Cabozantinib-induced serum creatine kinase elevation and rhabdomyolysis: a retrospective study

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Research Article

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Abstract

Background

Rhabdomyolysis is a potentially fatal disease, and elevated serum creatine kinase (CK) is one of the key laboratory findings suggestive of this disease. It is important to distinguish rhabdomyolysis from other diseases because CK elevation can occur in a variety of etiologies. Cabozantinib is one of the standard treatments for patients with renal cell carcinoma, but the frequency of CK elevation with this drug is still unknown.

Methods

To investigate the frequency of serum CK elevation induced by cabozantinib, we retrospectively reviewed the electronic medical records of patients with advanced renal cell carcinoma who received cabozantinib at our institution from April 2020 to March 2021.

Results

Seven patients were included in the study; six experienced serum CK elevation, four were classified as grade 1, and the remaining two as grade 3 according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. In five patients, the time from cabozantinib administration to CK elevation was 14 days. Hypothyroidism can be one of the causes of CK elevation; however, two patients who had hypothyroidism caused by previous treatment were in the euthyroid condition due to hormone replacement. One patient with grade 1 CK elevation developed late-onset immune-related adverse event (irAE) myositis comorbid with suspected myasthenia gravis. One patient with grade 3 CK elevation developed muscle weakness and rhabdomyolysis.

Conclusions

CK elevation is a common adverse event induced by cabozantinib. Most patients are asymptomatic and may not be clinically ill. However, physicians should be careful with the rare occurrence of symptomatic serum CK elevation, indicating rhabdomyolysis and neuromuscular irAEs, especially in patients who receive immune checkpoint inhibitors (ICls).

Background

Rhabdomyolysis is a syndrome characterized by muscle necrosis and leakage of muscle cell contents into circulation. Common symptoms include muscle pain, weakness, and acute kidney injury, the severity of which ranges from asymptomatic to life threatening. Serum creatine kinase (CK) elevation is one of the most important laboratory findings for diagnosing rhabdomyolysis; however, multiple conditions elevate CK, such as hypothyroidism, myocardial injury, trauma, and medications, including chemotherapy [1,2]. Therefore, it is necessary to differentiate these conditions in clinical practice.
Cabozantinib, an orally administered small-molecule multi-kinase inhibitor of vascular endothelial growth factor receptor (VEGFR)-2, MET, and AXL, is a standard treatment for patients with advanced renal cell carcinoma (RCC). The frequency of serum CK elevation induced by cabozantinib remains to be elucidated because routine measurement of serum CK level is not common even in clinical trials, such as global, randomized phase III trials [3,4] and phase II trials conducted in Japan [5], as well as in clinical practice. This retrospective study aimed to investigate the frequency of CK elevation and reveal the detailed clinical features induced by cabozantinib.

Methods

We performed a retrospective analysis to investigate the change in serum CK level, which is included in the routine set of blood chemistry tests at our institution, in patients with advanced RCC who received cabozantinib from April 2020 to March 2021. Data were retrieved from electronic medical records and the RCC database of our institution. Data collection and analysis were approved by the Institutional Review Board of Toranomon Hospital (approval number 1879).

Results

Patient characteristics

Seven patients were included in the study. The patient characteristics are shown in Table 1. The median age of the patients was 68 (range, 54–83) years. Five of the seven patients were male, and two were female. The median number of previous systemic treatments was three (range, 1–5). All patients had previously received immune checkpoint inhibitor (ICI) therapy. The median period from the date of the last ICI administration to the date of cabozantinib administration was 390 (range, 49–642) days. The initial dose of cabozantinib was 60 mg/day in two cases and 40 mg/day in five cases. Additional information on comorbidities and concomitant medications is shown in Table 1. Six of the seven patients had chronic kidney disease as a comorbidity, and none had cardiovascular diseases. Two of them had hypothyroidism due to previous treatment with VEGFR inhibitors other than cabozantinib with or without immune checkpoint inhibitors, and their thyroid function was stabilized by adequate levothyroxine dosing. None of the patients were taking CYP3A4 inhibitors or CYP3A4 inducers.

CK elevation and clinical courses

Six of the seven patients had elevated serum CK levels (Table 2). In most patients (five of six patients), CK elevation was detected at the first visit (14 days after administration of cabozantinib). Four patients were classified as having grade 1 CK elevation according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

One of the four patients with grade 1 CK elevation was diagnosed with late-onset immune-related adverse event (irAE) myositis comorbid with suspected myasthenia gravis. The patient presented to the hospital with a chief complaint of neck drooping on day 5 after initiating cabozantinib (121 days after the last ICI administration).
dose), bilateral eyelid drooping on day 8, and trunk muscle weakness on day 14. A neuromuscular disease was suspected, and the patient was referred to a neurologist. Magnetic resonance imaging showed high signal intensity on short tau inversion recovery-weighted images in the muscles of the posterior neck to the back. Needle electromyography showed fibrillation potential and positive sharp waves in the paraspinal muscles, suggesting myositis. Myocarditis was ruled out by cardiological examinations, such as electrocardiography, serum troponin test, and echocardiography. The patient had a symptom of easy fatigability, a typical clinical finding in patients with myasthenia gravis, despite the Tensilon test and anti-Ach antibodies being negative, and repetitive stimulation electromyography showed no waning. These findings suggest that the patient was diagnosed with irAE myositis concurrent with possible myasthenia gravis. He received intravenous immunoglobulin therapy, and his symptoms improved within a week.

Among the two patients with grade 3 CK elevation, one with a CK level of 1736 mg/dL (Case 1 in Table 1) developed rhabdomyolysis with grade 3 muscle weakness and acute kidney injury. Figure 1 shows the detailed clinical course of the patient. Cabozantinib was discontinued on day 15 due to grade 2 serum CK elevation and grade 1 muscle weakness. However, serum CK levels continued to increase to grade 3. On day 25, he was admitted to our hospital with a chief complaint of grade 3 muscle weakness in the upper and lower limbs. On admission, hypothyroidism, adrenal dysfunction, infection, and cardiovascular disease were ruled out. We diagnosed rhabdomyolysis with acute kidney injury and performed fluid replacement and electrolyte correction. Serum CK levels decreased, and symptoms were relieved within 7 days.

Discussion

The current study revealed that elevated serum CK levels commonly occurred in patients who received cabozantinib. However, in most cases, it is asymptomatic; therefore, careful observation is required, and no dose reduction or interruption of cabozantinib is necessary. In the case of symptomatic patients with CK elevation, physicians should consider life-threatening conditions such as severe rhabdomyolysis and late-onset irAEs, as in our report. To the best of our knowledge, a case report described serum CK elevation and rhabdomyolysis induced by cabozantinib [6]. In that report, serum CK levels were elevated nine days after cabozantinib initiation. We also found that serum CK elevation occurred relatively early after cabozantinib administration. Additionally, the report emphasized the possibility of hypothyroidism-induced serum CK elevation, unlike patients in our analysis whose thyroid function was adequately controlled with levothyroxine, regardless of complications of hypothyroidism due to previous treatments.

The mechanisms underlying cabozantinib-induced serum CK elevation or rhabdomyolysis are not well understood. One possible mechanism is the inhibition of Fms-like tyrosine kinase 3 (FLT-3) by cabozantinib. FLT-3 is a receptor tyrosine kinase expressed mainly on the membrane of hematopoietic progenitor cells, and a previous study demonstrated that the FLT-3 ligand and FLT-3 signaling pathway are expressed in differentiating myoblasts, and their signaling is a key regulator of skeletal myogenesis.
[7]. In addition, the FLT-3 inhibitor gilteritinib is known to cause CK elevation [8], which also suggests the possibility of this mechanism.

Recently, cabozantinib has been one of the key drugs in renal cell carcinoma practice, either as monotherapy after immune checkpoint inhibitor therapy or in combination with ICI. In the current study, we encountered a case of late-onset myositis irAE possibly complicated by myasthenia gravis. Physicians should consider the possibility of not only cabozantinib-induced rhabdomyolysis but also irAEs in patients who received ICIs previously or concurrently. The precise mechanisms and typical clinical and laboratory findings of neuromuscular irAEs remain unclear. In addition, these diseases are among the most common fatal irAEs, especially when complicated by myocarditis. Therefore, a collaboration between neurologists and cardiologists is essential.

This study includes some limitations. First, this is a single-center retrospective study with a limited number of cases. Second, it is unclear whether this CK elevation is specific to cabozantinib, as there is no data on routine CK measurements in other VEGFR inhibitors. Further research is warranted as more cases of cabozantinib are expected to be used in the future. Nevertheless, to the best of our knowledge, this is the first study to suggest a higher frequency of CK elevation in cabozantinib use.

**Conclusions**

In conclusion, CK elevation was a common adverse event induced by cabozantinib treatment. Most patients are asymptomatic and do not require routine dose reductions or interruptions. However, physicians should be careful with the rare occurrence of symptomatic serum CK elevation, indicating rhabdomyolysis and neuromuscular irAEs, especially in patients who receive ICIs.

**Abbreviations**

CK, creatine kinase; VEGFR, vascular endothelial growth factor receptor; RCC, renal cell carcinoma; ICI, immune checkpoint inhibitor; CTCAE, Common Terminology Criteria for Adverse Events; irAE, Immune-related adverse event

**Declarations**

*Ethics approval and consent to participate*

The protocol for this research project was approved by a suitably constituted ethics committee of Toranomon Hospital (approval no. 1879), and it conforms to the provisions of the Declaration of Helsinki. Informed consent was obtained from all participants in the form of opt-out on the website.

*Consent for publication*
Not applicable.

**Availability of data and materials**

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

**Competing interests**

There are no conflicts of interest to declare except for Yuji Miura: personal fees from Ono Pharmaceutical, Bristol Myers Squibb, MSD, and Takeda; Advisory Board personal member of Chugai Pharmaceutical Co. and Takeda; local PI and institutional financial interests from MSD and Ono Pharmaceutical. All of these were outside the submitted work.

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**Authors' contributions**

TY and YM contributed to data collection and manuscript writing. TY and YM were the major contributors to the analysis and interpretation of patient data. KT, MH, KS, and SU contributed to the study design. KT, MH, KS, and SU contributed to the interpretation of the data and the draft of this work and revisions. All authors have read and approved the final manuscript.

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**References**


Tables

Tables 1 and 2 are available in the Supplementary Files section.

Figures

Figure 1

Clinical course of case 1
Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- BMCcancerTable1final.xlsx
- BMCcancerTable2final.xlsx