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The frequency of hyponatremia during the course of small cell lung cancer and its effect on prognosis

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ABSTRACT:

BACKGROUND AND AIM: Small-cell lung cancer (SCLC) is fast-growing disease with high mortality and prognosis is worse when hyponatremia develops. In our study, we aimed to determine the frequency of hyponatremia in SCLC and the relationship with the prognosis.

MATERIALS AND METHODS: Patients diagnosed with SCLC between 2012 and 2017 were retrospectively screened. Stages, hyponatremia levels, and survival times were recorded.

RESULTS: A total of 466 patients diagnosed with SCLC, 423 (90.8%) of whom were male were included in the study. The average age was 67 ± 10 years. About 126 (27%) of the patients were hyponatremic and 340 (73%) were normonatremic. Hypertonic saline treatment was performed in 52 (41.3%) patients. In total, hyponatremia improved in 49.2% ($n = 62$). While the expected survival means were 12.6 months in those with improved hyponatremia, 5.0 months in those with not improved, and 12.3 months in the normonatremic group. Survival in the group of whom hyponatremia could not be corrected was found to be statistically different ($P < 0.05$).

CONCLUSION: The improvement of hyponatremia was found to be a positive independent factor on the survival of SCLC.

Keywords:

Biochemistry, hyponatremia, prognosis, small-cell lung cancer, treatment

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Introduction

Small-cell lung cancer (SCLC) is cancer with serious morbidity and mortality, although its frequency is gradually decreasing among lung cancers.[1] About 60% of SCLC is metastatic at the time of diagnosis, and it is a very aggressive tumor. Median survival is 6–9 weeks without treatment.[2] In addition, hyponatremia is a serious electrolyte disorder that occurs at the onset or course of the disease. As it may progress asymptomatically, it can cause serious neurological symptoms and death.[3] The most common causes of hyponatremia in lung cancer are inappropriate antidiuretic hormone secretion and consumption.[4] Other causes of hyponatremia are chemotherapy-induced renal sodium (Na) excretion, gastrointestinal Na and water loss, or tumor-induced atrial natriuretic peptide secretion, Na loss due to chronic heart failure, nephritic syndrome, diuretics,

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angiotensin-converting enzyme inhibitors, and selective serotonin reuptake inhibitors.[4,5]

There are studies evaluating the effect of hyponatremia on prognosis in SCLC.[3,4,6] Morbidity and mortality of lung cancer increase with hyponatremia, so the management of hyponatremia is controversial.[6] In our study, we aimed to determine the frequency of hyponatremia in SCLC and to determine the relationship between prognosis and hyponatremia.

Materials and Methods

Patients diagnosed with SCLC between January 2012 and January 2017 in our hospital were retrospectively screened. Approval was obtained from the local ethics committee of the Ankara Atatürk Chest Diseases and Thoracic Surgery Training and Research Hospital (No: 624/19.04.2019). Written informed consent was not obtained due to retrospective design.

After the patients were diagnosed with SCLC, they were staged and received their treatment according to the guidelines.[7] The Na values determined at the time of diagnosis were recorded.

Normal Na values were accepted as 135–145 mEq/L. Values <135 mEq/L were considered hyponatremia. Patients with hyponatremic were divided into three groups as mild (Na = 130–135 mEq/L), moderate (Na = 120–-30 mEq/L), and severe hyponatremia (Na <120 mEq/L). In patients with hyponatremia, treatments for hyponatremia, treatment response, and recovery time were recorded. The lifetime and the time of diagnosis, the presence of metastases, the number of metastases, and cancer stages were recorded. The relationship between the severity of hyponatremia and the survival and cancer stages of the patients was evaluated. The effect of improvement of hyponatremia on survival was analyzed.

The patients were further grouped and analyzed according to whether the hyponatremia improved after the treatment. Hypertonic Na replacement was performed in symptomatic patients who did not respond to fluid restriction and these patients were further grouped and analyzed.

Statistical analysis

Statistical analysis of the study was performed with IBM SPSS for Windows, Version 16.0. Chicago, SPSS Inc package program. First, descriptive statistics of the patients were given; mean and standard deviation for normally distributed data and median (minimum/maximum values) for the data which were not normally distributed were expressed. The frequency distributions of ordinal parameters were compared with the Chi-square test. The method of Kaplan–Meier was used to calculate survival curves and log-rank was performed to assess the statistical significance of the difference between the groups according to hyponatremia, treatment, and stages. Multivariate survival analysis was performed using the Cox regression method for statistically significant parameters. P <0.05 was used for statistical significance.

Results

A total of 466 patients of whom 423 (90.8%) were males and 43 (9.2%) were females diagnosed with SCLC were included in the study. The mean age was 67 ± 10 years. The median Na value was 137 mEq/L (minimum–maximum = 107–155). About 126 (27%) patients were hyponatremic, 340 (73%) patients were normonatremic. In the hyponatremic patient group (n = 126), 12 patients (9.5%) were severe hyponatremic, 52 patients (41.3%) were moderate hyponatremic, and 62 patients (49.2%) were mild hyponatremic [Table 1].

At the time of diagnosis, 147 patients (31.5%) had limited disease, and 319 patients (68.5%) had extended disease. The patients had received chemotherapy or chemoradiotherapy according to their stages and the

Table 1: Demographic data

	Mean±SD	Median (minimum–maximum)
Gender, *n* (%)		
Male	423 (90.8)	
Female	43 (9.2)	
Age (year)	67±10	66 (31-94)
Sodium level (mEq/L)	136±6	137 (107-155)
Hyponatremia, *n* (%)		
No	340 (73)	
Yes	126 (27)	
Hyponatremia stage (*n*=126), *n* (%)		
Severe	12 (9.5)	
Moderate	52 (41.3)	
Mild	62 (49.2)	
Hyponatremia follow-up, *n* (%)		
Not improved	64 (50.8)	
Improved	62 (49.2)	
Hyponatremia treatment, *n* (%)		
None	74 (58.7)	
Hypertonic NaCl	52 (41.3)	
Hyponatremia improved time (month)	1.7±1.5	1.0 (0.3-7.0)
Metastasis, *n* (%)		
No	147 (31.5)	
Single	128 (27.5)	
Multiple	191 (41)	

SD: Standard deviation

current guidelines. While metastasis was detected in 77% (*n*: 97) of the hyponatremic group at the time of diagnosis, 65.3% (*n*: 222) of the normonatremic patients had metastasis ($P < 0.05$). In addition, the rate of multiple metastases in the hyponatremic group was 50% (*n*: 63), while it was 37.6% (*n*: 128) in the normonatremic group ($P < 0.05$).

In the hyponatremic group, 74 (58.7%) of the patients were followed up with chemotherapy or chemoradiotherapy for primary disease. On the other hand, the hypertonic saline infusion was performed in 52 (41.3%) patients. In total, hyponatremia improved in 49.2% (*n*: 62). Hyponatremia improved in 43 (58%) of 74 patients those without hypertonic saline treatment. On the other hand, hyponatremia improved in 19 (36.5%) of 52 patients who underwent hypertonic saline treatment.

The expected mean survival time of all patients was 11.4 months (95% confidence interval [CI]: 9.9–12.9). While it was 8.8 months (95% CI: 7.0–10.7) in the hyponatremic group and 12.3 months (95% CI: 10.4–14.2) in the normonatremic group ($P = 0.117$; log-rank). In addition, the expected mean survival time in the groups according to the severity of hyponatremia was 7.0 months (95% CI: 3.9–10.0) in severe hyponatremia, 6.9 months (95% CI: 4.8–8.9) in moderate hyponatremia, 11.3 (95% CI: 7.8–14.8) months in the mild hyponatremia group, and 12.2 months (95% CI: 10.3–14.2) in the normonatremia group. These differences were statistically significant [$P = 0.029$; log-rank; Table 2 and Figure 1].

Only when evaluated within the hyponatremic group, the expected mean survival time was 12.6 months (95% CI: 9.6–15.6) in those with hyponatremia improved and 5.0 months (95% CI: 3.4–6.6) in which did not. These differences were statistically significant [$P < 0,001$; log-rank; Table 2 and Figure 2].

In addition, the effects of gender, age, stage, presence of brain metastases, hyponatremia, and improvement of the hyponatremia on survival were evaluated by multiple Cox regression analysis [Table 3]. Since the stage and number of metastases were found to be related in multicollinearity analysis, the number of metastases was not included in this analysis. According to the results of this analysis, improvement of hyponatremia reduces the mortality risk by 2.4 times compared to not being improved. Furthermore, it has been found that mortality increases 1.033 times with each age increase.

Discussion

SCLC is an aggressive and mortal type of cancer.[7,8] The most important prognostic factors in SCLC are stage, performance status, weight loss,

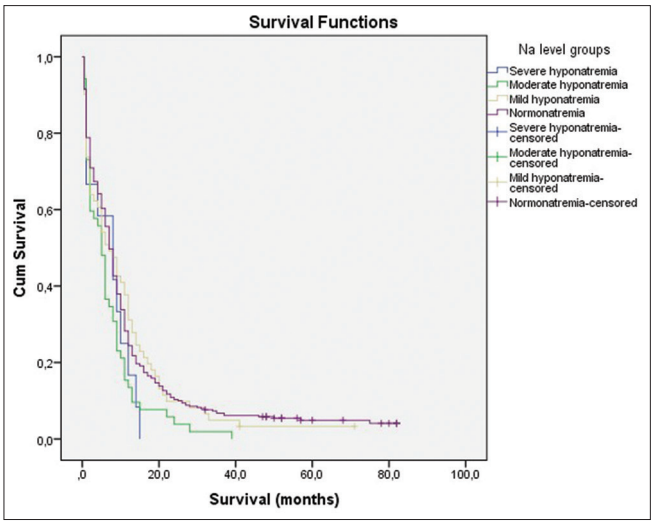

Figure 1: Survival for groups according to sodium level

and increased tumor-related marker such as lactate dehydrogenase (LDH).[5] Young age, good performance status, normal creatinine level, normal LDH, and single metastatic focus are positive prognostic factors in common disease.[9]

In addition, hyponatremia is common in many types of cancer, but it is most common in SCLC.[10] Symptoms of hyponatremia may be weakness, fatigue, nausea, disorientation, headache, muscle cramps, and coma.[5] In the light of the data determined in this study, in which we investigated the relationship between hyponatremia and SCLC prognosis, we can state that the improvement of hyponatremia in SCLC may have a positive effect on survival.

In the retrospective cohort series, according to the lower cut-off value of 136 mEq/L, 24.6% hyponatremia was detected in SCLC.[11-13] In our study, 27% of the patients had hyponatremia at the time of diagnosis. In previous similar study, severe hyponatremia was found to be 4.68%.[8] In our study, severe hyponatremia was detected in 9.5%.

There was a statistical difference according to the hyponatremia severity; expected survival times were 12.2, 11.3, 6.9, and 7.0 months in the normonatremic group, mild hyponatremia, moderate hyponatremia, and severe hyponatremia, respectively. In the study, in which 7689 patients with hematological malignancies were included, 6766 patients with the Na level of < 130 mEq/L, were found to have higher hospital mortality (odds ratio [OR]: 2.47; CI: 1.70–3.60).[10] It was shown before that existence of the hyponatremia during the diagnosis is a poor prognostic factor.[13-15] Our study supports these findings, but the high rate of simultaneous metastases in the hyponatremic patient group suggests that it contributes to poor prognosis.

Table 2: Means and medians for survival time-log-rank analysis (univariate)

Variables	Estimate survival (95% CI)		*P* Log-rank
	Mean[a]	Median	
Gender			
Male	10.8 (9.3-12.3)	7.0 (6.2-7.8)	0.021
Female	17.8 (10.5-25.0)	11.0 (9.4-12.6)	
Metastasis count			
None	20.9 (16.9-24.9)	11.0 (9.1-12.9)	<0.001
Single	9.3 (7.2-11.4)	6.0 (4.7-7.3)	
Multiple	5.8 (5.0-6.6)	4.0 (2.0-6.0)	
Brain metastasis			
None	12.9 (11.0-14.7)	8.0 (7.1-8.9)	<0.001
Yes	5.5 (4.1-6.9)	2.0 (1.4-2.6)	
Stage			
Limited	20.9 (16.9-24.9)	11.0 (9.1-12.9)	<0.001
Extended	7.3 (6.3-8.2)	6.0 (4.7-7.3)	
Na-stage			
Normonatremia	12.2 (10.3-14.2)	7.0 (6.2-7.8)	0.029
Mild hypoNa	11.3 (7.8-14.8)	8.0 (4.1-11.9)	
Moderate hypoNa	6.9 (4.8-8.9)	5.0 (3.6-6.4)	
Severe hypoNa	7.0 (3.9-10.0)	8.0 (1.3-14.7)	
HypoNa			
Not improved	5.0 (3.3-6.6)	2.0 (1.3-2.7)	<0.001
Improved	12.6 (9.6-15.6)	10.0 (7.9-12.1)	
Overall	11.4 (9.9-12.9)	7.0 (6.2-7.8)	

Estimation is limited to the largest survival time if it is censored. Na: Sodium; hypoNa: Hyponatremia, CI: Confidence interval

Table 3: Cox regression for survival analysis

	B	*P*	Exp (B)
Gender	−0.292	0.418	0.747 (0.369-1.513)
Age	0.033	0.002	1.033 (1.012-1.055)
Stage	0.413	0.111	1.512 (0.909-2.514)
Brain metastasis	0.259	0.272	1.296 (0.816-2.059)
Na-stage			
Normonatremia		0.429	Reference
Mild hypoNa	0.550	0.193	1.733 (0.757-3.966)
Moderate hypoNa	0.697	0.101	2.008 (0.873-4.619)
Severe hypoNa	0.601	0.258	1.824 (0.644-5.170)
Improvement of hypoNa	0.889	<0.001	2.432 (1.563-3.785)

Na: Sodium, hypoNa: Hyponatremia

In the 2-year study of Petereit *et al*., which included 2145 patients, the median survival in the group with hyponatremia in lung cancer was 5.16 months, while it was 13.32 months in the normonatremic group ($P < 0.05$).[14] In another study, the mean survival time in the hyponatremic group was found to be significantly lower than the normonatremic group (9 months vs. 13 months, $P < 0.01$).[5] In our study, survival in the hyponatremic group was found to be shorter in the normonatremic group (8.8 months vs. 12.3 months, $P = 0.117$); although this difference was not statistically significant, it was considered clinically significant.

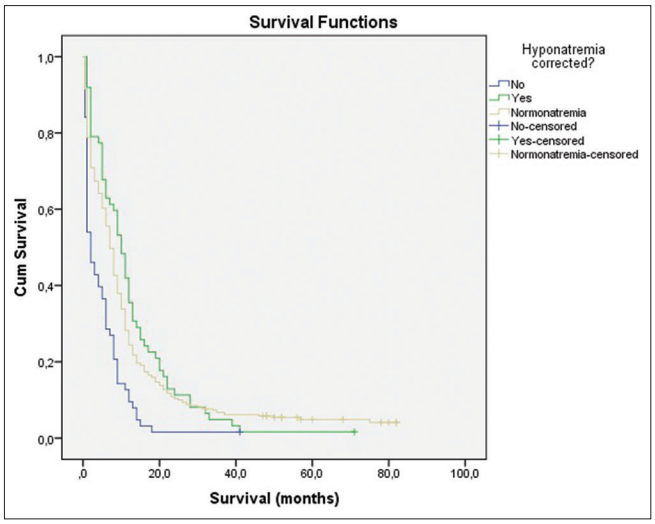

Figure 2: Survival for groups according to hyponatremia correction

Improvement of hyponatremia is important in terms of the prognosis of lung cancer. In a current meta-analysis, the improvement of hyponatremia was found to increase survival,[16] and with this improvement patients' performance status improved, and chemotherapy tolerance increased.[16,17] Fluid restriction and hypertonic saline infusion and tolvaptan are the most frequently used treatment options.[18] Apart from these, hyponatremia may improve after the treatment of the primary disease. In our study, it improved in 58% of the hyponatremic patients followed with conservative treatment. In Hansen *et al*. study, it was stated that if hyponatremia is not corrected and does not return to normal after one or two rounds of chemotherapy, it is an important negative prognostic factor.[13]

In previous studies, survival was found to be better in the groups whose hyponatremia improved.[5,8,13] Similarly, in our study survival was shorter in hyponatremia which did not improve despite treatment. Furthermore, in the study conducted by Hermes *et al*. in which 395 SCLC patients were evaluated, it was found that survival is shorter in those with hyponatremia (9 months vs. 13 months) and hyponatremia is an independent negative prognostic factor for extended and limited disease after the correction according to age, gender, LDH level, and performance status.[5] In our study, hyponatremia was found to be an independent poor prognostic factor. Although the mechanisms of hyponatremia are not fully known, it is thought to be associated with tumor burden, but new studies are needed to investigate the relationship between the improvement of hyponatremia with medications and prognosis.

In our study in the group of patients with hyponatremia, the extended disease was 77%, and the multiple metastasis rate was 50%, and these rates were both statistically significantly

higher than the normonatremic group. In Hermes *et al*. study, hyponatremia was detected 24% in extended stage-SCLC and 11% in limited stage-SCLC.[5] In the same study, the rate of 2 or more metastases was found to be 61.3% in the hyponatremic group and 41% in the normonatremic group. We could consider that the rate of hyponatremia increases as the total tumor load increases. However, this should be supported by further studies.

The fact that it is a retrospective and single-center study is the most important limitation. Since it is a retrospective study, symptoms associated with hyponatremia could not be determined. Therefore, the necessity of treatment in asymptomatic patients could not be discussed. In addition, hypertonic Na treatment has been decided according to Na level and standardization has not been established in this regard. Although performance status and weight loss are important variables for mortality, these data are not available due to retrospective design, so they could not be included in the analysis.

Conclusion

As a result, although there are many studies presented that hyponatremia is a poor prognostic factor in the course of cancer management, especially in SCLC. When hyponatremia is corrected by treatment, there is no difference in surveillance with the normonatremic patient group, but there is no evidence to suggest that nonsymptomatic hyponatremia should be corrected with direct hyponatremia treatment such as Na replacement, tolvaptan. In the light of the results and the current literature, we can say that the improvement of hyponatremia has a positive effect on survival. However, these data are insufficient to comment on the treatment of hyponatremia. Prospective, randomized multicenter studies are needed to evaluate the effect of hyponatremia on cancer prognosis and to examine the effects of treatment with new-generation treatment agents.

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Conflicts of interest
There are no conflicts of interest.

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