinib, n (%)	8 (14.8)	2 (12.5)	6 (14.6)	1.00
Sorafenib, n (%)	6 (11.1)	1 (12.5)	5 (12.2)	1.00
Pazopanib, n (%)	6 (11.1)	1 (12.5)	5 (12.2)	1.00
Cabozantinib, n (%)	1 (1.9)	1 (12.5)	0	0.24
EF (%), mean (SD)	72.2	67.6 (8.6)	70.7 (6.9)	0.18

Values are median (range) or n (%). VEGFR-TKI indicates vascular endothelial growth factor receptor-tyrosine kinase inhibitor; BMI, body mass index.

Table 2. Comparison of echocardiographic systolic function parameters and general condition between before and after VEGFR-TKI treatment in study subjects (n = 54)

	TKI-HT (−) (n = 13)			TKI-HT (+) (n = 41)		
	Baseline	Endpoint	*P*-value	Baseline	Endpoint	*P*-value
LVEF	67.6 (8.6)	67.1 (11)	0.83	70.7 (6.8)	68.3 (7.8)	0.03
LVDd	46.8 (4.7)	47.0 (7.6)	0.88	44.6 (5.3)	44.1 (5.0)	0.36
LVDs	29.1 (4.5)	29.7 (8.2)	0.75	26.6 (3.9)	27.2 (4.2)	0.24

Values are mean ± standard deviation. VEGFR-TKI indicates vascular endothelial growth factor receptor-tyrosine kinase inhibitor; LVEF, left ventricular ejection fraction; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter.

When the change in ventricular diastolic function markers before and after VEGFR-TKI administration was compared between the two groups, no significant difference was observed in any item (Table 5).

3.5. Other Side Effects

Twenty seven patients experienced side effects such as hand-foot syndrome (2

Table 3. Comparison of echocardiographic diastole function parameters and general condition between before and after VEGFR-TKI treatment in study subjects (n = 54).

	TKI-HT (−) (n = 13)			TKI-HT (+) (n = 41)		
	Baseline	**Endpoint**	***P*-value**	**Baseline**	**Endpoint**	***P*-value**
E/A	1.02 (0.4)	1.00 (0.4)	0.82	0.90 (0.3)	0.86 (0.2)	0.12
Dct	227.3 (53.7)	224.1 (79.8)	0.92	226.6 (60.7)	231.2 (44.9)	0.58
E/e'	9.7 (3.1)	13.3 (10.8)	0.29	11.9 (3.6)	10.3 (3.0)	0.02
Septal e'	8.2 (2.1)	7.5 (1.3)	0.40	6.9 (1.4)	7.1 (2.3)	0.92

Values are mean ± standard deviation. VEGFR-TKI indicates vascular endothelial growth factor receptor-tyrosine kinase inhibitor; E/A, peak velocity of E-wave/peak velocity of A-wave; Dct, deceleration time; E/e', peak velocity of E-wave/peak velocity of e'-wave; e', peak velocity of e'-wave; and HR, heart rate.

Table 4. Comparison of the Changes in echocardiographic systolic function parameters between before and after VEGFR-TKI treatment

	TKI-HT (−) (n = 13)	TKI-HT (+) (n = 41)	***P*-value**
ΔLVEF	−0.5 (8.4)	−2.4 (6.9)	0.42
ΔLVDd	0.3 (5.9)	−0.5 (3.5)	0.67
ΔLVDs	0.5 (5.9)	0.5 (2.9)	0.99

Values are mean ± standard deviation. VEGFR-TKI indicates vascular endothelial growth factor receptor-tyrosine kinase inhibitor; LVEF, left ventricular ejection fraction; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter. The amount of change was defined as the value obtained by subtracting the value before VEGFR-TKI use and the value after administration.

Table 5. Comparison of the changes in echocardiographic diastole function parameters between before and after VEGFR-TKI treatment.

	TKI-HT (−) (n = 5 - 13)	TKI-HT (+) (n = 14 - 41)	***P*-value**
ΔE/A	−0.02 (0.4)	−0.04 (0.2)	0.79
ΔDct	−3.2 (93)	4.5 (49)	0.80
ΔE/e'	3.7 (10)	−1.6 (3.6)	0.14
Δseptal e'	−0.7 (1.8)	0.07 (2.4)	0.52

Values are mean ± standard deviation. VEGFR-TKI indicates vascular endothelial growth factor receptor-tyrosine kinase inhibitor; E/A, peak velocity of E-wave/peak velocity of A-wave; Dct, deceleration time; E/e', peak velocity of E-wave/peak velocity of e'-wave; e', peak velocity of e'-wave; and HR, heart rate. The amount of change was defined as the value obtained by subtracting the value before VEGFR-TKI use and the value after administration.

patients, 3.7%), thrombocytopenia (2 patients, 3.7%), hypothyroidism (6 patients, 11.1%), proteinuria (2 patients, 3.7%), decreased appetite (5 patients,

9.3%), fatigue (2 patients, 3.7%), nausea (2 patients, 3.7%), liver dysfunction (4 patients, 7.4%), pneumonia (1 patient, 1.9%), hypercalcemia (1 patient, 1.9%), and gastric ulcer (1 patient, 1.9%). There was no significant difference in expression between the two groups, TKI-HT (+) and TKI-HT (−).

4. Discussion

The present study suggests that elevated blood pressure due to VEGFR-TKI may have adverse effects on cardiac function, such as decreased LVEF.

VEGFR-TKIs exert their antitumor effects by inhibiting the tyrosine kinase activities of VEGFR and PDGFR, thereby suppressing tumor angiogenesis and tumor cell growth. However, it has been reported that the inhibitory effect of these receptors causes hypertension by inactivation of endothelial nitric oxide synthase in the vascular endothelium and production of endothelin-1, resulting in accelerated vasoconstriction and dilution of capillaries [10]. In the present study, 75% (41/54) of the patients developed hypertension, and a high percentage of patients had increased blood pressure with the use of VEGFR-TKI.

Inhibition of VEGF receptors also induces the density/number of the myocardial capillaries and hypoxia in the myocardium causing cardiac dysfunction [10]. Among the patients included in this study, cardiac function was affected in some patients, such as a decrease in LVEF up to the 30% range and confirmed signs of coronary artery stenosis. Therefore, hypertension may induce VEGFR-TKI-derived cardiac dysfunction.

First, a comparison of patient backgrounds showed no difference between the two groups, suggesting that the increase in blood pressure produced by VEGFR-TKI is unlikely to be related to patient factors (**Table 1**). Liu *et al.* reported that the risk of developing all grades of hypertensive events was 7.91 (95% confidence interval (95% CI): 5.4 - 11.57) for sunitinib, Risk Ratio (RR): 9.17 (95% CI: 0.72 - 116.54). 72 - 116.54) and RR: 9.17 (95% CI: 3.08 - 18.62) for pazopanib. This existing study reported a possible overestimation of the above risk because the meta-analysis included clinical trials that excluded patients with uncontrolled hypertension [11]. However, in this study, there was no significant difference in the number of patients who developed blood pressure elevation for each VEGFR-TKI between the two groups; hence, it is considered that specific TKIs do not affect blood pressure elevation.

In addition to hypertension, VEGFR-TKIs are associated with hand-foot syndrome, hypertension, and diarrhea, as well as thrombocytopenia, hypothyroidism, decreased appetite, liver dysfunction, and proteinuria with sunitinib [12]. In this study, the incidence of hypothyroidism and decreased appetite was in the 10% range; however, no other serious side effects were observed.

Compared to the TKI-HT (−) group, the TKI-HT (+) group showed a significant decrease in LVEF and E/e' after VEGFR-TKI administration (**Table 2** and **Table 3**).

LVEF is an index that reflects the systolic left ventricular function. The criteria

for CTRCD were a reduction in LVEF of >10% but <53% from baseline values [5]. In this study, some patients had a decline in LVEF of ≥10% after VEGFR-TKI administration, but none of the patients had an LVEF of <53, a criterion for reduced systolic function. In clinical trials of heart failure using LVEF as an indicator, the follow-up period was approximately 6.5 years and the measurement interval was every three months [13]; however, the median (range) observation period in this study was six months (0.5 - 59.7), and the number of measurements was not constant, so we believe that a marked decrease in LVEF was not found. Left ventricular systolic dysfunction occurs in 3.2% of VEGFR-TKI patients [14], and the median time to symptom onset is reported to be approximately 3 - 34 weeks [15]. Unlike other antineoplastic agents that induce cardiac dysfunction, such as anthracyclines, the effects of VEGFR-TKIs have been reported to be reversible [7]. Since most of the measurement timings after TKI were after the end of treatment, the timing of the echocardiographic measurements after TKI use was after the end of treatment, which may explain why the decrease in LVEF was not confirmed.

The decrease in E/e' in the TKI-HT (+) group after VEGFR-TKI administration indicates an improvement in diastolic function, but whether this is due to the effect of TKI cannot be examined causally because this was a retrospective study. In a previous study, E/e was not significantly different, but an increase was observed after TKI administration [15] [16]. Recently, Catino *et al.* showed that sunitinib causes impaired vascular function as blood pressure increases and that baseline vascular function (total peripheral resistance, arterial elastance, and aortic impedance) is associated with diastolic dysfunction [17]. Although it has long been noted that left ventricular diastolic dysfunction precedes left ventricular systolic dysfunction [15], diastolic dysfunction is more susceptible to myocardial ischemia associated with coronary artery stenosis than systolic dysfunction [18]. It has also been conventionally thought that increased hypertension accelerates the progression of arterial stiffness; however, it has been suggested that hypertension may be caused by prior arterial stiffness [19].

Left ventricular diastolic function in the study population included several patients with E/e' values greater than 14 at baseline. This is because several patients had been using antihypertensive medications prior to the start of treatment, and because of their older age range, left ventricular diastolic dysfunction may have progressed before the start of treatment. It has been reported that diastolic failure occurs in the early stages after the start of treatment with TKIs, and no change is seen three months after the start of treatment [15]. Therefore, it is thought that the diastolic function recovers over time while the systolic function decreases.

Currently, echocardiography for VEGFR-TKIs is not performed in the absence of the subjective symptoms of heart failure. The median interval from the start of TKI use to the next echocardiographic measurement was six months. For this reason, the fact that asymptomatic patients do not understand the changes in cardiac function has also become an issue. Therefore, it is necessary to increase

the frequency of echocardiographic examinations in the future by advising physicians to perform echocardiographic examinations at short intervals from the start of treatment.

The limitation of this study was that echocardiography after VEGFR-TKI administration was performed only when symptoms associated with significant left ventricular systolic dysfunction, such as shortness of breath and palpitations, became apparent. Consequently, this did not reflect the patient population that developed asymptomatic cardiac dysfunction, and the causal relationship between LVEF and E/e' is not clear. Therefore, it is necessary to conduct prospective studies in the future.

In this study, it was suggested that VEGFR-TKIs that increase blood pressure may affect cardiac function. These drugs may be associated with a decrease in LVEF (as evidenced by cyanosis, dyspnea, edema, and impaired consciousness). Hence, it is necessary to inform patients of these side effects during medication counseling and, if necessary, propose that echocardiography and measurement of markers such as brain natriuretic peptide may lead to early detection of cardiac dysfunction caused by VEGFR-TKI administration. We hope that this study will help pharmacists in the field of cardio-oncology in pharmaceutical management.

5. Conclusion

Appropriate antihypertensive therapy and early monitoring through regular echocardiography may help prevent the exacerbation of systolic dysfunction induced by VEGFR-TKIs, regardless of whether patients are symptomatic or asymptomatic.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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