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NEPHROLOGY - ORIGINAL PAPER

Tolvaptan treatment in hyponatremia due to the syndrome of inappropriate secretion of antidiuretic hormone (SIADH): effects on survival in patients with cancer

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Abstract

Purpose To investigate the clinical outcomes of patients with hyponatremia who received supportive treatment or tolvaptan plus supportive treatment and the effects of treatment and other variables on overall survival

Methods This study included oncology patients who were hospitalized at two oncology centers between January 1, 2016 and December 31, 2019 for hyponatremia (sodium levels < 135 mEq/L) and who received tolvaptan plus supportive treatment ($n = 22$) or supportive treatment only ($n = 42$).

Results The median age of all the patients was 59 years (range 26–85) and 64.1% of the patients were male. There was no statistically significant difference between patients in the tolvaptan plus supportive treatment (TpST) group and the supportive treatment only (ST) group in terms of gender and age ($p > 0.05$). In the TpST group, recovery days of the hyponatremia after treatment and the length of hospital stay was shorter and hyponatremia symptoms and hospital complications were less frequent compared to the ST group ($p < 0.05$). There was no significant difference between the TpST group and the ST group in terms of overall survival (OS). OS was shorter in men who were non-responders to hyponatremia treatment and had recurrent hyponatremia. Multivariable analysis showed that normal sodium levels after treatment decreased the risk of death.

Conclusion In the treatment of hyponatremia in cancer patients, TpST was found to have more positive effects on blood sodium levels, length of hospital stay, hospital complications, and hyponatremia symptoms compared to ST. A decreased risk of death was observed in patients with normal sodium levels after treatment.

Keywords Cancer · Hyponatremia · Tolvaptan · Survival

Introduction

Hyponatremia is one of the most common electrolyte disorders in patients with cancer. Although it may occur due to the cancer itself, it could be related to treatments such as cyclophosphamide, vinca alkaloids, and platinum-based antineoplastic drugs [1, 2]. Hyponatremia due to ectopic antidiuretic hormone (ADH) production is seen in many types of cancers, especially small cell lung cancer, head and neck cancers, breast cancer, non-hodgkin lymphoma, and central nervous system tumors [3]. In acute hyponatremia, the clinical presentation is closely linked to the severity of the cerebral edema and can progress, ultimately leading to death, if no intervention is applied in the early period. The development of cerebral edema is often slower among cases of chronic hyponatremia [1, 2]. The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) should be diagnosed differently from other causes of hyponatremia, using the diagnostic criteria for SIADH: plasma Na concentration < 130 mEq/L, urine Na concentration > 20 mEq/L, and clinical absence of dehydration or edema. In the differential diagnosis, hypovolemic hypoosmolar hyponatremia etiologies should be ruled out. Cerebral salt-wasting

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syndrome (CSWS) is one of the causes of hypovolemic hyponatremia. In this syndrome, low plasma osmolality, urine osmolality above 100–150 mOsm/kg, and urine Na concentration above 20 mEq/L make the differential diagnosis. Mechanism of CSWS is associated with humoral and neural mechanisms. Atrial natriuretic peptide (ANP) and Brain natriuretic peptide (BNP) increase and they also increase the glomerular filtration rate, providing diuresis and natriuresis [4, 5].

Cancer-related hyponatremia generally has a poor prognosis. It is resistant to the treatments applied and requires long-term hospitalization of the patients, thereby increasing the cost of treatment [6–8], hypertonic saline solution is generally preferred in cases of severe hyponatremia. In addition, fluid restriction and tolvaptan therapy can be used as the first-line treatment in moderate hyponatremia. Fluid restriction is not often possible in oncology patients because hydration is required in intravenous chemotherapy applications [9]. Therefore, medical treatment is a life-saving option for the hyponatremia of cancer patients. Although medical treatment options are limited, tolvaptan is a frequently preferred agent due to its role as a selective vasopressin V2-receptor antagonist. It is also used for treating hyponatremia secondary to inappropriate ADH syndrome [10]. However, tolvaptan treatment requires hospitalization and recipients require of blood sodium level monitoring. The need for hospitalization in order to administer tolvaptan may lead to some hospital-related risks, such as infection, especially in patients with cancer [11].

The general condition of cancer patients is negatively affected by the effects of their disease and the quick management and treatment of additional conditions such as hyponatremia, can prevent patients from getting worse. In this study, we aimed to investigate the clinical outcomes of patients receiving supportive treatment or tolvaptan for hyponatremia and the effects of the treatment and other variables on overall survival (OS).

Materials and methods

This study included cancer patients who were hospitalized at two centers of the University of Health Sciences (Ankara Dr. A. Y. Ankara Oncology Hospital and Gulhane Hospital) between January 1, 2016 and December 31, 2019 for hyponatremia and who received supportive treatment with or without tolvaptan. The data were scanned retrospectively through the hospital database. Patients' demographic characteristics, performance status (Eastern Cooperative Oncology Group Performance Status, ECOG PS) [12], disease characteristics (type and stage of cancer, comorbidities), treatment types (tolvaptan plus supportive, supportive), laboratory values before and after treatment (sodium, urea, creatinine, potassium), length of hospital stay, complications related to hospitalization, progression free survival, final control, and date of death were obtained from hospital records.

Overall survival was defined as the length of time from the date of hyponatremia diagnosis and treatment to the day of death.

Hyponatremia was defined as blood sodium levels < 135 mEq/L. The blood sodium levels of patients were also grouped as follows: 130–135 mEq/L = mild hyponatremia, 120–129 mEq/L = moderate hyponatremia, < 120 mEq/L = severe hyponatremia.

Patients consulted with clinical endocrinologists and nephrologists for the management of hyponatremia. Fluid restriction, hypertonic infusion, and normal saline applications to hospitalized oncology patients were classified as the supportive therapy group. Patients who were administered tolvaptan plus supportive treatment in the treatment of hyponatremia were classified as the tolvaptan plus supportive treatment group. In this study, the sodium value targeted with the treatment of patients was 135–145 mEq/L. Discharge criteria were the improvement of patients' hyponatremia symptoms, and the sodium value was equal and higher than 135 mEq/L.

Statistical analysis

All analyses were performed using SPSS v21 (SPSS Inc. Chicago. IL. USA). Normally distributed variables (age and potassium) were analyzed using the independent samples *t* test, while non-normally distributed variables (urea, creatinine, length of stay in hospital) were analyzed using the Mann Whitney *U* test. Repeated measurements of sodium values were analyzed using Friedman's analysis of variances by ranks. Post-hoc pairwise comparisons were performed with the Bonferroni correction method. Between-group comparisons of sodium values were performed by analyzing differences between the measurements using the Mann Whitney *U* test. Categorical variables were evaluated using the Chi-square test or Fisher's exact test. Survival analyses were performed using the Kaplan–Meier method. Survival comparisons between groups were performed using the Log-Rank test. Significant prognostic factors of death were determined using the Cox-regression analysis by employing the forward selection (conditional) method. Two-tailed *p* values of less than 0.05 were considered statistically significant.

Results

Of the 66 hyponatremia patients evaluated in this study, 34.4% ($n = 22$) were treated with TpST and 65.6% ($n = 42$) were treated with ST. The median age of all the patients was 59 years (range 26–85) and 64.1% of the patients were male.

The most frequent cancer types in patients were as follows: lung cancer 21.9% ($n=14$), breast cancer 29.7% ($n=19$), and rectum/colon cancer 10.9% ($n=7$). A total of 52 patients (82.54%) were at the metastatic stage. There was no statistically significant difference between patients TpST and ST groups in terms of gender and age ($p>0.05$). Compared to the ST group, the blood sodium level was higher, length of hospital stay was shorter, and hyponatremia symptoms and hospital complications were less frequent in the TpST group ($p<0.05$, Table 1).

Table 1 Summary of patients' characteristics according to treatment

	Tolvaptan + supportive	Supportive	Total	*p*
n	22	42	64	N.A
Age	57.64 ± 12.80	58.36 ± 8.65	58.11 ± 10.17	0.790
Gender				
Male	15 (68.18%)	26 (61.90%)	41 (64.06%)	0.824
Female	7 (31.82%)	16 (38.10%)	23 (35.94%)	
Type of cancer				
Lung	11 (50.0%)	8 (19.0%)	19 (29.7%)	
Breast	2 (9.1%)	7 (16.7%)	9 (14.1%)	
Nasopharynx	1 (4.5%)	1 (2.4%)	2 (3.1%)	
Rectum/colon	1 (4.5%)	6 (14.3%)	7 (10.9%)	
Neuroendocrine	2 (9.1%)	4 (9.5%)	6 (9.4%)	
Stage				
2 and 3	5 (23.81%)	6 (14.29%)	11 (17.46%)	0.483
4	16 (76.19%)	36 (85.71%)	52 (82.54%)	
ECOG PS				
0 and 1	17 (77.27%)	30 (71.43%)	47 (73.44%)	0.838
> 1	5 (22.73%)	12 (28.57%)	17 (26.56%)	
Hyponatremia type				
Acute	14 (63.64%)	34 (80.95%)	48 (75.00%)	0.224
Chronic	8 (36.36%)	8 (19.05%)	16 (25.00%)	
Hyponatremia severity				
Moderate (120–129)	9 (40.91%)	27 (64.29%)	36 (56.25%)	0.127
Severe (< 120)	13 (59.09%)	15 (35.71%)	28 (43.75%)	
Hyponatremia symptoms	13 (59.09%)	37 (88.10%)	50 (78.13%)	**0.012**
Sodium				
Before treatment	120 (108–126)[a]	122 (102–129)[a]	121 (102–129)	**0.004**
6th hour	123 (111–141)[b]	125 (99–130)[a]	124 (99–141)	
24th hour	128.5 (120–138)[bc]	128 (117–137)[b]	128 (117–138)	
10th day	135 (125–142)[c]	131 (106–141)[b]	132 (106–142)	
p (within groups)	< 0.001	< 0.001		
Hyponatremia severity after treatment				
Normal	10 (45.45%)	10 (23.81%)	20 (31.25%)	0.140
Mild (130–135)	6 (27.27%)	21 (50.00%)	27 (42.19%)	
Moderate and severe (< 130)	6 (27.27%)	11 (26.19%)	17 (26.56%)	
Urea	13.5 (5–43)	14.97 (3.3–104)	14.35 (3.3–104)	0.136
Creatinine	0.8 (0.31–1.5)	0.79 (0.23–3.28)	0.8 (0.23–3.28)	0.581
Potassium	4.25 ± 0.46	4.29 ± 0.75	4.28 ± 0.66	0.821
Length of stay in hospital (day)	4.5 (0–12)	10 (5–30)	8.5 (0–30)	**< 0.001**
Hospital complications	5 (22.73%)	27 (64.29%)	32 (50.00%)	**0.004**

Same letters denote the lack of statistically significant difference between repeated measurements. Data are given as mean ± standard deviation or median (minimum–maximum) for continuous variables with regard to normality of distribution and as frequency (percentage) for categorical variables

ECOG PS Eastern Cooperative Oncology Group Performance Status

All the patients received tolvaptan at a dose of 15 mg and the median daily tolvaptan application frequency was 1 (1–4). As an adverse effect after tolvaptan treatment, xerostomia was observed in 9.1% ($n=2$) and polydipsia in 4.6% ($n=1$) of patients (Table 2).

The most commonly used supportive treatment methods were as follows: normal saline + hypertonic infusion, 31.0% ($n=13$); hypertonic infusion, 26.2% ($n=11$); and fluid restriction + hypertonic infusion + normal saline + oral salts, 23.8% ($n=10$).The median follow-up period in the TpST group Tolvaptan group was 71 days (IQR: 32—182 days), and the ST group supportive group was 47 days (IQR: 15–127 days, $p=0.081$). Seven patients in the TpST group Tolvaptan group and 11 patients in the supportive group died at their first hospitalization ($p=0.634$). 10 of 15 patients (66.7%) in the TpST group Tolvaptan group; In the ST group supportive group, 30 (96.8%) of the 31 patients were hospitalized for the second time due to recurrent hyponatremia ($p=0.010$). Four patients in the TpST group Tolvaptan group and 15 patients in the ST group supportive group died at their second hospitalization ($p=0.161$).

There was no significant difference between the TpST and ST groups in terms of OS after hyponatremia has occurred ($p=0.302$). When survival after the occurrence of hyponatremia was evaluated, the OS of men was determined to be shorter compared to that of women ($p=0.035$). It was also determined that OS was shorter in patients who had refractory hyponatremia after treatment ($p=0.048$, Table 3). We performed Cox regression analysis using OS after hyponatremia as a dependent variable and found that higher sodium levels (with the meaning of normalization of blood sodium levels) after treatment decreased the risk of death (HR: 0.94, 95% CI [0.90–0.98]).

Discussion

Hyponatremia is an electrolyte disorder that is frequently encountered in cancer patients and may lead to acute and serious effects when not promptly and correctly treated. In this study, which examined the outcomes of TpST and ST in hyponatremic oncology patients, it was determined that blood sodium level increased, the length of hospital stay was shorter, and the symptoms of hyponatremia and hospital complications were lower in recipients of TpST. Although there was no significant difference between the TpST and ST groups in terms of OS, having higher sodium levels after treatment was found to decrease the risk of death, suggesting that the correction of hyponatremia is critical in such patients. This also suggests that TpST may be beneficial in terms of OS, even though we did not observe a significant difference in the OS.

Table 2 Characteristics and adverse effect of the Tolvaptan + supportive treatment

n	22
Median Tolvaptan tablet per day, (range)	1 (1–4)
Adverse effect	3 (13.64%)
Polydipsia	1 (4.55%)
Xerostomia	2 (9.09%)

Data are given as median (minimum–maximum) for continuous variables with regard to the normality of distribution and as frequency (percentage) for categorical variables

In hyponatremia cases, tolvaptan treatment improves hyponatremia and prevents possible neurological complications [3]. Spasovski et al. stated that a 5-unit increase in sodium level significantly improved the symptoms of hyponatremia [9]. In a study having a similar design as ours, the results of supportive treatment and tolvaptan treatment in patients hospitalized for hyponatremia were compared and found that the blood sodium level of the tolvaptan group was normalized faster and the length of hospital stay was significantly shorter [13]. Gralla et al. reported that the blood sodium levels and symptoms of patients treated with tolvaptan improved rapidly when compared to the placebo group in their subanalysis of the cancer patients those included in the Study of Ascending Levels of Tolvaptan in Hyponatremia (SALT)-1 and SALT-2 studies [14]. In our study, when compared to the ST group, it was determined that the blood sodium level increased, the length of hospital stay was shorter, and the symptoms of hyponatremia and hospital complications were less frequent in the TpST group. In fact, all the results found in our study were related to the normalization of the blood sodium level. Patients with improved symptoms were treated faster and discharged more quickly. As the duration of hospitalization decreases, the frequency of hospital complications also decreases. In summary, it can be said that the key role in the treatment of hyponatremia in such patients is to regulate and normalize blood sodium level in a swift manner, while also accounting for the possible risks of excessively rapid increase.

Studies conducted in cancer patients have suggested that the use of tolvaptan is associated with survival through normalization of the blood sodium level [8, 14, 15]. In our study, it was found that the survival results of TpST and ST groups were similar in cases of hyponatremia. In our study, it was thought that the survival of ST patients who were selected as the control group could also have been positively affected; therefore, when compared, the positive effect of tolvaptan on survival could not be determined statistically. Alternatively, the lack of a significant difference may also be associated with the fact that the number of patients in each group were considerably different. It is important to show the effect of tolvaptan on the survival of patients with cancer. The survival outcomes were similar between

Table 3 Survival after occurrence of hyponatremia (months) with Kaplan Meier method and comparisons of groups with log rank test

	n	Death	Mean	Std error	%95 confidence interval		*p*
					Lower bound	Upper bound	
Overall survival	64	48	9.32	2.02	5.35	13.28	N.A
Treatment							
Tolvaptan plus supportive	22	15	13.29	4.02	5.41	21.17	0.065
Supportive	42	33	6.39	1.60	3.26	9.53	
Gender							
Male	41	34	7.18	2.15	2.97	11.38	**0.035**
Female	23	14	12.5	3.57	5.56	19.57	
Stage							
2 and 3	11	6	14.42	4.20	6.19	22.65	0.134
4	52	41	8.03	2.04	4.03	12.02	
ECOG PS							
0 and 1	47	35	11.04	2.51	6.12	15.96	0.051
> 1	17	13	3.42	0.99	1.49	5.36	
Hyponatremia type							
Acute	48	35	8.20	2.18	3.93	12.47	0.243
Chronic	16	13	11.67	4.02	3.78	19.55	
Hyponatremia severity							
Moderate (120–129)	36	28	9.81	2.38	5.15	14.47	0.841
Severe (< 120)	28	20	7.23	2.85	1.66	12.81	
Hyponatremia symptoms							
Absent	14	9	15.96	4.52	7.11	24.81	0.056
Present	50	39	6.10	1.78	2.61	9.59	
Hyponatremia after treatment							
Absent	20	12	12.74	4.20	4.52	20.97	**0.048**
Present	44	36	7.25	1.94	3.44	11.05	
Hospital complications							
Absent	32	22	10.60	2.69	5.34	15.87	0.220
Present	32	26	8.06	2.84	2.50	13.62	

ECOG PS Eastern Cooperative Oncology Group Performance Status

the groups in our study. However, oral usage, short time of hospitalization, reducing the complications associated with hospitalization and a positive effect on blood sodium were the advantages of tolvaptan treatment. Thus, if this study was to be carried out with a placebo group or a larger number of patients, the tolvaptan-sodium-survival relationship might be demonstrated.Various variables can affect the survival of patients after initiation of hyponatremia treatment. In our study, among the variables evaluated in this regard, it was determined that the persistence of hyponatremia and male gender had negative effects on survival. Berardi et al. reported that keeping sodium level within reference values in non-small cell lung cancer cases showed a significant difference in terms of progression-free and overall survival [16]. There are studies on cancer patients showing that clinical symptoms that occur due to the persistence of hyponatremia even after treatment worsen the prognosis [6, 17, 18]. In a cohort study, Castillo et al. evaluated the importance of hyponatremia as a prognostic factor in cancer patients. They evaluated patients with breast, colorectal, and lung cancers and found that hyponatremia showed a significant relationship with survival. They reported that patients with one or more hyponatremia episodes for each type of cancer had an increased likelihood of death (HR: 2.7). In addition, they found that the risk of mortality increased proportionally with the stage of the cancer [19]. Corona et al. showed longer survivals in hyponatremia cases where the sodium value was increased to normal limits [20]. In our study, patients with many different types of cancers were evaluated. For this reason, the number of patients per group was not sufficient to perform cancer-specific analyses. Clinical studies with larger participants may reveal statistically significant results.

The role of hyponatremia on survival is still controversial. Hyponatremia; may cause symptoms such as headache, weakness, nausea, vomiting, muscle cramps, various levels of consciousness from somnolence to coma and impairs the quality of life [21]. Hyponatremia can also lead to disruptions in systemic cancer treatments, especially with agents

requiring intensive hydration, such as cisplatin and cyclophosphamide. Therefore, hyponatremia causes delay in cancer treatment and may increase morbidity and mortality in cancer patients [22]. Renal or endocrine problems that may occur secondary to disease or treatment in cancer patients, excessive release of ADH synthesized from cancerous cells, and the effects of this hormone are among the proposed mechanisms for the development of hyponatremia [19]. In this regard, the relationship between hyponatremia and survival should be revealed in more detail by conducting new studies examining pathophysiological changes.

Our study has some limitations. First, this study was conducted, retrospectively. Second, only two oncology centers were included and third, the inclusion of a relatively small number of patients. Oral salt intake is not recommended for the management of hyponatremia in patients with SIADH. Although a patient who received oral salt was a limitation in our study, we do not think that only one patient's treatment may affect the outcome of the study. Another limitation was that even though the fluid restriction was planned, not all patients could adapt to this treatment. In our country Tolvaptan could be given with sodium level monitorization in hospitalized patients. For this reason, the usage of tolvaptan after discharge was not evaluated in our study.

Conclusion

In the treatment of hyponatremia in cancer patients, TpST was found to have a more positive effect on blood sodium levels, length of hospital stay, hospital complications, and hyponatremia symptoms compared to the supportive treatment. Therefore, tolvaptan treatment is effective in correcting the negative clinical outcomes due to hyponatremia. Although the effect of ST and TpST on survival were similar in this study, it was determined that the increase in sodium level after the use of tolvaptan was associated with reduced risk of death. In hyponatremic cancer patients, using tolvaptan for effective treatment and keeping sodium levels within normal limits is important for survival. In future studies, examining the specific types of cancers and evaluating the effect of tolvaptan and different treatment modalities on survival may yield more valuable results.

Data availability Data are available at Dr Abdurrahman Yurtaslan Oncology Training and Research Hospital and Gulhane Training and Research Hospital.

Compliance with ethical standards

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

Ethical approval Ethical approval was approved by the local ethical committee of the University of Health Sciences, Dr Abdurrahman Yurtaslan Oncology Training and Research Hospital (TUEK meeting number: 85-31.12.2019) in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.

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