Cardiovascular toxicities following the use of tyrosine kinase inhibitors in Hepatocellular Cancer Patients: A Retrospective, Pharmacovigilance Study

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Abstract

ABSTRACT Aims: With the extensive use of tyrosine kinases inhibitors(TKIs) in hepatocellular cancer, cardiac adverse events(AEs) emerged in recent years. This study explored the cardiac AEs of TKIs through the Food and Drug Administration's Adverse Event Reporting System (FAERS). Methods: Disproportionality analysis and Bayesian analysis were utilized for data mining of the suspected cardiac AEs of TKIs, based on FAERS data from January 2004 to December 2021. Results: A total of 4708 cardiac AEs reports of sorafenib, regorafenib, lenvatinib and cabozantinib were identifed. Among them, 17 cardiac AEs signals were detected in regorafenib, 15 cardiac AEs signals were detected in lenvatinib, 57 cardiac AEs signals were detected in sorafenib while 27 cardiac AEs signals were detected in cabozantinib. Hypertension accounts for the most reported cardiac AE. Lenvatinib appears to induce cardiac failure with the highest signals strength [ROR=7.7(3.46,17.17)]. Acute myocardial infarction were detected in lenvatinib [ROR=7.91(5.64,11.09)] and sorafenib[ROR=2.22(1.74, 2.84)]. Acute coronary syndrome were detected in lenvatinib[ROR=11.57(6.84, 19.58)] and sorafenib [ROR=2.81(1.87,4.24)]. Atrial fibrillation were detected in sorafenib [ROR=1.82(1.55,2.14)] and regorafenib [ROR=1.36(1.03,1.81)]. Meanwhile, aortic dissection were detected in sorafenib [ROR=5.08(3.31,7.8)] and regorafenib [ROR=3.39(1.52,7.56)]. Most patients developed hypertension and cardiac failure within 30 days after TKIs treatment. Patients taking lenvatinib developed acute coronary syndrome increased in the periods of 180 days(64.29%) . Conclusion: Analysis of FAERS provides more precise profile on the characteristics of cardiac AEs after different TKI regimens. Distinct monitoring and appropriate management are needed in the care of the TKIs recipients.

1 Introduction

Primary hepatocellular cancer was one of the major threat to human health worldwide, in 2020, primary liver cancer has become the sixth leading malignancy and the third cause of cancer-related deaths worldwide[1]. Hepatocellular carcinoma (HCC), with a five-year survival rate only 18%, accounts for 75%-85% of primary liver cancer cases[2]. Besides, incidence rate of HCC were much higher in Eastern Asia followed by Northern Africa and South-Eastern Asia[3]. For patients diagnosed at early- or intermediate-stage HCC, curative treatments such as surgical procedures, which including whole or partial hepatectomy and liver transplant, and locoregional therapies including radiofrequency ablation, transarterial chemoembolization, and radiation therapy could improve survival[4, 5]. However, more than half of the patients with HCC diagnosed at advanced or incurable stage, making systemic therapy one of few treatments available to improve survival[6, 7].

Great advances in understanding the mechanisms and progression of HCC over the past decades have promoted the development of novel drugs such as tyrosine kinases inhibitors (TKIs) to prolong the survival of patients with advanced HCC. In 2007, FDA approved sorafenib for HCC targeted therapy. Sorafenib was an anticancer agent with multi-targent, it could prevent the proliferation of tumor cells and inhibit cancer angiogenesis by suppressing the RAF/MEK/ERK pathway as well as inhibiting vascular endothelial growth

factor receptor 2/3 (VEGFR-2/3) and platelet-derived growth factor receptors (PDGFR)[7, 8].In the SHARP trial[9] and ORIENTAL trial[10], the investigators demonstrated that sorafenib could significantly increased survival of advanced HCC patients with different territories. Thus, sorafenib became the first line systemic therapy approved by european medicines agency(EMA) and FDA. It almost took 10 years until lenvatinib was approved as the second TKI for advanced HCC treatment. It acts as a potent inhibitor of VEGFR1-3 and other receptor tyrosine kinases, including fibroblast growth factor receptor(FGFR), KIT, and RET[11, 12]. The open-label,multicenter, non-inferiority phase III REFLECT trial enrolled 954 aHCC patients, the result demonstrated that lenvatinib was non-inferior compared to sorafenib. Lenvatinib group reached a median overall survival(OS) of 13.6 months compared to 12.3 months in the sorafenib group. Furthermore, lenvatinib group exhibit higher objective response rates(ORR) compared to sorafenib group(24.1% vs 9.2%)[13].The REFLECT study established lenvatinib as first line therapy in systematic treatment of unresectable HCC. Combination of lenvatinib and other immunotherapies has achieved encouraging clinical benefit. In 2017, another TKI small molecular, regorafenib was approved for patients with advanced HCC[14] Regorafenib targets VEGFR, PDGFR, and FGFR, RAF, RET, KIT[15]. In the phase III RESORCE study[16], 573 aHCC patients who tolerated sorafenib in 21 countries were enrolled. Regorafenib improved overall survival with a hazard ratio of 0.63 (95% CI 0.50-0.79; one-sided $p<0.0001$) and median survival was 10.6 months for regorafenib versus 7.8 months for placebo. Hence, Regorafenib was approved for second line treatment of HCC who have been previously treated with sorafenib. Cabozantinib was another oral multiple tyrosine kinase receptor inhibitor with activity against the VEGFR(VEGFR-1, VEGFR-2, VEGFR-3), RET and KIT. It also inhibits MET and AXL, which have previously been associated with sorafenib resistance[17].In phase III CELESTIAL trail[18], 707 patients with previously treated HCC were enrolled, and the results showed a median OS of 10.62 months in cabozantinib group compared to 8.0 months in the placebo group. Median progression-free survival(PFS) was 5.2 months in cabozantinib group and 1.9 months in placebo (HR for disease progression or death, 0.44; 95% CI, 0.36 to 0.52; $P < 0.001$), demonstrated cabozantinib as a second-line agent in the treatment of HCC. Nowadays, most advanced HCCs could benefit from the sound "transformation therapy", which indicated that transformed inoperable advanced HCC into resectable cancer with multimodal therapy options, targeted therapy became one of the important strategies.

However, some serious adverse events(AEs) that may induced by TKIs were emerged, some even fatal in cardiac system. Hypertension, QT prolongation, arrhythmias, left ventricular systolic dysfunction, and heart failure were the most common cardiac AEs reported[19-21]. Safety profiles of TKIs were evaluated primarily in clinical trials, which due to the strict study entry criteria, small sample sizes and relatively short length of time, were scattered and insufficient to provide a detailed overview of the risk of cardiac AEs induced by those above four TKIs. Therefore, Pharmacovigilance study using post-marketing safety reports can be an great supplement to the detection of cardiac AEs of TKIs. Currently, the FDA Adverse Events Reporting System (FAERS) was one of the largest global repository of post-marketing drug surveillance. It contains adverse event reports, medication error reports that were submitted to FDA.

2 Aims

This study aimed to comprehensively evaluate the cardiovascular safety profile of these four TKIs in a real-world setting by analysing cardiac AEs in the FAERS database(Figure 1).

3 Materials and methods

3.1 Data source and collection

We used data from the FAERS database published between January 2004 and December 2021. Reports on adverse event and medication error in the FAERS database was spontaneous reported by medical workers, consumers, and manufacturers globally[22]. Each FAERS report contain patients demographic information(age, gender and weight), drug information(indication, dosage, and interval of administration), adverse events information(occurrence time, outcome) and other information(report year, report country and reporter occupations). In the circumstances that there were multiple reports of the same event, deduplicated procedure were perform in accordance with FDA recommendation.

3.2 Data mining

In current study, we selected reports containing products "lenvatinib", "sorafenib", "cabozantinib" and "regorafenib" as "primary suspect" for further study. Arbitrary drug names may be reported in the FAERS, therefore, the MICROMEDEX® (Index Nominum) was utilized as a dictionary for TKIs(Table 1). The suspected adverse events(AEs) were coded according to the Medical Dictionary for Regulatory Activities (MedDRA®). We grouped cardiac AEs in the MedDRA classification (version 25.1) that are related to the same medical condition.

3.3 Statistical Analysis

Mean and standard deviation for continuous variables as well as numbers and percentages for categorical variables were used to describe the baseline characteristics of patients with cardiac AEs after exposed to TKIs. The reporting odds ratio (ROR), the proportional reporting ratio (PRR), the Bayesian confidence propagation neural network (BCPNN) and the multi-item gamma Poisson shrinker (MGPS) algorithms were used to identify the association of drugs and AEs [23]. AEs were considered statistically significant when at least 1 of the above 4 criteria was met(Table 2).

4 Results

4.1 Characteristics of Patients

Overall, A total of 14464087 reports were documented in the full FAERS database during the study period, of whom 82682[sorafenib, n=31361(37.93%); regorafenib, n=13826(16.72%); lenvatinib, n=8884(10.74%); cabozantinib, n=28611(34.6%)] were reported as TKIs-related AEs. Moreover, 4708 cardiac AEs reports identified TKIs as the primary suspected drugs. Among them, 1994 reports were identified as the suspected drug related to sorafenib; 630 reports were identified as the suspected drug related to regorafenib. 318 reports were identified as the suspected drug related to lenvatinib. 1766 reports were identified as the suspected drug related to cabozantinib. According to our results, males were more prone to be affected by cardiac AEs than females in patients taking sorafenib, cabozantinib(69.9% vs 26.1%, 68.4% vs 28.8%, respectively), while the ratio of male to female was similar among patients taking regorafenib or lenvatinib(56.8% vs 40.3%, 48.7% vs 51.3%, respectively). Age may be a risk factor, as most patients who experienced cardiac AEs while taking sorafenib(52.6%), lenvatinib(55.7%) or regorafenib(45.7%) were over 65 years of age. Reports were mainly submitted by health-care professionals. Most of the reports came from the US, Japan and France, with the exception of those whose origin could not be identified. All the clinical characteristics of these patients with cardiac AEs were presented in Table 3.

4.2 Cardiovascular Adverse Event Signal Detection Using the FAERS Database

Based on the criteria for the 4 algorithms (ROR,PRR,BCPNN, MGPS), there were 17 cardiac AEs signals detected in regorafenib, 15 cardiac AEs signals detected in lenvatinib, 57 cardiac AEs signals detected in sorafenib and 27 cardiac AEs signals detected in cabozantinib, respectively(Table 4, Fig 2). Among all the cardiac AEs signals, hypertension accounts for the most reported cardiac AEs in all these four TKIs. Furthermore, cardiac failure or cardiac failure acute signals were detected in all these four TKIs. Lenvatinib had the highest ROR[7.7(3.46,17.17)], while the ROR in regorafenib sorafenib and cabozantinib was 1.42(1.05,1.92), 2.48(1.44,4.27) and 5.92(4.13,8.47), respectively. There were cardiac AEs that show no class effect but significantly were over-reported in specific TKI. Acute myocardial infarction were mainly detected in lenvatinib[ROR=7.91(5.64,11.09)] and sorafenib[ROR=2.22(1.74, 2.84)]. No acute myocardial infarction signal were detected in regorafenib nor cabozantinib. Furthermore, acute coronary syndrome were also detected in lenvatinib[ROR=11.57(6.84, 19.58)] and sorafenib[ROR=2.81(1.87,4.24)]. When it comes to atrial fibrillation, signals were detected in sorafenib[ROR=1.82(1.55,2.14)] and regorafenib[ROR=1.36(1.03,1.81)] . Besides, aortic dissection were detected in sorafenib [ROR=5.08(3.31,7.8)] and regorafenib [ROR=3.39(1.52,7.56)].

4.3 Time to onset of TKI associatied cardiovascular adverse event

The times of cardiac AEs occurrence were shown in Fig 3. Over 70% patients developed hypertension within

30 days after the first dose of TKIs treatment. Identical pattern were found in cardiac failure. However, the proportion of patients who developed cardiac failure within 30 days were higher in patients administered with sorafenib (70.31%) and regorafenib(75%), compared with lenvatinib (32.14%) and cabozantinib(46.15%). In the case of atrial fibrillation, most patients developed atrial fibrillation within 30 days after the first dose of sorafenib or regorafenib. We also found that the proportion of patients developed acute coronary syndrome increased after 180 days use of lenvatinib compared with the first 30 days(64.29% vs 28.57%). The proportion of patients developed acute myocardial infarction(AMI) within 30 days were higher in patients taking sorafenib(42.86%) when compared with lenvatinib(13.64%). On the contrary, lenvatinib seemed to induce cardiac AEs in a longer period, as the proportion of patients developed acute myocardial infarction were higher in patients taking lenvatinib(65.15%) when compared with sorafenib(20%) after 180 days administration.

5 Discussion

With the extensive use of selective, mechanism-based TKIs in the treatment of HCC, cardiac AEs following the use of TKIs has gradually became a challenge. Some patients had to withdraw the treatment of TKIs due to the unbearable side effects. Currently, the safety information of TKIs were largely came from clinical trials, though it had limitations. Drug safety information that from real-world profile had advantages in sample size as well as follow-up time, so that attracted much attention these years. Pharmacovigilance based on the real world data can be an important supplement to the safety profile of TKIs. Our study mainly focused on TKIs related cardiac AEs by analysing data from FAERS pharmacovigilance database.

In our pharmacovigilance study, the association between hypertension and all the four TKIs were demonstrated and was consistent with the previous reports. In previous clinical study, all grade hypertension occurring in 42%, 31%, 5% and 7% of patients taking lenvatinib, regorafenib, sorafenib and cabozantinib respectively[13, 16]. When it comes to the onset time of hypertension, most of the hypertension occurred within 30 days of TKIs therapy according to our results. The occurrence of hypertention gradually leveled off from 30 days to 180 days, which indicated hypotensive drugs administration and carefully regular blood pressure monitor in the first month. Most studies have unveiled the fact that TKI-induced hypertension was associated with VEGF signaling, which played vital role in producing nitric oxide(NO), as well as inhibiting the production of the vasoconstrictor endothelin-1[24, 25]. Consequently, inhibition of VEGF by TKIs resulting in disruption of NO and endothelin-1, thus leading to the occurrence of hypertension. VEGF signal blocking also resulted in suppression of capillary endothelial cell survival, which could lead to apoptosis and microvascular sparseness, and contributed to increasing of peripheral vascular resistance. NO held the balance of redox equilibrium, as NO could scanvenge free radicals that may injury vascular endothelium. The reduction of NO production would lead to endothelial injury, which may result in further reduction of microvessel density and vascular perfusion. Though VEGF signalling block may lead to hypertention as well as other cadiac side effects, it was well accepted that angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and beta blockers were all suitable anti-hypertension drugs for TKI-induced hypertension[26]. Consequently, hypertention was well under-control after ocurrence. Besides, as hypertension represented an on-target effect of TKIs, some physician suggest that TKI-induced hypertension may be a sign of drug efficacy. In the SELECT trial, which included 392 patients, patients with treatment-induced hypertension in the lenvatinib group benifit from both progression-free survival and overall survival in the univariate analysis[27]. Above all, hypertention as an “on-target” sign of efficacy should be monitored carefully, especially in the first months of TKIs administration in HCC patients. Additionally, clinicians should be aware of the risk of other cardiovascular events caused by hypertension, especially those life-threatening cardiac AEs.

Aortic dissection was a life-threaten condition involved the separation of the different layers of the aortic wall due to a tear in the intimal layer of the aorta or bleeding within the aortic wall[28]. There have been case reports[29, 30] as well as observational studies[31] reported the association of sorafenib administration and, aortic dissection. The results of the present study confirmed the association of sorafenib and aortic dissection. Importantly, our results also indicated that regorafenib could also induce aortic dissection with a much higher incidence, which was not reported nor listed in FDA instruction. It was reported that the risk factor for aortic dissection include hypertension, atherosclerosis, age and dyslipidemia[32]. According to our results, one of

the most common side effects followed the use of TKIs was hypertension, which also played vital role in the occurrence of TKI-induced aortic dissection. As reported by Dorks, M., et al [33], the degree of hypertension induced by TKIs had positive correlation with the incidence of aortic dissection.However, the conclusion seems controversial, as there have been case reports/studies reported patients with baseline or normal blood pressure also developed aortic dissection after the use of TKIs[34, 35]. Thus, additional mechanisms besides hypertension may also involved in the pathogenesis of TKIs induced aortic dissection. Some studies suggest that inhibition of VEGF could increase the stiffness of arteries by impairing NO mediated vasodilation and vasoconstriction[34], it is also known that VEGF participate in endothelial-mediated regeneration and healing after vascular injury, in this way the inhibition of VEGF would result in the occurrence of dissection[36].

According to our results, sorafenib, regorafenib, lenvatinib and cabozantinib were all associated with cardiac failure. Thus, it seems to be a class effect that TKIs may induce cardiac failure. Moreover, lenvatinib and cabozantinib seems to have a stronger association with cardiac failure compared with sorafenib and regorafenib. Our analyse found a relative higher incidence of lenvatinib compared to the sorafenib and regorafenib. Although the real incidence rates need to be further comfiremd by well-designed clinical trials, the current results demonstrate a higher risk of cardiac failure in sorafenib and regorafenib long-term usage. An hypothesis has been proposed to explain how TKIs treatment can lead to cardiac failure[37]. Hypertension, one of the most common cardiac AEs of TKIs, could lead to afterload stress on the heart. Under normal physiological conditions, the heart would adapt to the afterload stress through compensatory mechanisms mediated by PDGFR-β. In cardiomyocytes afterload stress models, deletion of the PDGFR-β gene resulted in ventricular hypertrophy, ventricular dilation and heart failure[37, 38]. PDGFR-β was reported to be one of the targets of anti-angiogenic TKIs[39]. Inhibition of PDGFR-β would disrupt the cardiac adaptation mechanism to afterload stress, thus lead to heart failure ultimately. In addition to PDGFR-β signaling inhibition, there was another mechanism may also contribute to cardiac failure. The interaction between endothelial cells(ECs) and cardiomyocytes was essential for maintaining cardiac homeostasis and angiogenesis[40]. VEGFR-2 on cardiac ECs inhibited by TKIs initiated downstream signaling changes, leading to cardiomyocyte apoptosis, hypertrophy, and finally resulted in cardiac failure[41].

Besides, acute myocardial infarction(AMI) was also a fatal side effects that may induced by TKIs in HCC patients according to our results.The observed associations of TKIs with acute myocardial infarction(AMI) and acute coronary syndrome(ACS) have been demonstrated in some cases and studies [42, 43].We found a significant positive correlation between sorafenib or lenvatinib usage with AMI or ACS incidence. Besides, according to our results, lenvatinib seems to be more prone to induce AMI as well as ACS in the long-term use HCC patients. According to Prof. Jason et al's study, sorafenib induced myocyte kind of programed form of necrosis. In addition, sorafenib also potently induced stem cell apoptosis and inhibited stem cell proliferation both in vitro and in vivo experiments, which may ultimately result in suppression of the generating new cardiac myocytes after AMI[44].

Another fatal AE signal induce by TKIs was atrial fibrillation. Reports of TKI-induced atrial fibrillation was most commonly with patients taking sorafenib. In a phase II trial of 39 patients with advanced HCC, the incidence of atrial fibrillation was 5.1% when used in combination with 5-fluorouracil[45]. Besides sorafenib, our study also identified the association between regorafenib treatment and atrial fibrillation, the pathogenetic mechanism of which may be due to the inhibition of the PI3K/Akt pathway. Inhibition of PI3K-Akt signaling has been implicated in the development of atrial fibrillation, while increasing PI3K activity led to reduction of atrial fibrosis and improved conduction in a mouse model. Atrial appendage PI3k activity is lower in patients with atrial fibrillation than it is in those with sinus rhythm[46].

According to the reports collected in the current study, most of the hypertension, cardiac failure and atrial fibrillation cases happened within the first 30 days since the initiation of TKI treatment. However, the proportion of patients who developed ACS increased after 180 days use of lenvatinib or sorafenib. When it comes to lenvatinib, the incidence of AMI also increased after 180 days use of lenvatinib. Consequently, recognition of the difference in the onset time of varied cardiac AEs may be worthful to guide distinct monitoring and management strategies in TKIs recipient HCC patients. Indicating that cardiac AEs management

are necessary while patients are under anti-tumor therapy.

The FAERS database is one of the largest global repository of post-marketing drug reporting systems, which could help to make identifcation of pharmacovigilence signals of TKIs in a real-world setting. However, there were also several limitations, first, the reports in the FAERS database was spontaneous submited by drug users or medical stuff, thus, false reporting, incomplete reporting, or inaccuracy reporting are inevitable. Second, In addition to basic information such as age, gender, weight, and medication, other information such as lifestyle habits and family history is also very helpful for the judgment and analysis of AEs, but this part of information is not recorded in the system. Thus, the FAERS database is only used in qualitative research and it is insufficient to prove a causal relationship between certain AEs and drugs. Despite its limitations, pharmacovigilance study based on FAERS database is an important supplement to drug safety research, and could provide rational evidence for drug safety research after marketing.

6 Conclusion

Our analysis of the FAERS database identified cardiac AEs for TKIs in a real-world setting. Our study found similar cardiovascular adverse effects with TKIs, Patients over 65 whose taking sorafenib, lenvatinib and regorafenib were at increased risk for developing cardiac AEs. These four TKIs were associated with increased risk of developing hypertension and cardiac failure. Furthermore, aortic dissection was a new complication with regorafenib. Use of lenvatinib may increase the risk of developing acute coronary syndrome and myocardial infarction. Clinicians should be aware of the various cardiac AEs associated with TKIs and the assessment of cardiovascular risk should be done before starting TKI treatments.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Author contributions

Concept and design the work: HW-P, JF-H. Acquisition, analysis, or interpretation of data: XL, QW. Management and checking of all data: SF-J and XC-S. Drafting the article: XL and QW. All authors critically reviewed the manuscript and interpreted the results. The final manuscript was read, checked, and approved by all authors.

Data availabilty statement

Publicly available datasets were analysed in this study. This data can be found at

https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html.

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Figure legends

Figure 1 Post-marketing data of tyrosine kinase inhibitor (TKI)-associated cardiac toxicities in the FAERS database

FAERS, Food and Drug Administration's Adverse Event Reporting System; TKI, tyrosine kinase inhibitor.

Figure 2 Reporting odds ratios (RORs) of TKI-induced cardiac AEs. The graph presents the RORs of each cardiac adverse events(AEs) compared to reports in the full database. A lower limit of the ROR 95% CI above 1 is considered signifcant. (a):Sorafenib;(b): Lenvatinib; (c):Regorafenib;(d):Cabozantinib

*CI values exceeded graph limits.

&:only the top 20 repored PT were listed.

#:some of the RORs were too big to be presented

AE,adverse events; TKI, tyrosine kinase inhibitor.

Figure 3 Time to event onset of TKI-induced cardiac AEs. (a):Hypertension; (b):Cardiac failure; (c):Atrial fibrillation; (d):Acute myocardial infarction; (e):Acute coronary syndrome;

AE,adverse events; TKI, tyrosine kinase inhibitor.

Table 1. Summary of FDA-approved TKIs for HCC

Initial US FDA approval year	Generic name
2005	Sorafenib
2012	Regorafenib
2012	Cabozantinib
2015	Lenvatinib
FDA,US Food and Drug Administration; Hepatocellular cancer; TKIs, Ttyrosine kinases inhibitors.	FDA,US Food and Dr

Table 2.

Summary of major algorithms used for signal detection.
Method
ROR
PRR
BCPNN
MGPS
a:the number of reports with suspect drug adverse event of the suspect drug; b:the number of reports with the suspect AE

Table 3. Clinical characteristics of patients with cardiac AEs using TKIs in the FAERS database (January 2004 to Dem 2021)

Characteristics
Country
United States
Japan
France
others
Unknown or missing
Reporter
Medical staff
Non-medical staff
Unknown or missing
Reporting time
2006
2007
2008
2009
2010
2011
2012

2013	
2014	
2015	
2016	
2017	
2018	
2019	
2020	
2021	
Gender	
Female	
Male	
Unknown or missing	
Age (year)	
< 18	
18-64	
65	
Unknown or missing	

Cardiac AEs, Cardiac adverse events; FAERS, Food and Drug Administration's Adverse Event Reporting System; TKI, Tty

Table 4. Disproportionality analysis of TKI-associated cardiac AEs

Drugs	
Cabozantinib[a]	
Drugs	
Lenvatinib	

a:only the top 20 repored PT were listed; N:the number of reports of TKI-associated cardiac AEs; ROR:reporting odds ratio