Hyponatremia and thrombocytopenia associated with sorafenib treatment for renal carcinoma: an alert of an adverse event

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Abstract To date, the manufacturer of sorafenib has reported that the hyponatremia and thrombocytopenia associated with its use are generally moderate and tolerable and have resulted in no mortalities. In this article we describe a Japanese patient with severe hyponatremia and thrombocytopenia that were likely related to sorafenib treatment for metastatic renal carcinoma. Oncologists should be aware of hyponatremia and thrombocytopenia as an adverse effect related to this agent.

Keywords Hyponatremia · Renal carcinoma · Sorafenib · Thrombocytopenia

Introduction

Renal carcinoma (RC) accounts for approximately 3 % of adult malignancies and 90–95 % of neoplasms arising from the kidneys [1]. Approximately 30 % of patients with RC present with advanced metastatic disease that is highly resistant to chemotherapy and is associated with a notoriously poor prognosis [2]. Sorafenib is a novel, orally administered, multi-targeted kinase inhibitor that was approved for the treatment of advanced RC. In Japan, sorafenib was approved for the treatment of advanced RC in April 2008.

Sorafenib is an effective treatment option for RC, resulting in stable disease in 74 % of patients [3]. In addition, unlike some traditional anticancer therapies indicated for RC, adverse events associated with sorafenib

are generally moderate and tolerable. Common adverse events include diarrhea (experienced by 43 % of patients), rash (40 %), fatigue (37 %), hand-foot skin reaction (30 %), alopecia (27 %), and nausea (23 %). In this article, we describe a Japanese patient with severe hyponatremia and thrombocytopenia likely related to sorafenib treatment for metastatic RC.

Case report

A 75-year-old Japanese woman with a right renal mass incidentally found during an annual checkup was referred to our hospital in December 2009. Dynamic computed tomography (CT) confirmed a well-defined, hyperdense right renal mass measuring 5.7×6 cm, with multiple metastatic tumors of the liver and pancreas (Fig. 1). The clinical diagnosis was RC clinical T3aN0M1. The patient had a history of cardiac events such as hypertension and ischemic heart disease, which were controlled, but no history of hyperlipidemia, hypothyroidism, or diabetes mellitus. Her medications included aspirin, nifedipine, and digoxin. She had a 20-pack-year smoking history which ended 5 years previously and she rarely consumed alcohol. At that time, the patient seemed to be unable to undergo radical nephrectomy and metastasectomy because of the local extent of the disease. The patient's performance status was assessed as 0 according to the Eastern Cooperative Oncology Group (ECOG) performance status criteria and she had a Memorial Sloan–Kettering Cancer Center risk factor of 1. Since sunitinib is more frequently associated with cardiovascular events [4], the patient and clinician selected sorafenib at the standard oral dose of 800 mg/day as the primary treatment option. At the start of therapy, the patient's complete blood count was normal. Chemistry

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Fig. 1 CT images at diagnosis showed a tumor of the right kidney measuring 5.7×6 cm

values included sodium 139 nmol/l, potassium 4.1 nmol/l, chloride 102 nmol/l, blood urea nitrogen (BUN) 10.7 mg/dl, creatinine (Cr.) 0.5 mg/dl, and calcium 9.1 nmol/l. However, C-reactive protein (CRP) level was high (5.79 mg/dl), but there was no evidence of fever or bacterial prodromes. She showed normal thyroid function, including serum thyroid-stimulating hormone (1.08 μ IU/ml, normal range 0.35–4.94 μ IU/ml), free triiodothyronine (1.76 pg/ml, normal range 1.71–3.71 pg/ml), and free thyroxine (1.16 pg/ml, normal range 0.7–1.48 pg/ml). On day 10 of sorafenib therapy, the patient had several symptoms including nausea, loss of appetite, lethargy, fatigue, and a slight deterioration of consciousness. However, no dry mouth, dry axilla, or swelling of extremities were observed. The patient's serum sodium level decreased to 124 nmol/l and reached a nadir of 116 nmol/l on the day 14; the urinary sodium level remained normal. BUN and creatinine levels were 31.4 and 1.1 mg/dl, respectively. During the hyponatremia we confirmed that the antidiuretic hormone was 59.8 pg/ml (normal range 0.30–3.5 pg/ml). Furthermore, the albumin level decreased from 3.2 to 1.5 g/dl. Laboratory analysis showed a white cell count of 4.2×10^3 cells/ μ l. Platelet count was 30×10^3 cells/ μ l, which was believed to be an adverse effect of sorafenib therapy. There was no evidence of hypothyroidism.

Sorafenib treatment was discontinued and the patient was treated with water restriction and 3 % saline solution intravenously. At day 17 (after the initiation of sorafenib therapy), although the serum sodium level began to increase (127 nmol/l) and the patient received a platelet transfusion, platelet count (Plt) remained low (8×10^3 cells/ μ l). The patient's albumin level also remained low at 1.4 g/dl and laboratory data showed severe hepatotoxicities such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (G-GTP), total

Table 1 Hematological and biochemical data before and after sorafenib therapy

		Day 0	Day 15	Day 18	Day 19
Hb	g/dl	10.1	11.6	11.3	11.8
Plt	10^3 cells/ μ l	24.9	9.6	3.0	0.8
BUN	mg/dl	10.7	12.9	31.4	40.9
Cr.	mg/dl	0.5	0.6	1.1	1.4
Na	nmol/l	139	124	116	127
Alb	g/dl	3.2	2.1	1.5	1.4
T-BIL	mg/dl	0.87	0.85	2.39	2.26
AST	IU/l	39	72	164	351
ALT	IU/l	30	56	82	177
G-GTP	IU/l	114	214	181	153
ALP	IU/l	691	1379	1132	979
LDH	IU/l	198	286	797	1530
CRP	mg/dl	5.79	7.16	8.40	8.79

bilirubin (T-BIL), and alkaline phosphatase (ALP) levels (Table 1). The CT showed no findings of brain bleeding, cerebral edema, interstitial pneumonia, or progression of disease. However, the patient's level of consciousness and dyspnea gradually worsened, and nasal inhalation of O_2 was required to maintain the O_2 saturation, which increased from 2 to 10 l/min O_2 . According to the wishes of the patient's family, an intratracheal intubation was not performed. The patient died during the night from cardio-respiratory arrest. We were not allowed to perform an autopsy to establish the cause of death and determine the pathology of the renal mass.

Discussion

Sorafenib targets the activity of angiogenic growth factors and has had promising results for the treatment of metastatic RC. Sorafenib has been associated with a multitude of adverse effects but is better tolerated than interleukin-2 and interferon-alpha, which have been the standard therapies for patients with metastatic RC [5]. A search of the literature did not identify any prior reports of sorafenib-induced adverse events with regard to critical hyponatremia. In 2008, the manufacturer of sorafenib amended the safety information after Japanese patients experienced adverse events of hyponatremia (9 patients) and thrombocytopenia (6 patients) [6]. However, these adverse events associated with sorafenib were generally moderate and tolerable and none of the patients died. The nature of the disorder is enigmatic. The mechanisms underlying hyponatremia include dysregulation of the neurohypophyseal hormone arginine vasopressin (AVP), which helps to regulate fluid and electrolyte balance in the body [7]. Hyponatremia can be classified as hypotonic, isotonic, or

hypertonic on the basis of serum tonicity or effective osmolality, which is determined by the presence of solutes such as sodium and glucose that cannot move freely across cell membranes [8]. Hypotonic hyponatremia, defined as an excess of water relative to sodium [9], can be hypovolemic, euvolemic, or hypervolemic and may be associated with renal and endocrine disorders, diuretic use, the syndrome of inappropriate secretion of antidiuretic hormone (SIADH), gastrointestinal sodium loss from vomiting and diarrhea, acute water overload because of intravenous fluid administration, chronic heart failure, and cirrhosis [10].

Generally, a common cause of hyponatremia in patients with cancer is SIADH, which may result from ectopic antidiuretic hormone (ADH) production by the tumor tissue. In small cell lung cancer, SIADH is well described and has been associated with a reduced survival [11]. Although SIADH is a likely explanation, no reports exist on SIADH disturbance in RC. Hyponatremia and volume depletion are also seen in Addison's disease. Although this disease may be seen in patients with RC with extensive adrenal metastases, there was no evidence of metastatic disease in the adrenals of this patient. Another reason for the hyponatremia may be a renal dysfunction in the exchange mechanism of sodium in the tubules. Jeppesen et al. [12] reported that low values of serum sodium were significantly prognostic and predictive factors in patients with metastatic renal cell carcinoma. Although we were not able to specify the mechanism of hyponatremia in our case, the toxic effects of sorafenib include decreased papillary solute content and maximal urinary osmolality, which are major factors for increasing vasopressin secretion. Chemotherapeutic agents including vincristine, vinblastine, cyclophosphamide, cisplatin, and melphalan stimulate AVP secretion [13]. Therefore, the stimulate for such vasopressin release probably was hypovolemia caused by renal salt wasting. These potential mechanisms remain speculative and further studies are needed to confirm the mechanism behind low serum sodium related to sorafenib.

According to a phase II study in Japan serious hematologic toxicities from sorafenib therapy were rare and mainly associated with cytotoxic effects [14]. It has been proposed that sorafenib-related thrombocytopenia results from increased platelet consumption secondary to damaged endothelium rather than inhibition of normal hematopoiesis [15]. Our patient suffered from grade 4 sorafenib-related thrombocytopenia. Although one limitation of our report is the lack of pathological evidence, we doubt that disseminated intravascular coagulation caused by thrombocytopenia and congestive heart failure contributed to death in this patient. Despite regular monitoring, this adverse event

failed to resolve spontaneously. This may suggest that patients with antivascular endothelial growth factor therapies might have one or more manifestations of a wide spectrum of disorders and require close monitoring. Although our findings are limited by the inability to examine the pathology of RC, our experience with the present patient suggests that sorafenib can potentially induce serious hyponatremia and thrombocytopenia in patients with metastatic RC.

Conflict of interest The authors declare that they have no conflict of interest.

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