[CASE REPORT]

Life-threatening Hyperkalemia Associated with Axitinib Treatment in Patients with Recurrent Renal Carcinoma

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Abstract:
Axitinib has emerged as a promising antineoplastic agent for the treatment of advanced renal cell carcinoma. Although the administration of axitinib was well-tolerated in clinical trials, the real-world safety and tolerability remain unverified. We herein report a patient with metastatic renal cell carcinoma who suddenly developed life-threatening hyperkalemia following the initiation of axitinib treatment. Although hyperkalemia has been reported with an incidence of <10%, acute severe hyperkalemia may be a considerably critical adverse event of axitinib therapy, especially in patients with risk factors for hyperkalemia. An abundance of caution for unusual and unpredictable toxicities is warranted when using axitinib.

Key words: adverse event, axitinib, hyperkalemia, renal cell carcinoma


Introduction

Over the past few decades, novel forms of molecular-targeted agents have become available in cancer treatments, including the second-generation tyrosine kinase inhibitor axitinib (Inlyta Tablets; Pfizer, New York, USA) (1, 2). Since 2012, axitinib has been used worldwide as an antineoplastic agent for the treatment of metastatic or unresectable renal cell carcinoma after failure of a prior first-line therapy (1-4). Although hypertension, cardiac failure, and hemorrhaging have been reported as the most common dose-limiting toxicities of axitinib, the majority of cases have been suggested to be manageable with dose modification and standard supportive care (3, 4). However, the need to be alert for acute severe hyperkalemia has never been emphasized. Given that targeted agents like axitinib have emerged as remarkable anticancer therapies in the current era, the awareness of un-emphasized critical adverse effects provides important clinical implications, particularly with regard to oncologic emergency.

We herein report a patient with metastatic renal cell carcinoma who developed acute severe hyperkalemia following the initiation of axitinib treatment.

Case Report

An 85-year-old woman presented with profound bradycardia due to acute hyperkalemia. She had a history of chronic kidney disease secondary to a left nephrectomy for renal clear cell carcinoma (pT3N0M0) at 64 years of age and was diagnosed with multiple pancreatic metastases at 83 years of age. She also had hypertension, which was treated with olmesartan (10 mg/day) and nifedipine (20 mg/day), and was prescribed lansoprazole (15 mg/day), estazolam (2 mg/day) and etizolam (0.5 mg/day) as well.

Three weeks before her presentation, she had been hospitalized for the initiation of axitinib (6 mg/day) treatment following progressive disease with sunitinib that had been administered as the first-line therapy for her metastatic renal...
cell carcinoma (5, 6) (Fig. 1). The starting dose of axitinib was reduced from 5 mg twice daily (standard dose) to 3 mg twice daily due to concerns about her advanced age, concomitant hypertension, and a slight increase in plasma brain natriuretic peptide at baseline (Table). During the two-week hospitalization, she showed no adverse events related to the administration of axitinib, with serum levels of potassium within the normal range (4.5-4.8 mEq/L) and a trough plasma level of axitinib of 5.1 ng/mL, which was only marginally higher than the trough concentration to achieve a tumor response (>5.0 ng/mL) (7). After discharge, she remained in her usual state of health and had a performance status 0, consumed a regular diet without high potassium-content foods, and was not taking any natural or manufactured CYP3A4 inhibitors (e.g., macrolides, tetracyclines,azole antifungals, protease inhibitors, or grapefruit juice) that might affect the metabolism of axitinib. Three days after her discharge (17 days after the initiation of axitinib treatment), she complained of the sudden onset of general fatigue, nausea, and dizziness and was transferred to our emergency department.

On presentation, she showed a decreased level of consciousness (Glasgow Coma Scale score of E3V4M6) with the following vital signs: heart rate, 25 beats/min; blood pressure, 98/58 mmHg; body temperature, 35.4°C; respiratory rate, 18 breaths/min, and oxygen saturation 100% in ambient air. Her height, weight, and body mass index were 141 cm, 45.0 kg, and 22.6 kg/m², respectively. The electrocardiogram showed sinus arrest with a slow junctional escape rhythm (25 beats/min) (Fig. 2). Acute coronary syndrome was ruled out based on the normal findings of echocardiography and cardiac biomarkers, and her volume status evaluated by echocardiography was normal. Notably, laboratory data showed profound hyperkalemia of 7.7 mEq/L associated with hyperphosphatemia, hyperuricemia, a deteriorated renal function with modest metabolic acidosis, and liver dysfunction, none of which had been noted on the day of the discharge 3 days before the presentation (Table). Her hyperkalemia was acute and critical enough to cause sinus arrest and could not be attributed to metabolic acidosis (Table).

We initiated prompt therapies for the severe hyperkalemia with resultant sinus arrest via the intravenous administration of calcium gluconate, sodium bicarbonate, and insulin with glucose, in addition to intermittent furosemide infusions with saline hydration in order to facilitate urinary potassium excretion. She returned to a normal sinus rhythm immediately after the correction of hyperkalemia (Fig. 2). Her liver
Table.  Laboratory Data.

<table>
<thead>
<tr>
<th></th>
<th>Reference</th>
<th>Baseline†</th>
<th>On admission</th>
<th>On discharge</th>
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<tbody>
<tr>
<td>Blood gas analysis</td>
<td></td>
<td></td>
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<tr>
<td>Fraction of inspired oxygen</td>
<td>0.21</td>
<td>NA</td>
<td>7.328$</td>
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<td>pH</td>
<td>NA</td>
<td>36.5$</td>
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<td>pO2 (mmHg)</td>
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<td>22.1$</td>
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<tr>
<td>pCO2 (mmHg)</td>
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<td>-1.1$</td>
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<tr>
<td>HCO3$⁻ (mmol/L)</td>
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<td>10.8$</td>
<td>+8.8$</td>
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<tr>
<td>Base excess (mmol/L)</td>
<td>NA</td>
<td>0.37-1.65</td>
<td>3.2</td>
<td>0.5$</td>
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<tr>
<td>Others</td>
<td></td>
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<td>BUN (mg/dL)</td>
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<td>23</td>
<td>50</td>
<td>18</td>
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<td>Cre (mg/dL)</td>
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<td>eGFR (mL/min/1.73 m²)</td>
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<td>Ca (mg/dL)</td>
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<td>Plasma glucose (mg/dL)</td>
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<td>BNP (pg/mL)</td>
<td>&lt;18.4</td>
<td>149.5</td>
<td>158.3</td>
<td>74.2</td>
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</table>

†Two days before the initiation of axitinib treatment;$venous;$arterial and on discharge from ICU.


function normalized as well within a few days, a compatible course in the setting of shock liver. She did not show recurrence of hyperkalemia or bradyarrhythmia after the cessation of axitinib and olmesartan (Fig. 3), and she was discharged home in her premorbid state seven days after presentation.

Discussion

The present case highlighted two important clinical issues. First, serious hyperkalemia unexpectedly developed following the administration of axitinib in an elderly patient with moderate chronic kidney disease and hypertension who was being treated with an angiotensin II receptor antagonist. Second, physicians should be alert for unusual and unpredictable treatment-related hyperkalemia, especially in patients susceptible to develop hyperkalemia such as those with an advanced age, chronic kidney disease, and the concomitant use of drugs that may increase the serum potassium levels. To our knowledge, this is the first case report describing acute life-threatening hyperkalemia associated with the initiation of axitinib treatment.

Clinicians should consider the possibility of axitinib-induced hyperkalemia, especially in patients with predisposing factors for this electrolyte disturbance, such as those with an advanced age, preexisting renal insufficiency, and the concomitant administration of drugs that inhibit the renin-angiotensin-aldosterone system. Axitinib is metabolized predominantly in the liver through CYP3A4, and the renal function does not affect its clearance (1). The label instructions of axitinib describe the frequency of potassium disturbances of both hyper- and hypokalemia to be <10%. However, in phase I, II, and III trials, common adverse events related to axitinib included hypertension, fatigue, hand-foot syndrome, and gastrointestinal symptoms (8-13), and no unexpected adverse events, including severe hyperkalemia, occurred. Consistent with these clinical trials, recent real-world data have described no adverse events of hyperkalemia associated with the use of axitinib (4). Our patient was treated with axitinib at a reduced dose (3 mg twice daily) due to concerns associated with her advanced age, concomitant hypertension, and a slight increase in the plasma brain natriuretic peptide level at baseline (Table). This treatment was well-tolerated without adverse events during the two-week hospitalization with repeated monitoring of the liver and renal function, electrolytes, and blood pressure. Nonetheless, she developed an abrupt hyperkalemic emergency only three days after the discharge.

The mechanism by which axitinib causes hyperkalemia is
or a high chemosensitivity (18-20). By definition, these elec-syndrome most commonly occurs in patients with hema-diarythmia, acute kidney injury, and seizure (18). This pocalcemia in response to anticancer therapy, leading to car-
hyperlactemia, hyperphosphatemia, and hy-
slysis syndrome, which is characterized by acute and severe sudden onset of hyperkalemia in this patient may be tumor
sion, and infections (15). An alternate explanation for the inflammatory drugs, volume depletion, systemic hypoten-
high potassium-content foods (17), use of non-steroidal anti-
tment of hyperkalemia, including the excessive intake of
patient did not have such additional risk factors for the develop-
ment. Although no specific treatment of axitinib-induced hy-
pertension is described in the literature, it has been reported
that standard antihypertensive therapy is suitable for most
patients with tyrosine kinase inhibitor-related hyperten-
sion (25). The current guidelines for the management of hy-
pertension (26-28) recommend angiotensin-converting en-
zyme inhibitors and angiotensin-receptor blockers as the
drug of choice for the treatment of hypertension in patients
with a variety of underlying renal and cardiovascular dis-
eses, including chronic kidney disease, proteinuria, and
heart failure. Indeed, angiotensin-receptor blockers are the
second-most common antihypertensive drugs prescribed in
Japan (27). Considering that hypertension is one of the most
common adverse events in patients administered axitinib, the
patients are likely to be prescribed renin-angiotensin-
ardosterone inhibitors, which carry a risk of hyperkalemia,
The authors state that they have no Conflict of Interest (COI).

References


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