Tolvaptan corrects hyponatremia and relieves the burden of fluid/dietary restriction and hospitalization in hyponatremic patients with terminal lung cancer: a report of two cases

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Received: 10 May 2018 / Accepted: 6 January 2019 / Published online: 14 January 2019
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Abstract

Case 1: A 45-year-old man, admitted for symptomatic hyponatremia, was diagnosed with advanced small-cell lung cancer and severe hyponatremia due to the syndrome of inappropriate secretion of antidiuretic hormone. In addition to chemotherapy, the patient was treated with increased dietary salt intake (15 g/day), fluid restriction of 500 mL/day, and amino acid supplementation to maintain a urea load of 31 g/day. Due to the difficulty in changing his habit of drinking 2–3 L/day after discharge, tolvaptan was started. This resulted in correction of hyponatremia, which facilitated earlier discharge and improved his quality of life by eliminating the need for dietary restriction.

Case 2: An 88-year-old man with asymptomatic hyponatremia was admitted for assessment of pleural effusion. He was diagnosed with small-cell lung cancer with mild hyponatremia due to the syndrome of inappropriate secretion of antidiuretic hormone. He was treated with best supportive care and dietary modification (salt intake of 15 g/day and fluid restriction of 400 mL/day). He found it difficult to comply with the dietary changes, and prolonged hospitalization was required for hyponatremia correction. Therefore, tolvaptan was initiated, which corrected his hyponatremia, and the patient was discharged. In summary, tolvaptan results in stable correction of hyponatremia in patients with terminal small-cell lung cancer complicated by the syndrome of inappropriate secretion of antidiuretic hormone. Furthermore, it improves the quality of life of these patients by relieving the burden of strict dietary modifications and prolonged hospitalization.

Keywords Tolvaptan · Small-cell lung cancer · Syndrome of inappropriate secretion of antidiuretic hormone · Quality of life

Introduction

Hyponatremia is a common electrolyte disorder in the course of small-cell lung cancer (SCLC), and the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) occurs in approximately 11–15% of cases [1, 2]. Ectopic production of antidiuretic hormone (ADH) by the tumor, as well as enhanced secretion of ADH due to adrenal metastases; anti-cancer agents, like cisplatin; drugs, including non-steroidal anti-inflammatory drugs, opioids, and antidepressants; and side effects, such as nausea, vomiting, stress, and pain as

part of the disease or following chemotherapy are the main causes of SIADH [3].

Hyponatremia due to SIADH in SCLC patients is often diagnosed as chronic and asymptomatic, although patients may present with non-specific symptoms, such as malaise, fatigue, cognitive symptoms, and decline in the activities of daily living (ADL), which are commonly recognized as cachectic symptoms of the malignancy itself. However, these symptoms are actually derived from hyponatremia, indicating that they can be reversible by correcting the hyponatremia. Given that these symptoms are associated with reduced quality of life (QOL) in patients with terminal cancer, their diagnosis and treatment are crucial.

Nevertheless, patients with terminal cancer have limited life expectancy (5-year survival rate of limited stage SCLC of 15% [4]), and therefore best supportive care (BSC) is often selected as a terminal treatment modality; likewise, if hyponatremia is not severe or progressive,

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only water restriction is selected as previously reported in 11.8% of SCLC patients with SIADH [5], in spite of the challenges in its correction [3, 6].

Tolvaptan is a selective vasopressin V2-receptor antagonist, which is administered orally and increases the renal electrolyte-free water clearance and serum sodium concentrations ($s[Na^+]$) in the body [7, 8]. Although the use of tolvaptan for the treatment of SIADH is not covered by health insurance in Japan, it has been reported as an effective treatment of hyponatremia in SCLC patients with SIADH [6, 9–11]. However, to date, only a few reports have demonstrated that tolvaptan improves the QOL in patients [10, 11]. Furthermore, no studies have evaluated whether tolvaptan can relieve the burden associated with strict dietary restriction and prolonged hospitalization, and thus, unintentionally improve the QOL of patients with terminal stage SCLC requiring treatment for SIADH.

We present herein the efficacy and safety of tolvaptan, and its influence on QOL in two terminal lung cancer patients with SIADH.

Case reports

Case 1

A previously healthy 45-year-old man was admitted with symptomatic hyponatremia associated with personality disorder and agitation. Figure 1 illustrates the clinical course of his first admission. Although he was hypertensive and tachycardic at admission, the symptoms resolved following administration of intravenous fluids. Physical examination showed dryness in the oral cavity and abdominal ultrasonography revealed respiratory variation in the inferior vena cava. Blood and urine tests showed hyponatremia (serum sodium concentration ($s[Na^+]$) of 113 mEq/L), low urine $[Na^+]$ ($u[Na^+]$) (10 mEq/L), and hemoconcentration (Fig. 2). Based on these results, we assumed that the patient was volume-depleted and administered normal saline (NS), following which $s[Na^+]$ was corrected to 122 mEq/L after 22 h, and the patient was euvoletic; however, 4 h later, hyponatremia progressed ($s[Na^+]$ of 120 mEq/L), serum uric acid concentration decreased from 2.1 to 0.6 mg/dL, and $u[Na^++K^+]$ increased to 126 mEq/L, despite NS treatment. The chest computed tomography performed on admission revealed a tumor, which was subsequently diagnosed

Fig. 1 Clinical progress of Case 1 during his first admission. The white arrow indicates the total hospitalization period, and the black arrow within indicates the treatment time required to correct hyponatremia. The amount of salt intake shown in the table refers to the total amount of salt administered intravenously and orally, and that in the parentheses indicate the orally ingested salt content. The black line

in the graph represents the $s[Na^+]$ and the gray one, body weight. ADH antidiuretic hormone, BW body weight, $In([Na^++K^+])$ input of sodium plus potassium concentrations, I.V. intravenous administration, $u([Na^++K^+])$ urine sodium plus potassium concentrations, $uOsm$ urine osmolality, $s[Na^+]$ serum sodium concentration

CBC		Chemistries				Serology			Urinalysis	
WBC	1.1 × 10 ³ /mm ³	TP	7.8 g/dL	AST	30 IU/L	ADH	4.0 pg/mL		pH	6.0
Neutro	84.0 %	Alb	5.0 g/dL	ALT	29 IU/L	NSE	13.8 ng/mL		protein	+1
Lympho	8.0 %	BUN	14.8 mg/dL	ALP	330 IU/L	Pro	612 pg/mL		uric blood	-
Mono	7.0 %	Cr	0.6 mg/dL	CK	220 IU/L	-GRP			glucose	-
Eosino	0.0 %	UA	2.1 mg/dL	Glu	135 mg/dL				ketone	+3
Baso	1.0 %	Na	113 mEq/L	CRP	1.51 mg/dL				uCr	126 mg/dL
Myelo	0.0 %	K	4.1 mEq/L	pOsm	226 mOsm/kg				uUN	480 mg/dL
RBC	4.72 × 10 ⁶ /mm ³	Cl	75 mEq/L						uNa	10 mEq/L
Hb	14.9 g/dL	Ca	9.6 mg/dL						uK	36.7 mEq/L
Ht	44.8 %	P	4.6 mg/dL						uCl	20 mEq/L
Plt	27.6 × 10 ⁴ /mm ³								uOsm	402 mOsm/kg

Fig. 2 Laboratory studies of Case 1 (on admission). *ADH* antidiuretic hormone, *Alb* albumin, *ALP* alkaline phosphatase, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *Baso* basophil, *BUN* blood urea nitrogen, *Ca* calcium, *CBC* complete blood count, *CEA* carcinoembryonic antigen, *CK* creatine kinase, *Cl* chloride, *Cr* creatine, *CRP* C-reactive protein, *Glu* glucose, *Hb* hemoglobin, *Ht* hematocrit, *K* potassium, *Lympho* lymphocytes, *Mono* monocyte, *Myelo* myelocyte, *Na* sodium, *Neutro* neutrophil, *NSE* neuron-specific enolase, *P* phosphate, *Plt* platelet, *Posm* plasma osmolality, *Pro-GRP* pro-gastrin-releasing peptide, *RBC* red blood cell, *TP* total protein, *UA* uric acid, *uCl* urine chloride, *uCr* urine creatinine, *uK* urine potassium, *uNa* urine sodium concentration, *Uosm* urine osmolality, *uUN* urine urea nitrogen, *WBC*, white blood cell

Fig. 3 Chest CT of Case 1 (on admission). CT demonstrating left hilar tumor and enlarged peripheral hilar lymph nodes. *CT* computed tomography

as SCLC (pT2bN3M0) (Fig. 3). Additional investigations revealed an ADH concentration of 5.0 pg/mL on day 13, which was disproportionately high for hypotonic hyponatremia, and thus the diagnosis of cancer-related SIADH was confirmed [12].

Following this diagnosis, $s[Na^+]$ was carefully corrected with 3% hypertonic saline and reached 135 mEq/L after 1 week. Oral intake was started on day 4 and subsequently, the patient was started on a high-salt diet (a salt content of 15 g/day) with fluid restriction (400 mL/day),

and $s[Na^+]$ was stabilized at approximately 133 mEq/L until discharge. However, after discharge, he felt that it was difficult and burdensome to comply with the strict fluid restriction regimen since he used to routinely consume 2–3 L water as per his habit, and his appetite was good at all the times.

He was readmitted for his first course of cisplatin-based chemotherapy when $s[Na^+]$ was 138 mEq/L; however, 8 days after starting chemotherapy, hyponatremia ($s[Na^+]$ of 120 mEq/L) relapsed with increased fluid intake (about 700 mL/day) and chemotherapy-related side effects (intravenous fluid load and cisplatin-associated ADH secretion) (Fig. 4). In addition to fluid restriction, a solute: protein jelly and amino acid formula in the form of urea was added to his dietary regimen, because urea is not commercially available in Japan. As a result, hyponatremia was corrected to 134 mEq/L in 1 week; however, he was advised to continue with the strict restricted diet and fluid intake and tolerate the bitter taste of the nutritional formula. As a result of these challenges, the initially planned hospital stay of 1 week extended to more than 1 month until the next chemotherapy session to correct the $s[Na^+]$ levels. Nevertheless, despite the restrictions placed, hyponatremia worsened after the second chemotherapy session.

Therefore, given the patient's dissatisfaction with both, the dietary modification and prolonged hospital stay, tolvaptan was started at a dose of 3.75 mg/day and gradually increased up to a maintenance dose of 7.5 mg/day. This resulted in stabilization of the $s[Na^+]$ levels at around 140 mEq/L, and he was discharged 5 days after starting tolvaptan. Subsequent chemotherapy treatments were performed on an outpatient basis, and the patient was permitted to drink 2–3 L/day and dietary restrictions were discontinued. Initiation of tolvaptan therapy improved the patient's quality of life and allowed him to return to work as a construction worker, which required copious intake of water to prevent a heat stroke.

Four months after the initiation of tolvaptan therapy, the patient developed brain metastases, and second-line chemotherapy was started. He was re-hospitalized due to loss of appetite, nausea, and exacerbation of pain owing to metastases in the pelvis, which developed during the second-line chemotherapy, and to facilitate administration of third-line chemotherapy and analgesia using opioids. Despite the presence of various stimuli of ADH secretion and water load during the third-line chemotherapy, only mild hyponatremia was noted. One month later, a palliative approach was adopted and treatment of tolvaptan was discontinued when oral ingestion became difficult. As a result, hyponatremia was worsened, and he died approximately 1 year after diagnosis.

Fig. 4 Progress chart after the second admission when cisplatin-based chemotherapy was started. The white arrow indicates the total hospitalization period, and the black period in it indicates the treatment period required to correct hyponatremia. The horizontal axis shows the patient's progress from the admission day (X day) in units of months. The black line in the graph represents the $s[Na^+]$ and

the gray one, body weight. ADH antidiuretic hormone, AMR amrubicin, CDDP cis-diamminedichloro-platinum, CPT-11 camptothecin, $ln([Na^++K^+])$ input of sodium plus potassium concentrations, $s[Na^+]$ serum sodium concentration, $u([Na^++K^+])$ urine sodium plus potassium concentrations, $uOsm$ urine osmolality, VP-16 etoposide

Case 2

An 88-year-old man with asymptomatic hyponatremia was admitted for further evaluation of pleural effusion. The clinical course is illustrated in Fig. 5. Initial investigations revealed mild hyponatremia ($s[Na^+]$ of 129 mEq/L), clinical euolemia, urine osmolality (488 mOsm/kg) higher than serum osmolality (268 mOsm/L) (Fig. 6), and ADH concentration of 1.5 pg/ml, which was disproportionately high given his hypotonic state. He was advised a high-salt diet (a salt content of 16 g/day) with fluid intake 2 L/day, and a relatively hypotonic fluid was administered. After 5 days, the $s[Na^+]$ decreased by 5 mEq/L; however, he continued to produce hypertonic urine. He was subsequently diagnosed with SCLC (pT4N2M1a) complicated by cancer-related SIADH. Given his advanced age, he was administered BSC, but he maintained a good appetite. A high-salt (15 g/day) diet with fluid restriction (400 mL/day) was started by a nephrology consultant. However, his poor understanding regarding diet therapy often resulted in hyponatremia due to excessive unsupervised fluid intake.

Therefore, tolvaptan (initial dose of 3.75 mg/day and maintenance dose of 1.875 mg/2 days) was carefully initiated, as the patient grew dissatisfied with the prolonged hospital stay and need to adhere to strict dietary therapy. Tolvaptan was effective, and hyponatremia stabilized after

10 days. He was re-hospitalized due to increase in pleural effusion with nausea and loss of appetite, and subsequently discharged after 4 days without correction of hyponatremia. However, at the time of his third hospitalization due to exacerbation of respiratory distress and appetite loss, hyponatremia worsened as he had discontinued tolvaptan. A palliative care approach was adopted; however, he later died of carcinomatous lymphangitis.

In both cases, significant adverse events related to tolvaptan, including hypernatremia or liver dysfunction were not observed during the patients' clinical courses.

Discussion

Our cases demonstrated two important points related to the use of tolvaptan for SIADH in patients with advanced stage SCLC. First, a low dose of tolvaptan can correct hyponatremia more efficiently and stably than a high-salt diet with fluid restriction, without any adverse events, such as hypernatremia and liver dysfunction. Thus, tolvaptan can shorten the length of hospital stay, otherwise required to correct hyponatremia, as it can be administered in an outpatient setting. Second, treatment with tolvaptan can improve the patients' subjective QOL, such as eliminating the anxiety

Fig. 5 Progress chart of Case 2. The white arrow indicates the total hospitalization period, and the black period in it indicates the treatment period required to correct hyponatremia. The horizontal axis shows the patient's progress from the admission day (X day) in units of months. The black line in the graph represents the $s[Na^+]$ and

gray one, body weight. ADH antidiuretic hormone, BW body weight, $ln([Na^++K^+])$ input of sodium plus potassium concentrations, $s[Na^+]$ serum sodium concentration, $u([Na^++K^+])$ urine sodium plus potassium concentrations, uOsm urine osmolality

CBC	Chemistries	Serology	Urinalysis
WBC $6.3 \times 10^3 /mm^3$	TP 5.8 g/dL	AST 28 IU/L	ADH 1.5 pg/mL
Neutro 81.5 %	Alb 2.5 g/dL	ALT 33 IU/L	NSE 156 ng/mL
Lympho 5.4 %	BUN 12.9 mg/dL	ALP 357 IU/L	Pro-GRP 3290 pg/mL
Mono 12.3 %	Cr 0.76 mg/dL	CK 21 IU/L	uric blood +
Eosino 0.8 %	UA 3.1 mg/dL	Glu 138 mg/dL	glucose -
Baso 0.0 %	Na 127 mEq/L	CRP 7.73 mg/dL	ketone -
Myelo 0.0 %	K 4.3 mEq/L	pOsm 266 mOsm/kg	uCr 62.2 mg/dL
RBC $3.63 \times 10^6 /mm^3$	Cl 93 mEq/L		uUN 359.8 mg/dL
Hb 10.3 g/dL	Ca 8.1 mg/dL		uNa 28.3 mEq/L
Ht 31.4 %			uK 106 mEq/L
Plt $24.4 \times 10^4 /mm^3$			uCl 25.6 mEq/L
			uOsm 524 mOsm/kg

Fig. 6 Laboratory studies of Case 2 (on admission). ADH antidiuretic hormone, Alb albumin, ALP alkaline phosphatase, ALT alanine aminotransferase, AST aspartate aminotransferase, Baso basophil, BUN blood urea nitrogen, Ca calcium, CBC complete blood count, CEA carcinoembryonic antigen, CK creatine kinase, Cl chloride, Cr creatine, CRP C-reactive protein, Glu glucose, Hb hemoglobin, Ht hematocrit, K potassium, Lympho lymphocytes, Mono monocyte, Myelo myelocyte, Na sodium, Neutro neutrophil, NSE neuron-specific enolase, pH pounds Hydrogenii, Plt platelet, Posm plasma osmolality, Pro-GRP pro-gastrin-releasing peptide, RBC red blood cell, TP total protein, UA uric acid, uCl urine chloride, uCr urine creatinine, uK urine potassium, uNa urine sodium concentration, Uosm urine osmolality, uUN urine urea nitrogen, WBC white blood cell

and burden related to fluid/dietary restriction and improving aggressiveness for treatment.

Hyponatremia is found to be an independent predictor of mortality in SCLC after adjusting for confounding factors,

including age, sex, lactate dehydrogenase levels, and performance status (PS) in multivariate analysis [9]. Moreover, persistent hyponatremia is associated with a reduction in the opportunities for the aggressive treatment of lung cancer, and therefore adversely affects prognosis, PS, and the nutritional status of SCLC patients with SIADH [6, 9, 13–15]. Although it is reasonable to treat hyponatremia, clinicians often opt for BSC without correction of hyponatremia, since the prognosis of advanced stage lung cancer is very poor, and hyponatremia is often misdiagnosed as asymptomatic although non-specific symptoms, such as fatigue might be due to hyponatremia. Even if treatment for hyponatremia is selected for SCLC patients with SIADH, fluid restriction is the most frequently selected therapy (11.8%) even in severe cases, despite being ineffective [3, 5, 6].

The Hyponatremia Registry analyzed the current diagnostic and therapeutic management practices in cancer patients with SIADH, including patients with diagnoses other than SCLC; 53.4% of the patients included in the registry had a diagnosis of lung cancer, of which 25.1% had SCLC [5]. Tolvaptan was noted to have a corrective effect on hyponatremia (the greatest median rate of $s[Na^+]$ change (interquartile range), [3.0 (4.7) mEq/L/day], within the first 24 h after treatment initiation, followed by hypertonic saline [2.0 (7.0) mEq/L/day]). On the other hand, treatment with conservative monotherapy using fluid

restriction and isotonic saline was ineffective [0.8 (2.0) mEq/L/day and 1.3(3.0) mEq/L/day] and sometimes even exacerbated hyponatremia, and the combination of both therapies was more effective than monotherapy alone [1.9 (3.2) mEq/L/day]. The rate of overcorrection for tolvaptan and hypertonic saline was 14% and 16%, respectively; however, no case of osmotic demyelination syndrome was reported [5]. The above results demonstrate that tolvaptan is an effective and safe treatment for SIADH in SCLC patients.

Moreover, the effectiveness of tolvaptan in terms of QOL for the treatment of SIADH in SCLC patients has been reported in only a few areas of North America, Europe, and Asia, such as the improvement in the Eastern Cooperative Oncology Group (ECOG) score, which is an indicator of the performance status along with hyponatremia correction [10], and the effectiveness in terms of improvement in both medical cost and QOL, measured using quality-adjusted life years (QALYs) [11].

However, no study to date has evaluated the adverse effect on QOL related to diet restriction and mental stress during SIADH treatment in SCLC patients. Moreover, in Japan, tolvaptan is still underutilized for the treatment of hyponatremia, partly because it is expensive and not covered by the health insurance [16, 17]. In our cases, tolvaptan not only corrected hyponatremia more efficiently and stably than the conservative measures alone, but also improved the QOL of patients by eliminating the need for strict diet therapy and shortening the length of hospitalization. Importantly, tolvaptan was effective for both patients; the young patient receiving aggressive chemotherapy, and the elderly patient receiving BSC. In addition, in the former case, tolvaptan reduced patient's anxiety regarding his ability to continue working under strict fluid restriction conditions, whereas in the latter case, it resolved his dissatisfaction with strict fluid restriction regimen and allowed him to resume his previous eating habits. In the advanced stage SCLC patients with poor prognosis, rather than improving their survival, it may be more relevant to improve their QOL, and allow patients to resume their normal eating and drinking patterns and spend more time at home. Although our cases only referred to QOL related to diet and mental stress as reported by patients, it is likely that other symptoms related to hyponatremia such as fatigue, cognitive symptoms, and decline in ADL may also have been improved.

The limitation of this study was that we could not concretely present the ECOG PS score as an efficient indicator of QOL. In both cases, tolvaptan was used to correct hyponatremia, but we did not identify any changes in PS from a baseline score of 1, even after administration of tolvaptan. Thus, at the terminal stage, when the score suddenly worsened, we assumed that this was most likely due to the influence of SCLC itself. Therefore, it is necessary to have a

QOL score that can measure more minute changes, and to carry out prospective research with a larger number of cases.

In conclusion, our cases demonstrated that tolvaptan not only corrected hyponatremia more efficiently and stably than dietary and fluid restrictions, but also relieved the burdens of the latter, and the associated prolonged hospitalization required for correction of $s[Na^+]$. This resulted in improved QOL, and patient comfort in both the young SCLC patient receiving aggressive chemotherapy and the elderly SCLC patient receiving BSC. Moreover, tolvaptan has the added potential benefit of long-term use in an outpatient setting to improve the QOL of SCLC patients with SIADH.

Acknowledgements The authors thank Aya Sakurai, a pharmacist of the Renal Disease Integrated Care Center of St. Marianna University School of Medicine Hospital, for managing data of this case report. We would like to thank Editage (<http://www.editage.jp>) for English language editing.

Funding None.

Compliance with ethical standards

Conflict of interest Honoraria: Naoto Tominaga (Otsuka Pharmaceutical), and Yugo Shibagaki (Novartis pharma, Otsuka Pharmaceutical). Research funding: Yugo Shibagaki (Teijin Pharma, Otsuka Pharmaceutical, Takeda, Kyowa-Hakko Kirin).

Ethics approval This article does not contain any studies with human participants performed by any of the authors.

Informed consent The design of this report was approved and the requirement for informed consent was waived by our institutional review board (No. 3950).

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