CASE REPORT

Toxic cardiomyopathy leading to fatal acute cardiac failure related to vandetanib: a case report with histopathological analysis

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Abstract

Context: Medullary thyroid carcinoma (MTC) accounts for 3–4% of all malignant thyroid neoplasias. Vandetanib, a tyrosine kinase inhibitor (TKI) targeting vascular endothelial growth factor receptor 2, epidermal growth factor receptor, and RET, has been approved by the FDA for the treatment of locally advanced or metastatic MTC. The heart seems to be particularly susceptible to adverse effects associated with TKI therapy, and virtually all TKIs have been associated with cardiovascular events.

Clinical presentation: We report the case of a patient with metastatic MTC who was enrolled in the Phase III clinical study (NCT00410761) and presented a favorable response to vandetanib therapy, displaying marked decrease in the level of serologic tumor markers and shrinkage of metastatic lesions. After 14 months of therapy, the patient developed a fatal cardiac failure. Myocardial infarction was excluded by serial measurements of specific cardiac markers (serial troponin-T measurements varied from 0.037 to 0.042 ng/ml) and serologic tests for Chaga's disease were negative. Postmortem examination of the heart revealed cardiomyocyte hypertrophy and marked myocyte degeneration in the subendocardial zones and papillary muscles of the myocardium. These pathological changes are similar to those observed in TKI-treated rats and are suggestive of drug-induced cardiotoxicity.

Conclusion: This case illustrates a previously unreported serious vandetanib-related adverse effect and highlights the need for close monitoring of patients under TKI therapy in order to identify early signs of congestive heart failure or myocardium damage.

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Introduction

Medullary thyroid carcinoma (MTC) originates from the parafollicular C-cells and accounts for 5–10% of all malignant thyroid neoplasias. This tumor may occur sporadically (75% of cases) or as part of the inherited syndrome known as multiple endocrine neoplasia type 2 (1, 2). Gain-of-function mutations in the RET proto-oncogene are causative of MTC (1). Total thyroidectomy plus cervical lymph node resection is the standard treatment and offers the only possibility of cure. Currently, there is no effective treatment for patients with locally advanced or metastatic disease as this tumor is usually unresponsive to conventional chemotherapy or radiotherapy.

Small-molecule kinase inhibitors have been recently proposed as a potential therapeutic approach for metastatic MTC. Vandetanib, a tyrosine kinase inhibitor (TKI) targeting vascular endothelial growth factor receptor 2 (VEGFR2), epidermal growth factor receptor,

and RET, is a promising effective treatment for MTC. The results of a large Phase III randomized clinical trial of 331 patients with locally advanced or metastatic MTC revealed a significant increase in progression-free survival for patients receiving vandetanib compared with placebo (hazard ratio, 0.46; 95% CI, 0.31–0.69; $P < 0.001$) (3). Recently, this drug has been approved by the FDA for the treatment of locally advanced or metastatic MTC.

Common side effects of vandetanib (>20% of patients) included diarrhea/colitis, rash, nausea, hypertension, headache, fatigue, anorexia, abdominal pain, hypocalcemia, hypoglycemia, and increased transaminase levels. Severe cardiac adverse effects have been reported in association with vandetanib and other TKI, including QTc interval prolongation, torsades de pointes, heart failure, and sudden death (4).

Here, we report the case of a patient with metastatic MTC, enrolled in the above-mentioned Phase III clinical study (NCT00410761), who developed acute fatal

cardiac failure during vandetanib therapy. Postmortem examination of the heart revealed pathological changes suggestive of drug-induced cardiotoxicity.

Patient

A 43-year-old man with a diagnosis of MTC was referred to the Hospital de Clínicas de Porto Alegre (a tertiary care, university-based teaching hospital) for genetic evaluation and follow-up. He had undergone a total thyroidectomy and cervical lymph node resection about 2 years before. The histopathological analysis revealed a 2.9 cm tumor with capsular and angiolymphatic invasion. Metastases to 14 cervical lymph nodes were identified. Calcitonin levels were 1584 pg/ml (Immulite 2000, Diagnostic Products Corporation, Los Angeles, CA, USA; reference value (RV) <12 pg/ml). Thorax contrast-enhanced computed tomography (CT) scan showed multiple pulmonary metastases. *RET* molecular screening was negative for mutations in codons 8, 10, 11, and 13–16. One year later, CT scans obtained of neck, chest, and abdomen revealed new lesions suggestive of liver metastasis.

The medical chart revealed a previous hospital admission due to peptic ulcer disease and pneumonia. The patient reported a previous episode of supraventricular tachycardia 2 years before. At that time, an echocardiogram showed mild left ventricular segmental dysfunction (infero-apical–lateral hypokinesia) without impairment of systolic function (ejection fraction of 58%). No dilatation of cardiac chambers or changes in valve structure and function were observed. The patient was prescribed propranolol (40 mg twice daily), which was discontinued several months later, with no recurrence of tachycardia. No cardiovascular risk factors (past or present smoking, diabetes, hypertension, dyslipidemia, or relevant familial cardiovascular disease) were identified.

The patient was enrolled in the above-mentioned clinical trial for vandetanib vs placebo for metastatic MTC (3). In the screening visit, calcitonin and carcinoembryonic antigen (CEA) levels were 6123 pg/ml (RV <12 pg/ml) and 355.8 ng/ml (RV <4 ng/ml) respectively. His medications included levothyroxine (200 µg daily), omeprazole, and aspirin. The patient was randomized to receive vandetanib (300 mg daily). After 1 month of treatment, he developed severe skin rash (grade 3), which was initially treated with local and systemic therapy (antihistamines and glucocorticoids). Vandetanib dose was reduced to 200 mg daily. As the skin lesions showed no improvement, vandetanib was withdrawn (12 weeks) and restarted at a lower dose (100 mg daily). A marked sustained decrease in calcitonin and CEA levels (155 pg/ml and 233.7 ng/ml respectively) were observed 3 months after starting vandetanib (Fig. 1). At the 6-month follow-up visit, he achieved a durable partial response according to Response Evaluation Criteria in Solid

Figure 1 Serum levels of calcitonin and CEA during follow-up.

Tumors (RECIST, >30% shrinkage from baseline; the sum of the lesions from 23.1 to 12.1 cm). During the trial, the patient presented asymptomatic atrioventricular nodal reentrant tachycardia, controlled with the reintroduction of propranolol (40 mg twice daily). No signs or symptoms of congestive heart failure (CHF) were identified.

Fourteen months after the start of treatment, the patient was admitted to the emergency room following sudden onset of dyspnea and thoracic pain. At physical examination, the patient was pale, with a heart rate of 81 bpm and blood pressure of 64/54 mmHg. The thorax radiogram revealed bilateral infiltration and the electrocardiogram showed inversion of T wave in V4–V6 derivations with normal QTc interval. Laboratory tests showed hypoxemia and metabolic acidosis. Cardiac markers were not consistent with myocardial infarction (troponin-T varied from 0.037 to 0.042 ng/ml in the first 24 h of admission; normal range <0.01 and values >0.1 ng/ml are required to diagnose myocardial infarct). The patient underwent thorax and abdominal CT that excluded aortic disease. Thirty-six hours after the admission, the patient presented a cardiac arrest in pulseless ventricular tachycardia, recovering after cardiopulmonary resuscitation. An echocardiogram performed 8 h later showed severe left ventricular dysfunction (ejection fraction of 7%), dilated left ventricle, and mild dilation of left atrium. These findings persisted in the follow-up echocardiogram performed 3 days later. The pulmonary artery catheterization confirmed a cardiogenic etiology of the shock: central venous pressure of 15 mmHg (RV 1–6 mmHg), pulmonary artery pressure of 54/34 mmHg (RV 15–28/5–16 mmHg), pulmonary capillary wedge pressure of 32 mmHg (RV 6–12 mmHg), cardiac output of 1.69 l/min (RV 4.0–8.0 l/min), cardiac index 0.86 l/min per m² (RV 2.4–4.0 l/min per m²), and systemic vascular resistance index 695 dynes.sec¹.cm⁵/m² (RV 1600–2400 dynes.sec¹.cm⁵/m²). No clinical evidence or laboratory findings suggestive of infection were observed and hemocultures were negative. The patient received i.v. noradrenaline and dobutamine in an attempt to restore

hemodynamic parameters, broad-spectrum antibiotics, and hydrocortisone and was maintained on mechanical ventilatory support. Seven days after the admission, the patient died of irreversible ventricular tachycardia.

Postmortem gross pathological examination of the heart showed slight cardiomegaly and moderate biventricular hypertrophy. Optical microscopy of histological sections of both ventricles displayed findings that can be due to ischemia during the resuscitated cardiac arrest (cardiomyocyte hypertrophy and multiple areas of micro-infarct with coagulative necrosis at the center of lesions, black arrow, Fig. 2A). Moreover, signs suggestive of TKI cardiotoxicity were observed as marked myocyte degeneration in the subendocardial zones and papillary muscles of the myocardium (black arrowhead, Fig. 2A) and areas of subendocardial fibrosis and hyalinization containing a few isolated clusters of myocardial fibers in the subendocardial left ventricular wall and corresponding papillary muscles, suggesting chronic inflammatory response and tissue repair (Fig. 2C). Representative sections for histopathological examination of coronary arteries show no evidence of atherosclerotic disease (Fig. 2D).

Discussion

Vandetanib is the first and currently the only approved drug for patients with unresectable, locally advanced or metastatic MTC. Indeed, a recent Phase III, randomized, controlled trial of 331 patients has demonstrated a 54% reduction in the risk of disease progression among MTC patients treated with vandetanib compared with placebo (3). Here, we reported a case of a patient

enrolled in the above-mentioned trial, who presented a favorable response to vandetanib therapy, displaying marked decrease in the level of serologic tumor markers and shrinkage of metastatic lesions. After 14 months of therapy, the patient developed a fatal cardiac failure and postmortem heart examination indicated drug-induced cardiotoxicity.

The heart seems to be particularly susceptible to adverse effects associated with TKI therapy. This can be partially explained by the fact that the same TK pathways that promote cancer cell survival also have important roles in maintaining heart and vascular functions (5). Particularly, the cardiovascular function is likely to be affected by TKI effects on VEGF and its receptors, as VEGF signaling has an important role in regulating myocardial responses to hemodynamic forces, such as pressure overload, and also on physiological and pathological changes in cardiomyocytes (6). Off-target effects of these drugs might also induce cardiomyocyte toxicity due to TKI non-selectivity (7, 8). Indeed, virtually, all TKIs have been associated with cardiovascular events (9). In an observational study of 74 patients treated with the TKIs sunitinib or sorafenib for renal cell carcinoma, 40.5% presented ECG changes and 33.8% experienced a cardiac event. Of these, about 10% were seriously compromised and required intermediate care and/or intensive care admission (10). Additionally, in a Phase I/II trial to investigate the efficacy of sunitinib in imatinib-resistant gastrointestinal stromal tumor, 28% of patients presented ventricular dysfunction and 8% CHF (11). Consistently, echocardiographic evaluation in rats treated with TKI documented increased heart rate and contractility after the first dose and ventricular dysfunction with continuous treatment (12).

This case illustrates the enormous clinical significance of TKI effects on the cardiovascular system and demonstrates that vandetanib therapy may induce severe toxic cardiomyopathy. Several diseases can cause acute heart failure due to left ventricular systolic dysfunction (i.e. coronary artery disease, valve abnormalities, myocarditis, and Chaga's disease), associated or not with an intrinsic heart pathology. In the present case, myocardial infarction was excluded by serial measurements of specific cardiac markers (13). We also ruled out coronary artery disease or myocarditis in the postmortem histopathological examination and the patient displayed negative serologic tests for Chaga's disease. In fact, the heart histological findings are similar to those reported in TKI-treated rats, which show myocardial fibrosis and degeneration and suggest chronic aggression toward myocardial tissue (12). Of note, cardiomyocyte hypertrophy was also described in endomyocardial biopsies of two patients with sunitinib-associated CHF while transmission electron microscopy demonstrated aberrantly shaped, swollen mitochondria (11, 14).

A striking aspect was that, despite a rigorous clinical and laboratory follow-up, the patient displayed no

Figure 2 Postmortem histopathological analysis of the heart. (A) HE 400 $\times$, micro-infarct with coagulative myocardial necrosis, a finding that can be attributed to ischemia during the resuscitated cardiac arrest (black arrow) at the center surrounded by numerous macrophages and marked subendocardial myocyte degeneration (black arrowhead). (B) HE 400 $\times$, micro-infarct with macrophages containing hemosiderin pigment (black arrow). (C) HE 400 $\times$, micro-infarct with signs of chronicity (fibrosis and hyalinization). (D) HE 40 $\times$, left coronary artery showing normal lumen.

symptom or sign of myocardial injury before the fatal event, raising the question of whether the current follow-up protocol should be amended. Presently, the QT interval prolongation is considered the most stressed cardiac adverse event associated with vandetanib and close monitoring with a routine and tight electrocardiogram schedule is advised (4). The currently available serum markers of cardiac injury do not display enough sensitivity to detect chronic damage to the myocardium. Echocardiography is the primary modality used for ventricular function assessment in asymptomatic patients and may be helpful for detecting left ventricular dysfunction in patients under TKI therapy. Moreover, recent studies have shown that cardiac magnetic resonance imaging provide accurate and reproducible serial assessment of left ventricular ejection fraction, being able to detect damage affecting as little as 2% of the myocardial mass (15, 16). The most effective strategy to avoid toxic cardiomyopathy due to vandetanib remains to be established, but for now, routine echocardiography and electrocardiogram should be considered. The use of brain natriuretic peptide testing might be useful to identify patients at early stages of heart failure (17). Moreover, in those patients with risk factors for CHF, such as hypertension, one might consider the use of cardioprotective pharmacological agents. In this context, clinical studies have indicated a potential role of carvedilol (β -blocker), valsartan (angiotensin receptor blocker), and enalapril (ACE-I) in preventing myocardial dysfunction in patients under cancer therapy (18).

In conclusion, we report a case of toxic cardiomyopathy leading to fatal acute cardiac failure in a patient on vandetanib due to advanced MTC. Based on the present case and until more knowledge on the mechanisms associated with TKI-induced cardiotoxicity is gathered, one might consider a close monitoring of signs of CHF or myocardium damage in patients on TKI therapy.

Declaration of interest

R S Scheffel, J M Dora, D R Siqueira, L M Burtet, and M R Cerski have nothing to declare. A L Maia served as consultant/advisor for AstraZeneca within the past 2 years.

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