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Original Article

Frequency of ischemic cardiac events in patients receiving long-term multikinase inhibitor: A report of three cases

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ABSTRACT

Objective: To investigate the incidence and characteristics of ischemic cardiac events, specifically major adverse cardiac events (MACE), in patients undergoing long-term treatment with multikinase inhibitors (MKIs) such as lenvatinib and sorafenib.

Methods: A single-center retrospective analysis was conducted on 41 patients treated with lenvatinib or sorafenib for more than one year at our institution from 2015 to 2022. Patient records were reviewed to collect data on demographics, cancer type, cardiovascular risk factors, MKI treatment duration, and MACE incidence. MACE events, defined as acute heart failure, fatal arrhythmia, acute myocardial infarction, and coronary revascularization, were analyzed to determine potential correlations with MKI therapy.

Results: Among the 41 patients, three (7.3%) developed MACE, presenting as acute heart failure, fatal arrhythmia, and acute myocardial infarction, all associated with significant coronary artery stenosis. Notably, none of these patients had a prior history of cardiovascular disease. Despite variations in clinical presentation, all cases suggested a link between long-term MKI administration and accelerated coronary atherosclerosis. Factors involved in atherosclerosis were significantly older and tended to be more hypertensive in the non-MACE group.

Conclusions: Long-term MKI therapy may increase the risk of severe ischemic cardiac events, likely due to accelerated atherosclerosis. Clinicians and oncology nurses should monitor patients closely for early signs of angina, especially in an outpatient setting, to prevent acute cardiac events. Further large-scale studies are warranted to establish a clearer causal relationship between MKI therapy and cardiovascular risks.

Introduction

Lenvatinib and sorafenib are multikinase inhibitors (MKIs).[1,2] They are available as single-drug treatments for unresectable thyroid cancer, thymic cancer, and hepatocellular carcinoma (HCC).[3–7] Angiogenic inhibitors may accelerate arteriosclerosis.[8–11] However, the clinical phenotypes of arteriosclerosis as an adverse effect of angiogenesis inhibitors and their impact on cancer treatment remain unclear.[12,13] In clinical trials of MKIs, the median time to termination owing to progressive disease (PD) was approximately half a year, and the reporting period of all side effects was approximately 2 years.[14–16] Therefore, the adverse effects of longer treatment periods are poorly understood.

Coronary artery disease is the most common clinical manifestation of atherosclerosis. Acute coronary syndrome is fatal, and intensive care for hemodynamic failure can lead to long-term interruption of cancer treatment, which may not resume during recovery owing to worsened performance status.

This study aimed to clarify the association between long-term use of MKI and major adverse cardiac events (MACE).

Methods

This was a single-center retrospective analysis. We investigated patients who received lenvatinib or sorafenib for more than 1 year between

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2015 and 2022 at our hospital. From the medical records, we collected data on age, sex, cancer type, history or side effects of hypertension, history of diabetes mellitus, statin administration, cardiovascular disease, other anticancer drugs, and MACE during treatment. We defined as cardiac death, fatal arrhythmia, acute myocardial infarction (AMI), coronary revascularization, and acute heart failure (AHF). In MACE cases, we examined the details of the MACE. We also investigated the treatment period and calculated the cumulative MKI dose from the start of the MKI therapy to the incidence of MACE.

Fisher's exact test was used to compare two groups. Statistical comparisons between the paired groups were performed using the Wilcoxon signed-rank test. Statistical significance was set at $P < 0.05$. Data were analyzed using JMP9 software (SAS Institute Inc., Cary, NC, USA).

This study was approved by the Ethics Committee of Shizuoka Cancer Center (J2024-66-2024-1) and met the standards set forth in the Declaration of Helsinki. Informed consent was obtained using the opt-out methodology.

Results

Patient characteristics

A total of 41 patients were included: 38 with thyroid cancer, 2 with thymic cancer, and 1 with HCC. The median age of the patients was 69 years (range, 31–83 years) (Table 1).

Within the study period, 27 patients (66%) were prescribed only lenvatinib, 13 (32%) received lenvatinib and sorafenib, and 1 (2%) received only sorafenib. None of the patients had a history of cardiovascular disease. The two patients with thymic cancer received carboplatin and paclitaxel for four cycles before MKI treatment. The patient received transcatheter arterial chemoembolization (TACE) twice with cisplatin prior to MKI treatment and three times with TACE (once with epirubicin hydrochloride and twice with miriplatin hydrate) during MKI therapy.

Incidence of MACE

Of the 41 patients, three (7.3%) developed MACE during MKI treatment (Table 2). One patient died 10 days after the disease onset. Two patients were discharged; however, they took a considerable amount of time to resume cancer treatment. Case 1 involved AHF, case 2 involved fatal arrhythmia, and case 3 involved AMI. Table 3 shows the coronary risk factors for the MACE group (3 patients who developed MACE) and the non-MACE group (38 patients who did not develop MACE). The non-MACE group was significantly older, and hypertension was more common. There were no differences in other coronary risk factors between the two groups. Hypertension included past history and side effects of MKI. They were well controlled toward hypertension Grade1 to the Common Terminology Criteria for Adverse Events published by the National Cancer Institute. None of the patients experienced long-term interruption of MKI due to hypertension. Of the 21 patients with a history of smoking, 20 had quit smoking at the time they were notified of their cancer, with the exception of one in the non-MACE group.

Table 1
Patient characteristics.

Median age (range) (years)	69 (31–83)	
Male/Female	20/21	
Cancer type	Thyroid cancer	38
	Thymic cancer	2
	HCC	1
Coronary risk factor	Hypertension (Yes/No)	35/6
	DM (Yes/No)	7/34
Statin administration (yes/no)		11/30
History of CVD	0	
History of other anticancer drugs	3	
Prescribed MKIs	Lenvatinib only	27
	Lenvatinib and sorafenib	13
	Sorafenib only	1

Age: at the start of MKI administration.
HCC, hepatocellular carcinoma; DM, diabetes mellitus; CVD, cardiovascular disease; MKI, multi-kinase inhibitor.

Details of three MACE cases

Case 1

A 60-year-old man with no history of thymic cancer (cT1bN2M1a stage IVa) 6 years ago. The patient had started lenvatinib treatment five years previously. One year prior, the patient had been diagnosed with PD, but lenvatinib treatment was continued. He visited the emergency room two days prior to presentation with the chief complaint of shortness of breath. The patient was hospitalized for hypoxemia. Cardiac ultrasonography revealed akinetic left ventricular wall motion, severe hypokinesis, and an ejection fraction of 29%. He was referred to our department with suspected heart failure.

After hospitalization in the intensive care unit, he received medical treatment for heart failure with reduced ejection fraction. On the fifth day of hospitalization, the patient developed torsade de pointes and ventricular tachycardia/ventricular fibrillation storm. Cardiopulmonary resuscitation was immediately initiated and the patient was transported to a collaborating hospital. Upon arrival, the sinus rhythm returned to the 13th cardioversion, and the patient was promptly moved to emergency catheterization.

Emergency catheter findings were as follows: segment 5, 75%; segment 6, 99%; high lateral branch, 99%; segment 11, 99%; segment 1, 90%; and segment 2, 100% (collaterals from the left coronary artery) (Fig. 1). The patient was diagnosed with AHF and fatal arrhythmia secondary to severe angina. Emergency percutaneous coronary intervention for segment 5–6 was performed but was unsuccessful. Despite massive blood transfusions and high-capacity catecholamine support, his circulatory failure progressed and he died.

Case 2

A 40-year-old man with no relevant medical history showed no notable findings during physical examination. Nine years prior, he noticed a lump in his neck and was diagnosed with thyroid cancer. Eight years previously, he had undergone a total thyroidectomy. Subsequently, the patient underwent several surgeries and radiotherapy for the lymph node recurrence. Approximately 3 years prior, the patient had started lenvatinib treatment. Approximately 2 years and 3 months later, he experienced exertional chest pain a few times but did not report it to his attending physician. Four months after these episodes, the patient experienced a cardiopulmonary arrest during a Kendo match and was transported to the hospital by helicopter.

An emergency catheter was inserted using endotracheal intubation and an intra-aortic balloon pump. The findings were segment 5–6, 99%; segment 11, 99%), and segment 13, 90% (Fig. 2). Cardiopulmonary arrest was diagnosed as fatal arrhythmia due to severe stenosis of the left main trunk. Successful emergency percutaneous coronary intervention was performed, and one stent was implanted in segment 5–6. The patient was discharged 17 days later and returned to work the following month. However, lenvatinib could not be resumed for almost 1 year.

Case 3

A 50-year-old woman with no history of coronary risk factors experienced lower back pain and left lower limb numbness 6 years prior to presentation. Magnetic resonance imaging revealed a tumor in the thoracic spine, and the patient was diagnosed with bone metastasis from the thyroid cancer via biopsy. Lenvatinib treatment was initiated after radiation therapy of the thoracic and sacral vertebrae. The patient remained in a wheelchair because of the residual paralysis. Approximately 4 years ago, the drug was changed from lenvatinib to sorafenib because of PD. Two years prior, she developed prothoracic pain with

Table 2
Details for MACE cases.

	Age/Sex	Cancer type	Coronary risk factor	Kind of MKIs	Treatment span of MKIs	Cumulative dose	MACE	Outcome
Case 1	60-year-old/Male	Thymic cancer	Smoking	Lenvatinib	5 y 1 m	11,180 mg	AHF	Died
Case 2	40-year-old/Male	Thyroid cancer	Smoking Alcohol	Lenvatinib	2 y 7 m	9502 mg	Fatal arrythmia	Survived
Case 3	50-year-old/Female	Thyroid cancer	None	Lenvatinib and Sorafenib	3 y 7 m (l: 1 y 6 m; s: 2 y 1 m)	l: 3458 mg; s: 129,600 mg	AMI	Survived

Treatment Span and Cumulative Dose: From the Start of MKI Administration to the Onset of MACE.
MACE, major adverse cardiac event; AHF, acute heart failure; AMI, acute myocardial infarction; y, year; m, month.

Table 3
Coronary risk factors for the MACE group and non-MACE group.

	MACE group ($n = 3$)	Non-MACE group ($n = 38$)	*P*-value
Median age (range)	50 (42–62)	69.5 (31–83)	0.033
Male/Female	2/1	18/20	0.606
Hypertension (yes/no)[a]	1/2	34/4	0.051
DM (yes/no)	0/3	7/31	1.000
Statin administration (yes/no)	1/2	10/28	1.000
Smoking[b]	2/1	19/19	1.000
Alcohol	1/2	18/20	1.000

DM, diabetes mellitus; MACE, major adverse cardiac event.
[a] Hypertension includes past history and side effects of MKI.
[b] All but one patient in the non-MACE group had quit smoking at the time of cancer notification.

profuse cold sweats after dinner. The symptoms disappeared after 10 min, but appeared repeatedly at 20-min intervals. She endured the symptoms for a few days; however, after a week, she visited the hospital immediately after brushing her teeth. She was suspected to have AMI and was admitted directly to the hospital as an emergency, and an emergency catheter was inserted.

The findings were as follows: segment 5, 90%; segment 6, 75%; in segment 11, 25% (Fig. 3). One stent was implanted from the ostium of the coronary artery to segment 6. Coronary computed tomography on 7 days before the emergency catheter placement showed no calcification at the stenosis site. The patient was discharged 11 days later.

Discussion

In this study, the clinical phenotypes of the three MACE cases differed (AHF, fatal arrhythmia, and AMI); however, all MACE cases were the same. Hemodynamic disruption is caused by a mismatch between myocardial oxygen demand and supply due to severe coronary artery stenosis.[17–20] Coronary angiography and intravascular ultrasound revealed thick fibrous plaques without calcification despite severe

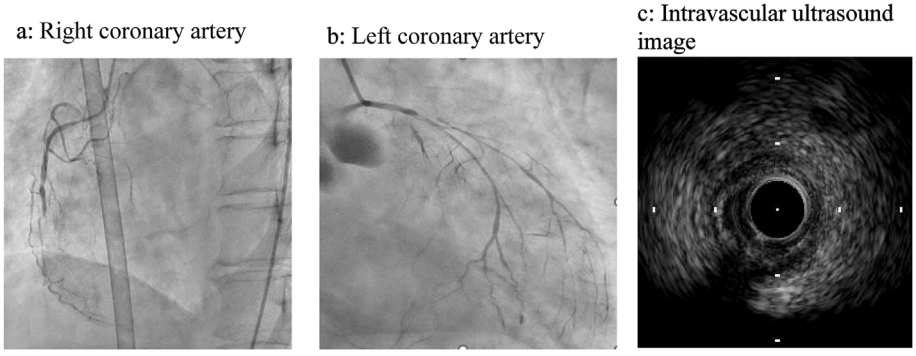

Fig. 1. Coronary angiography in Case 1. a: Right coronary artery segment 1, 90%; and segment 2, 100% (collaterals from the left coronary artery). b: Left coronary artery segment 5, 75%; segment 6, 99%; high lateral branch, 99%; segment 11, 99%. c: Intravascular ultrasound image in the right coronary artery.

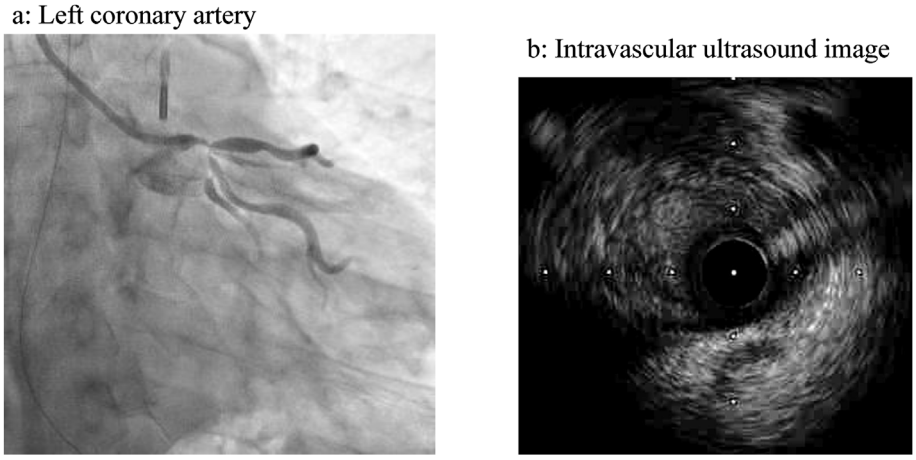

Fig. 2. a: Coronary angiography in Case 2 are as follows: segment 5–6, 99%; segment 11, 99%; and segment 13, 90%. b: Intravascular ultrasound image in segment 5–6.

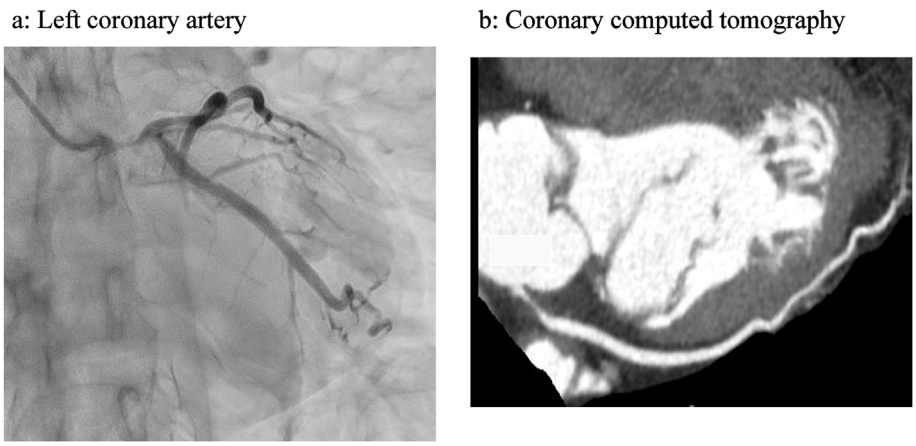

Fig. 3. a: Coronary angiography in Case 3 are as follows: segment 5, 90%; segment 6, 75%; and segment 11, 25%. b: Coronary computed tomography.

stenosis. These three patients had few or no coronary risk factors, and MKIs were used as single drugs for a long time. The patient with thymic cancer received other medical treatments for only 2 months before MKI, which were continued for over 5 years. The two patients with thyroid cancer had no history of cancer treatment. Therefore, we suspected that the long-term administration of MKIs is involved in the progression of coronary artery atherosclerosis.

Angiogenesis inhibitors exert their antitumor effects by blocking signals that induce angiogenesis in cancer cells, thereby cutting off the nutrient supply to cancer cells.[21–24] The vascular endothelial growth factor (VEGF) family is a crucial factor for angiogenesis.[25–28] MKIs mainly inhibit the VEGF cascade but also inhibit other small molecules such as epidermal growth factor, platelet-derived growth factor, and fibroblast growth factor. These molecules are expressed not only by cancer cells, but also by normal blood vessels when endothelial cells need repair.[29–31]

Atherosclerosis begins with vascular endothelial damage.[24,32–34] In normal arteries, vascular endothelial cells act as a barrier between the bloodstream and the vascular lining. If the restoration process is inhibited by MKIs, damaged endothelial cells are exposed to the bloodstream, resulting in plaque progression.[35–42] It takes time for the plaque to grow and cause vessel narrowing. Thus, recognizing and revascularizing the stable angina stage may prevent the onset of acute coronary syndrome.

In the three MACE cases in this study with left main trunk stenosis or multivessel disease, electrocardiogram or cardiac ultrasound findings were often normal until just before hemodynamic collapse. Therefore, even if these tests are performed regularly, the detection of angina pectoris progression remains difficult. It is also difficult to routinely perform exercise stress tests on patients with cancer.

MKIs can be administered outpatiently. Therefore, only the attending physician and nurse at the outpatient hospital could determine whether the patients had symptoms of angina pectoris.

However, it is difficult to suspect or deny angina during simple interviews with cancer patients. Patients have become accustomed to the indescribable malaise of long-term cancer treatments. According to the international phase III studies of lenvatinib, major side effects include diarrhea (60.9%), fatigue (44.8%), weight loss (47.1%), and decreased appetite (51.7%).[15] These side effects have been previously reported in many other MKIs.[43–46] They are prone to shortness of breath upon exertion, a common symptom of angina pectoris. As in Case 2, the patient did not always report new symptoms during the visits.

Therefore, patients should be interviewed with the intent of uncovering symptoms. It is effective to ask specific questions, such as whether the distance they can walk without rest has decreased, whether they can climb stairs without rest, or whether they experience chest pain when they start moving. Comparing their current conditions to longer periods, such as six months, one year, or before cancer onset, may also be helpful.

If angina symptoms cannot be ruled out, the attending physician should not hesitate to request a cardiologist to specifically evaluate the coronary arteries. The cardiologist aggressively tested for and treated angina on standby. Collaboration among medical staff will help minimize interruptions in cancer treatment.[47]

Limitations

This small retrospective study was conducted at a single institution in Japan. Therefore, it is difficult to establish a causal relationship between MACE and the long-term administration of MKIs.

Conclusions

The incidence of MACE during long-term administration of MKIs was 7.3%. In clinical practice, it is important to carefully monitor patients for angina symptoms and strive for early detection. Large prospective studies are required to examine the causal relationship between MKIs and these important adverse events.

CRediT authorship contribution statement

All authors contributed to the conception and design of this study. Material preparation and data collection were performed by Nao Muraoka, and analysis was performed by Takuya Oyakawa. All the authors have read and approved the final version of the manuscript.

Data availability statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics statement

This study was approved by the Ethics Committee of Shizuoka Cancer Center (IRB No. J2024-66-2024-1) and met the standards set forth in the Declaration of Helsinki. Informed consent was obtained using the opt-out methodology.

Declaration of generative AI and AI-assisted technologies in the writing process

No AI tools/services were used during the preparation of this work.

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Declaration of competing interest

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