Case Report

Sorafenib-Associated Heart Failure Complicated by Cardiogenic Shock after Treatment of Advanced Stage Hepatocellular Carcinoma: A Clinical Case Discussion

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Background. Sorafenib, an oral tyrosine kinase inhibitor (TKI), targets multiple tyrosine kinase receptors (TKRs) involved in angiogenesis and tumor growth. Studies suggest that inhibition of TKR impacts cardiomyocyte survival. Inhibition of VEGF signaling interrupts angiogenesis and is associated with the development of hypertension and compensatory hypertrophy. Compensated hypertrophy ultimately leads to heart failure.

Case Description. A 76-year-old man with a past medical history of systolic heart failure due to ischemic cardiomyopathy and stage IIIC hepatocellular carcinoma (HCC) presented with symptoms of decompensated heart failure. Four months prior to admission, he was started on sorafenib.

Results. Our patient was treated with intravenous furosemide and guideline directed therapy. Clinical status was complicated by the development of low cardiac output and shock requiring inotropic support. Careful titration of heart failure medication led to hemodynamic improvement and discontinuation of dobutamine.

Conclusion. Greater awareness of sorafenib cardiotoxicity is essential. As TKI usage grows for treatment of cancers, heart failure-related complications will increase. In our patient, routine heart failure management and cessation of sorafenib led to clinical improvement. Future studies on the treatment of sorafenib cardiotoxicity should be explored further in this unique patient population.

1. Introduction

Sorafenib is an oral multikinase inhibitor that targets pathways involved in angiogenesis and tumor growth by inhibiting tyrosine kinase receptors and is recommended as a first-line drug for the treatment of advanced hepatocellular carcinoma due to limited alternatives. The effect of sorafenib on the human body is not limited to hepatocellular cancer cells and has been linked to cardiovascular toxicity leading to the pathogenesis of clinical heart failure and resistant hypertension [1, 2].

This report presents the clinical case of a patient with ischemic cardiomyopathy and advanced HCC who was started on sorafenib and subsequently developed heart failure complicated by cardiogenic shock. We will review the clinical case, the biological basis for TKI cardiac toxicity, and the therapeutic challenges and considerations for the treatment of sorafenib-associated hypertension and heart failure.

2. Clinical Case

A 76-year-old man presented with worsening dyspnea at rest and on exertion, orthopnea, and lower extremity edema. The past medical history was significant for single-vessel coronary artery disease (s/p percutaneous coronary intervention), systolic heart failure with reduced ejection fraction (LVEF 37%) due to ischemic cardiomyopathy, severe ventricular hypertrophy, chronic atrial fibrillation, hypertension, hyperlipidemia, diabetes mellitus type two, chronic obstructive pulmonary disease, and Stage IIIC hepatocellular carcinoma. Family history was positive for hypertension and diabetes mellitus type two. He was previously treated with guideline
Figure 1: (a) At baseline, the transthoracic echocardiogram demonstrates moderately depressed LV function (LVEF-40%) with significant concentric and septal LV hypertrophy (LV mass 367 grams, IVSd-2.1 cm, PWT-1.5 cm, RWT-0.67). (b) There is further evidence of elevated filling pressures. There is left atrial enlargement (LA dimension - 4.6 cm), mildly elevated estimated right ventricular systolic pressure (RVSP ~ 36 mmHg), and restrictive filling on mitral inflow Doppler (E/A-2.3, deceleration time 190 milliseconds).

Table 1: The pertinent medication list and dose.

| Medication   | Dose                          |
|--------------|-------------------------------|
| Sorafenib    | 200 mg by mouth twice daily   |
| Carvedilol   | 3.125 mg by mouth twice daily |
| Furosemide   | 80 mg by mouth twice daily    |
| Lisinopril   | 10 mg by mouth daily          |
| Aspirin      | 81 mg by mouth daily          |
| Warfarin     | 2.5 mg by mouth daily         |
| Nitroglycerin| 0.4 mg sublingual as needed  |

The patient presented to the emergency department hypertensive (169/79 mmHg) and tachycardic with a ventricular rate of 127 beats per minute (Figure 2). The physical exam was consistent with volume overload, and admission labs were notable for elevated BNP, abnormal BUN/creatinine, and elevated liver function tests (Table 2). Chest X-ray demonstrated cardiomegaly with pulmonary venous congestion and a moderate-sized right-sided pleural effusion.

The clinical exam was consistent with decompensated heart failure. The patient was treated with intravenous furosemide, carvedilol, and lisinopril. After sufficient diuresis (10 liters of fluid), clinical symptoms improved minimally (Table 3). However, within the subsequent 18 hours, the patient developed persistent hypotension (MAP 60 mmHg), worsening renal function, and cool extremities indicative of impending cardiogenic shock. He continued to have elevation of JVP on physical exam, which suggested restrictive filling of the right ventricle (RV) as well as RV failure. A pulse wave Doppler across the LVOT suggested diminished stroke volume after calculation of the LV velocity time integral (Figure 3). A right heart catheterization was subsequently performed which showed mildly elevated right- and left-sided ventricular filling pressure, pulmonary hypertension, and low cardiac output (Table 3). He was then treated with continuous infusion of dobutamine and furosemide. An EKG at the time demonstrated improvement of the ventricular rate without evidence of ST-T wave changes (Figure 4).

Based on the antecedent history of recent initiation of sorafenib followed by deterioration in cardiac function, sorafenib-induced decompensated heart failure was diagnosed. This case report serves as an example of the therapeutic challenges of heart failure management in patients treated for hepatocellular carcinoma with sorafenib. The cardiac toxicity of sorafenib is known and while many patients who have preexisting heart failure are not initiated on tyrosine kinase inhibitors for this reason, limited therapies for cancers such as HCC may compel care providers to do
**Table 2: Admission physical exam and notable labs.**

| Physical exam | Vital signs | BP 169/79 mmHg, HR 129 bpm |
|--------------|-------------|--------------------------|
| Cardiovascular | Irregularly irregular rhythm, tachycardic, JVP 15 cm H₂O with head of bed at 30 degrees |
| Lungs | Symmetric chest rise with bibasilar rales |
| Extremities | 3+ lower extremity pitting edema to the mid-shins bilaterally |

| Laboratory results | Patient result | Normal |
|--------------------|----------------|--------|
| Sodium             | 139            | 135–145 mEq/L |
| Potassium          | 4              | 3.6–5.0 mEq/L  |
| BUN                | 21             | 7–21 mg/dL |
| Creatinine         | 1.48           | <1 mg/dL |
| Magnesium          | 1.6            | 1.4–1.8 mEq/L |
| BNP                | 3298           | <100 pg/mL |
| Troponin I         | 0.05           | <0.03 |
| AST                | 95             | 5–35 U/L |
| ALT                | 60             | 7–56 U/L |
| Alkaline phosphatase | 234        | 38–126 U/L |
| Total bilirubin    | 4.2            | 0.2–1.3 mg/dL |
| Procalcitonin      | +              | Undetectable |

**Figure 2: Atrial fibrillation with rapid ventricular response (ventricular rate 127 bpm) with evidence of prior septal infarct and nonspecific ST-T wave abnormalities in the precordium.** There are low QRS voltages noted across leads likely due to chronic obstructive pulmonary disease.

3. Discussion

Sorafenib is an oral tyrosine kinase inhibitor that targets multiple tyrosine kinase receptors involved in angiogenesis and tumor growth and is recommended as a first-line drug for the treatment of advanced HCC [1]. In cancer cells, tyrosine kinase activity is increased due to mutations in the genes associated with the fundamental regulatory components of the enzyme. Mutations in cancer cells can also lead to overexpression of the tyrosine kinase genes. Tyrosine kinase inhibition is mediated through binding of a ligand or antibody (inhibitor), thus preventing the receptor from achieving its activated form. Autophosphorylation of the tyrosine kinase subsequently activates a series of protein kinase cascades in one of two dominant pathways involved in cell proliferation, hypertrophy, function, and survival. These are the phosphatidylinositol 3-kinase (PI3K) pathway via AKT or the mitogen-activated protein kinase (MAPK) cascade via RAS and ERK (extracellular signal regulated kinase) [4, 5].

The Signaling Pathway of Tyrosine Kinases, Sites of Inhibition, and Cardiotoxicity Secondary to Trastuzumab following Treatment of HER2+ Breast Cancer. To further understand the reasons for sorafenib-associated cardiotoxicity, it is relevant to discuss the lessons learned from earlier generation TKIs, the exact cellular pathways affected, and the mechanisms behind the pathogenesis of clinical heart failure. Patients with ERBB2 receptor, also known as HER2 (human epidermal growth factor receptor), breast cancer that were receiving anthracycline-based chemotherapy were 3.5 times more likely (8% versus 27%, \( p < 0.001 \)) to develop asymptomatic cardiac dysfunction on echocardiography or clinical heart failure [6]. Clinically significant predictors for cardiac toxicity among several cohorts receiving trastuzumab were history...
Table 3: (a) The clinical exam and hemodynamic profile consistent with low output heart failure prior to treatment with dobutamine infusion. (b) The clinical exam and hemodynamic profile after treatment with dobutamine infusion.

(a)

| Physical exam | Vital signs | Right heart catheterization | Measurements |
|---------------|-------------|-----------------------------|--------------|
| General       | MAP 59–62 mmHg, HR 92 bpm, RR 20/min | Wrapped in blankets including head. Appears fatigued. | RA mean pressure 8 mmHg |
| Head, neck, throat | | Dry mucous membranes. | RV pressure 33/9 mmHg |
| Cardiovascular | Irregularly irregular. Parasternal holosystolic murmur. +RV gallop. JVP 20 cm H_2O at 30 degrees. | PA pressure 32/23 mmHg, mean 27 mmHg |
| Lungs          | Coarse breath sounds. No wheezes. Normal work of breathing. | PCWP 18 mmHg |
| Abdomen        | Moderate to severe hepatomegaly with hepatojugular reflux. | Pulmonary vascular resistance 3.8 WU |
| Extremities    | 2+ pitting edema to knees. No cyanosis or clubbing. | Cardiac output (L/min) (thermal dilution) 3.91 (L/min), Sv02-53%, Hgb 15.2 |
| Skin           | Slightly cool extremities. | Cardiac index 1.70 L/min/m^2 |

(b)

| Physical exam | Vital signs | Right heart catheterization | Measurements |
|---------------|-------------|-----------------------------|--------------|
| General       | MAP 72 mmHg, HR 85 bpm, RR 14/min | Brighter affect. | RA mean pressure 5 mmHg |
| Head, neck, throat | | Moist mucous membranes. | RV pressure 26/5 mmHg |
| Cardiovascular | Irregularly irregular. Parasternal soft holosystolic murmur. JVP 8 cm H_2O at 30 degrees. | PA pressure 26/15 mmHg, mean 19 mmHg |
| Lungs          | Clear breath sounds. No wheezes. Normal work of breathing. | PCWP 12 mmHg |
| Abdomen        | Soft, normoactive bowel sounds. Moderate hepatomegaly with firm liver edges, absent hepatojugular reflux. | Pulmonary vascular resistance 1.4 WU |
| Extremities    | No edema, cyanosis, or clubbing. | Cardiac output (L/min) (thermal dilution) 5.3 (L/min), Sv02-72-75%, Hgb 14.2 |
| Skin           | Pink fingertips and warm extremities. | Cardiac index 2.4 L/min/m^2 |

of cardiac disease at baseline, treatment with anthracyclines, and age > 70 years [7, 8].

The true incidence of heart failure secondary to trastuzumab alone was likely unknown due to treatment confounding with anthracyclines and taxanes. Assessing the true clinical risk of cardiomyopathy among patients receiving trastuzumab has therefore led to clinical trials with prespecified cardiac end points which estimate the incidence to be less frequent when administered alone (4–7%) [9, 10]. Clinical follow-up data from these trials further demonstrated that trastuzumab cardiac toxicity is reversible shortly after discontinuation and may be responsive to medical therapy [11]. This would suggest that the severity of cardiac toxicity secondary to TKIs is most pronounced when the cardiac myocyte is simultaneously weakened by another process that creates an energy deficit, and, subsequently, the required metabolic signaling needed to maintain survival is hindered through the disruption of these critical pathways. As will be described, the degree of cardiac toxicity caused by TKIs depends on the inhibitory effect on the dominant signaling pathway of the cardiac myocyte, the selectivity of tyrosine kinase inhibition, the concomitant treatment with older cardiotoxic chemotherapeutic agents, anthracyclines or taxanes, and the duration of treatment [10, 12].

Tyrosine Kinase Inhibition Promotes an Energy Deficit and Interferes with Cardiac Myocyte Survival Pathways. TKIs are considered very effective in the treatment of the respective cancers but, as was described, can have deleterious effects on the cardiovascular system. Both clinical experiences followed
by basic investigations regarding deficient cellular signaling due to trastuzumab and bevacizumab have furthered our understanding of the importance of tyrosine kinase signaling in the pathogenesis of heart failure and hypertension in patients receiving these treatments for cancer. As newer TKIs are being developed, there is greater scrutiny for reporting adverse cardiovascular events during clinical trials. In the search for better and more effective anticancer drugs, multikinase inhibitors were developed to achieve greater inhibition of TKR and downstream signaling. The ultimate effect of less selectivity is the shutting down of signaling, ATP utilization, and the cell machinery for cell division. Sorafenib, a multikinase inhibitor, was designed for the inhibition of cell proliferation.

Studies that have elucidated the cellular mechanisms behind cardiotoxicity due to sorafenib suggest that inhibition of RAF-1 and B-RAF kinase impact cardiomyocyte survival (Figure 5) [12]. RAF-1 signaling phosphorylates a series of kinases in the MAPK group, MEK1 and ERK1, which potentiates cardiac myocyte hypertrophic growth and survival [13, 14].

The RAF-1 kinase also inhibits cell death pathways mediated by apoptosis signal-regulating kinase 1 (ASK1) as well as mammalian sterile 20 kinase 2 (MST2). Both ASK1 and MST2 are proapoptotic kinases and have roles in oxidant stress-induced injury. Deletions of RAF-1 in the heart result in ventricular dilation, reduced contractility, and increased cell death [12, 15]. When mice with deleted RAF-1 are subjected to pressure overload, cardiomyocyte death was increased, indicating that RAF-1 kinase activity may be cardioprotective [16].

Nonselective TKIs such as sorafenib that target multiple kinases have great potential for intracellular toxicity. Myocardial cells require greater energy demands than other cells and therefore are particularly sensitive to deficiencies in energy production. Some case reports have indicated the potential for reversibility of sorafenib-induced cardiomyopathy after discontinuation though it is unclear to what extent or after what duration of treatment that reversibility is still feasible [17].
treatment of renal cell carcinoma (RCC) with sorafenib, 68% had some form of cardiovascular toxicity, with most cases (59%) having worsened hypertension. Newly diagnosed heart failure, defined as an elevation in NT-proBNP and a decline in LVEF, occurred in 40% of patients on sunitinib and in 4% of patients on sorafenib [2]. In a meta-analysis of 21 randomized controlled trials with patients undergoing treatment of HCC, there was a 2.7-fold greater heart failure risk in those that received TKIs compared to those who did not (2.39% versus 0.75%, \( p < 0.001 \)) [23].

**Therapeutic Challenges and Considerations in the Treatment of Hypertension.** Hepatocellular carcinoma is one of the most common cancers in the world and typically presents in advanced stages. Standard treatments during early stages include partial hepatectomy, local ablation, and liver transplantation. Sorafenib is recommended as a first-line drug for the treatment of advanced HCC [1, 2].

In the case of sorafenib-induced hypertension, blood pressure is treated with conventional therapy and appears not to impact or worsen progression-free survival among patients treated for metastatic RCC [24]. Early intervention of hypertension is essential to reduce subsequent risks of developing cardiomyopathy and heart failure. The Angiogenesis Task Force of the National Cancer Institute Investigational Drug Steering Committee recommends regular blood pressure monitoring before treatment as well as during treatment, weekly during the first cycle and then every 2-3 weeks, with a goal BP of less than 140/90 mmHg for most patients and a goal BP of less than 130/80 for those with diabetes or chronic kidney disease [25]. Sorafenib is also associated with the development of proteinuria, and it is recommended that urine protein be tested before and after treatment initiation. When patients develop proteinuria, clinicians should strive to control blood pressure with either angiotensin-converting enzyme inhibitors (ACE-I) or dihydropyridine calcium channel blockers (CCB), which have been recommended as first- and second-line agents (Figure 6) [26]. Treatment with ACE-I is contraindicated if patients develop hyperkalemia, severe cough, or angioedema or have advanced chronic kidney disease. Transitioning to angiotensin receptor blocker is possible in those patients intolerant to ACE-I though clinical data is limited. Discontinuation of sorafenib can be considered in patients with resistant hypertension.

**Therapeutic Challenges and Considerations in the Treatment of Systolic Heart Failure.** Although it is typically recommended that chemotherapy be discontinued when significant heart failure develops, case reports have shown that sorafenib can be used to treat advanced HCC for as long as 12 months and may be reduced in those that develop heart failure [1]. It is difficult to know which heart failure medications would benefit patients exposed to TKIs. Very few clinical studies have investigated the treatment of heart failure due to TKIs in a prospective fashion. Newer generation TKIs are less selective than their predecessors, and while the cancer cell growth is strongly halted, the potential for cardiac toxicity is higher. At this time there are no medications that specifically target and reverse TKI-related cardiotoxicity. The ACC/AHA guidelines recommend that patients receiving

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**Figure 5:** Sorafenib inhibits multiple tyrosine kinase and second messenger pathways. In the cardiac myocyte, inhibition of prosurvival pathways RAS/MAPK via BRAF and PI3K/AKT1 via VEGFR leads to diminished survival. Sorafenib further inhibits RAF1, which leads to loss of tonic inhibition of cell death pathways and death through activation of caspases.
chemotherapeutic agents should be monitored carefully. A baseline echocardiogram prior to treatment with TKIs in patients with cardiac risk factors and close follow-up in monitoring for heart failure symptoms is appropriate [27, 28].

In patients that develop clinical heart failure or systolic dysfunction on echocardiography, treatment with a combination of guideline directed ACE-I, and beta-blockers have been shown to reduce heart failure-associated mortality and improve cardiovascular morbidity [27]. The most well studied agents in the treatment of anthracycline-induced cardiomyopathy are carvedilol and enalapril though the mechanism, severity, and toxicity of anthracyclines differ from the cardiotoxicity of TKIs [29, 30]. Aldosterone antagonists have also been shown to further reduce mortality in advanced heart failure in patients with systolic heart failure, LVEF < 35%, and NYHA III-IV. Treatment of salt and water retention in systolic heart failure is further treated with loop diuretics. Implantable defibrillators used as primary prevention for sudden cardiac death are recommended in those with greater than a 1-year life expectancy with persistently severe LV dysfunction for greater than three months despite optimal medical therapy. In patients that develop heart failure symptoms and successfully complete treatment with TKIs, follow-up echocardiography is appropriate to assess for reversal of LV dysfunction [26].

Dobutamine Treatment May Be Considered in Those with Severe Heart Failure. Baseline diminished contractile reserve with subsequent exposure to sorafenib led to the development of cardiogenic shock in our patient who was subsequently treated with dobutamine, an inotrope with weaker chronotropic effects, which successfully restored a normal hemodynamic profile. While it is well known that inotropic support is associated with adverse long-term cardiovascular outcomes, the clinical efficacy of inotropes after exposure to cardiac toxic medications is unknown. Dobutamine's pharmacologic function does not depend on tyrosine kinases but rather on G-protein coupled receptors. Whether sensitivity to beta-1 adrenergic activation by dobutamine is increased after tyrosine kinase inhibition is unknown. In response to isoproterenol, the presence of genistein was shown to potentiate beta-adrenergic sensitivity in the heart of animal models [31].

4. Conclusion

In our patient with underlying ischemic cardiomyopathy and advanced hepatocellular carcinoma, the management of heart failure in the setting of coexisting malignancy poses interesting and new clinical challenges. Sorafenib is a tyrosine kinase inhibitor that targets multiple tyrosine kinase receptors involved in angiogenesis and tumor growth. Unfortunately, sorafenib-associated cardiotoxic effects such as hypertension, reduced LVEF, and heart failure are of great concern and contribute to the challenging nature of HCC management. It is essential that TKI-induced hypertension be treated aggressively with standard treatments and regular monitoring. Guidelines also recommend echocardiogram monitoring for patients started on chemotherapeutic agents, especially those with cardiac risk factors, prior to treatment initiation, once heart failure symptoms develop, and after treatment completion. There are currently no specific recommendations for managing TKI-induced heart failure, and patients are typically managed with standard heart failure treatments. Beta-adrenergic effects of dobutamine may actually be potentiated by tyrosine kinase inhibition.

We initially considered more common causes for heart failure exacerbation in our patient. Patients with restrictive heart failure often develop worsened heart failure symptoms due to sustained periods of atrial fibrillation with rapid ventricular response. Prior to hospitalization, however, the patient's ventricular rate was well controlled with beta blockade, and it is our belief that the interval decline in ventricular function led to increased left atrial pressure and presentation of atrial fibrillation with rapid ventricular response. Furthermore, there were no EKG abnormalities.
suggestive of myocardial infarction or evidence of severe valvular regurgitation on echocardiography. There was the possibility that overdiuresis due to an inability to accurately estimate the filling pressures on physical exam led to inadequate preload leading to low cardiac output shock. However, the patient’s right heart catheterization reflected that the filling pressures remained elevated after diuresis and that the etiology of low cardiac output was mainly attributed to diminished contractility.

After successful titration of guideline directed treatment and discontinuation of dobutamine, a repeat echo demonstrated baseline LV function. A repeat trial of sorafenib at a lower dose was offered to the patient but was declined. Although sorafenib is the potential predisposing factor for the patient’s decompensation, the causal relationship between this drug and heart failure is still unclear since rechallenge was not performed. The patient was discharged home with palliative care follow-up for coordination of hospice.

Abbreviations

| Abbreviation | Description |
|--------------|-------------|
| ACC          | American College of Cardiology |
| ACE-I        | Angiotensin-converting enzyme inhibitors |
| AFP          | Alpha-fetoprotein |
| AHA          | American Heart Association |
| ASK1         | Apoptosis signal-regulating kinase 1 |
| BP           | Blood pressure |
| BPM          | Beats per minute |
| CCB          | Calcium channel blocker |
| EGFR         | Epidermal growth factor receptor |
| ERK          | Extracellular signal regulated kinase |
| HCC          | Hepatocellular carcinoma |
| HER2         | Human epidermal growth factor receptor |
| JVP          | Jugular venous pressure |
| LV           | Left ventricle |
| LVEF         | Left ventricular ejection fraction |
| MAP          | Mean arterial pressure |
| MAPK         | Mitogen-activated protein kinase |
| MST2         | Mammalian sterile 20 kinase 2 |
| MRI          | Magnetic resonance imaging |
| NT-proBNP    | N-terminal prohormone of brain natriuretic peptide |
| NYHA         | New York Heart Association |
| PA           | Pulmonary artery |
| PCWP         | Pulmonary capillary wedge pressure |
| RAF1         | Rapidly accelerated fibrosarcoma |
| RCC          | Renal cell carcinoma |
| RHC          | Right heart catheterization |
| RV           | Right ventricle |
| TACE         | Transcatheter arterial chemoembolization |
| TKI          | Tyrosine kinase inhibitor |
| TKR          | Tyrosine kinase receptor |
| VEGF         | Vascular endothelial growth factor |
| VEGFR        | Vascular endothelial growth factor receptor |
| WHO          | World Health Organization |

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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