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ORIGINAL PAPER

Serum level of arginine-vasopressin influences the prognosis of extensive-disease small-cell lung cancer

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Abstract
Purpose The purpose of this study is to elucidate the influence of serum arginine-vasopressin (AVP) level on prognosis of extensive-disease small-cell lung cancer (ED-SCLC).
Methods We retrospectively investigated the clinical records of 163 patients with ED-SCLC, who were admitted to Okayama University Hospital or National Shikoku Cancer Center Hospital. The influence of 14 pretreatment variables on survival was analyzed.
Results In a multivariate analysis of 163 patients, elevation of serum LDH level ($P = 0.028$) and poor performance status (PS ≥ 2, $P = 0.002$) were independent poor prognostic factors. In 34 patients whose serum AVP levels were available, high serum AVP level was related to the poor prognosis ($P < 0.001$). The serum-sodium level did not affect the survival. Median serum level of osmotic pressure in 34 patients was normal (284.9 mOsm/kg), although, serum osmotic pressure was low in four of six patients with high serum AVP level. In all patients with high serum AVP level, serum LDH level was elevated.
Conclusions The data from the current study suggested that serum LDH level and PS were the poor prognostic factors for ED-SCLC. But we additionally identified the prognostic significance of serum AVP level, which may be a more useful factor than serum-sodium level.

Keywords Small-cell lung cancer · Prognostic factor · Arginin-vasopressin (AVP) · Sodium · Osmotic pressure

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Introduction

Lung cancer continues to be a serious global health problem, with 900,000 annual new cases in men and 330,000 in women (Ferlay et al. 2001; Parker et al. 1997). Small-cell lung cancer (SCLC) accounts for ~20% of all bronchogenic carcinomas (Boring et al. 1994). Disease extent at diagnosis is the most prominent prognostic factor of SCLC (Albain et al. 1990; Paesmans et al. 2000). Two-year survival rate of patients with extensive disease (ED) does not exceed 5%, whereas, it is 20–40% in patients with limited disease (LD) (Thatcher et al. 2005). Although, SCLC has the unique behavior such as paraneoplastic syndromes, the neuroendocrine properties are considered to be most likely responsible for it (Williams 1997). In general, tumors of the neuroendocrine origin are capable of producing arginine-vasopressin (AVP). The mRNA for AVP has been detected in SCLC

(Oh MS 2002). Generally, the secretion of AVP is down-regulated by the low-serum level (<1.0 pg/ml) in the situation of low plasma osmotic pressure (<280 mOsm/kg) (Zerbe et al. 1980). But in syndrome of inappropriate antidiuretic hormone secretion (SIADH) accompanied with malignancy such as SCLC, AVP is often excessively secreted in spite of low plasma osmotic pressure. The ectopically produced AVP binds to receptors in the kidney, causing retention of free water, which resulted in hyponatremia and low-osmotic pressure (Oh MS 2002). Hyponatremia, occasionally experienced in SCLC patients, has been previously reported to affect the survival of SCLC marginally (Sagman et al. 1991; Kawahara et al. 1997). However, the correlation of SIADH with the prognosis of SCLC is controversial (Tai et al. 2006; List et al. 1986; Harper et al. 1982). On the other hand, there are several cases whose serum-sodium level was normal despite elevation of serum AVP level (Johnson et al. 1997), and a third of patients with SCLC developing hyponatremia had no AVP activity in their plasma (Kamoi et al. 1987; Bliss Jr et al. 1990; Johnson et al. 1997). Then serum level of AVP is recently considered as a tumor marker for SCLC (North 1991). The purpose of the present study is to evaluate the serum level of AVP as a prognostic factor of patients with ED-SCLC.

Materials and methods

Clinical records of patients with histologically or cytologically proven ED-SCLC admitted to the Okayama University Hospital or National Shikoku Cancer Center Hospital between January 1981 and December 2001 were retrospectively investigated in this study.

All patients underwent staging work-ups consisting of a chest radiograph, computed tomographic (CT) scans of the chest and abdomen, bone scintigraphy, and magnetic resonance image scans of the brain. Routine blood chemistry included lactate dehydrogenase (LDH), neuron-specific-enolase (NSE), carcinoembryonic-antigen (CEA), and sodium. Disease extent was determined according to the AJCC Cancer Staging Manual (American Joint Committee on Cancer 2002). LD was defined as tumor confined to one hemithorax, mediastinum, and supraclavicular lymphnodes. Tumor invading beyond these sites was defined as ED. Survival was defined as the time between the date of diagnosis and the date of death. Follow-up time for each patient was at least 3 years.

Fifteen pretreatment variables were chosen for analysis. Each variable was used to divide the patients into two groups in order to determine its prognostic significance. The cut-off values used for hematological and biochemical variables were the normal limits of the variable. In our institutions, the normal serum AVP level was ≤6.3 pg/ml. Survival curves were constructed using the Kaplan–Meier method and the difference of survival was assessed with the log-rank test. Multivariate analysis was performed with the Cox proportional hazard model. $P < 0.05$ was considered to be statistically significant.

Results

A total of 163 patients were investigated in this study. Age was ranging from 29 to 86 with median of 68. Majority of patients (97.6%) had been previously treated with platinum-based doublet or alternating chemotherapy resulting in the objective response rate of 76%.

The results of univariate analysis are summarized in Table 1. Four factors consisting of serum level of LDH, number of metastatic site, performance status (PS) and body weight loss significantly affected the survival. But serum-sodium level did not affect the survival ($P = 0.6653$, Fig. 1).

Table 2 shows the result of multivariate analysis. The factors having prognostic significance in univariate analysis were analyzed in the multiple regression analysis. The independent relative risk (RR) of death was significantly high in patients with elevated LDH level and those with poor PS (≥2).

The data of serum levels of AVP were available in 34 patients. The correlation of serum AVP level with plasma osmotic pressure is summarized in Fig. 2. The median serum AVP level was 1.35 pg/ml (range 0.0–82.3), and the median serum osmotic pressure was 284.9 mOsm/kg. Six patients demonstrated high serum AVP level (>6.3 pg/ml). The results of univariate analysis of prognostic factors including serum AVP level in these 34 patients are summarized in Table 3. Serum AVP level ($P < 0.001$) and PS ($P = 0.0258$) were significantly related to the survival, however, the serum-sodium level did not affect the survival ($P = 0.1456$). The survival curves according to serum AVP level (Fig. 3) shows that survival time of patients having low serum AVP level (≤6.3 pg/ml) is significantly longer than those having high level (>6.3 pg/ml). The patients with high serum AVP level were listed in Table 4. Four of six patients had low serum osmotic pressure (<280 mOsm/kg). In the all patients with high serum AVP level, serum LDH level was elevated.

Table 1 Univariate analysis

	Number of patients	MST (months)	*P*-value
Total	163	8.8	
Gender			
Male	129	9.4	0.1709
Female	34	12.7	
Age (years)			
Median (range)	68 (29–86)		
<70	94	10.5	0.9569
≥70	69	9.1	
LDH			
Normal	66	14.2	**0.0061**
High	97	9.2	
NSE (ng/ml)			
<10	29	9.2	0.6925
≥10	134	10.5	
CEA (ng/ml)			
<5.0	74	10.5	0.1180
≥5.0	89	10.0	
Sodium (mEq/l)			
≥135	141	10.6	0.6653
<135	22	10.0	
Smoking history			
(−)	27	10.5	0.5436
(+)	136	10.1	
Clinical symptom			
(−)	31	14.0	0.0838
(+)	132	9.4	
Brain metastasis			
(−)	117	11.9	0.0953
(+)	46	8.6	
Bone metastasis			
(−)	120	12.5	0.3395
(+)	43	9.1	
Bone marrow involvement			
(−)	142	10.5	0.2699
(+)	21	8.9	
Distant metastasis			
0	15	15.5	**0.0478**
1	89	12.5	
2	59	8.9	
PS			
0, 1	118	13.1	**<0.0001**
≥2	45	6.2	
Body weight loss (%)			
<5	116	14.2	**0.0155**
≥5	47	9.4	

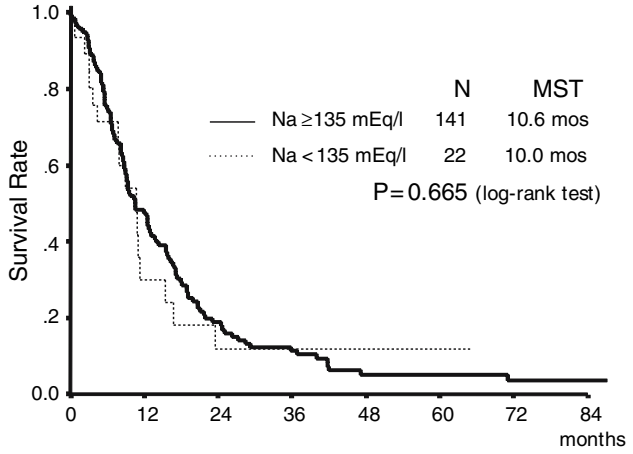

Fig. 1 Overall survival of patients with ED-SCLC according to serum-sodium level (≥135 mEq/l, $n = 141$; *solid line* versus <135 mEq/l, $n = 22$; *dotted line*)

Table 2 Multivariate analysis using Cox proportional hazard model

Variable	*P*-value	Relative risk
LDH (high)	**0.028**	**1.510**
Distant metastasis		
2	0.075	1.774
1	0.380	1.319
0	–	1.000
PS (≥2)	**0.002**	**1.932**
BW loss (≥5%)	0.090	1.384

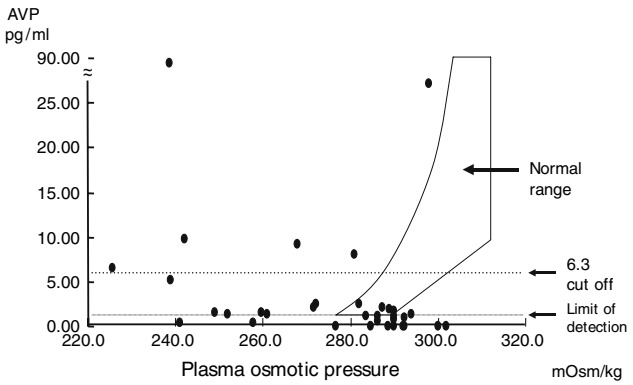

Fig. 2 The correlation of serum AVP level with plasma osmotic pressure ($n = 34$)

Discussion

Patients with SCLC currently benefit from favorable response to initial treatment. However, the majority of responding patients will subsequently manifest recurrent disease despite the favorable response rates over 80% (Morstyn et al. 1984). Many investigators have previously attempted to identify the factors predictive for the outcome (Singh et al. 2005; Jorgensen et al. 1996; Spiegelman et al. 1989). Disease extent at diagnosis is the most prominent prognostic factor of SCLC (Albain et al. 1990; Paesmans et al. 2000). Numerous former publications concerning prognostic and predictive factors in large populations pointed that PS and serum LDH level were important parameters for

Table 3 Univariate analysis in 34 patients whose serum AVP levels were available

	Number of patients	MST (months)	*P*-value
Total	34		
Gender			
Male	25	10.0	0.4895
Female	9	12.5	
Age (years)			
<70	21	10.5	0.2128
≥70	13	14.5	
LDH			
Normal	12	15.5	0.1897
High	22	10.0	
NSE (ng/ml)			
<10	5	18.2	0.0676
≥10	29	10.2	
CEA (ng/ml)			
<5.0	16	10.5	0.1610
≥5.0	18	10.5	
Sodium (mEq/l)			
≥135	19	14.2	0.1456
<135	15	10.0	
Smoking history			
(−)	9	10.6	0.9612
(+)	25	10.1	
Clinical symptom			
(−)	5	12.5	0.4219
(+)	29	10.5	
Brain metastasis			
(−)	24	12.5	0.1594
(+)	10	9.4	
Bone metastasis			
(−)	25	10.5	0.1670
(+)	9	10.5	
Bone marrow involvement			
(−)	27	10.5	0.6320
(+)	7	10.5	
Distant metastasis			
0	3	15.5	0.6707
1	20	10.6	
2	11	10.1	
PS			
0, 1	23	14.2	**0.0258**
≥2	11	7.3	
Body weight loss (%)			
<5	21	14.2	0.2440
≥5	13	9.4	
AVP (pg/ml)			
<6.3	28	12.5	**0.0006**
≥6.3	6	7.2	

predicting survival or response to chemotherapy (Cerny et al. 1987; Sagman et al. 1991; Albain et al. 1990; Osterlind and Anderson 1986; Yip and Harper 2000). Yip and Harper (2000) demonstrated that PS and disease extent were almost uniformly found to be the

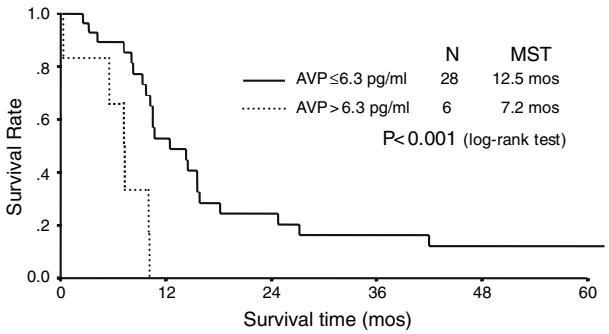

Fig. 3 Overall survival of patients with ED-SCLC according to serum AVP level (≤6.3 pg/ml, $n = 28$; *solid line* versus >6.3 pg/ml, $n = 6$; *dotted line*)

Table 4 The list of patient with high serum AVP level (>6.3 pg/ml)

Case	Age	Gender	Symptom	Sodium	AVP	LDH
1	47	Male	Cough	116	82.3	551
2	56	Male	Fatigue	140	27.1	556
3	69	Male	Nausea	116	9.8	490
4	59	Male	Dyspnea	129	9.2	764
5	70	Male	Cough	133	8.1	661
6	70	Male	Fatigue	105	6.5	1,400

most important clinical factors and LDH was the most important laboratory factor. Our study also suggested that PS and serum LDH level were the most important variables affecting the survival.

Water and sodium homeostasis is commonly disrupted in patients with lung cancer. Hyponatremia was observed in ~15–25% of patients with SCLC at presentation (Sagman et al. 1991; Kawahara et al. 1997; Sorensen et al. 1995). Among pretreatment laboratory variables, hyponatremia was reported to affect the survival marginally (Sagman et al. 1991; Kawahara et al. 1997). In this study, although hyponatremia was observed in 13.5% of patients with ED-SCLC, it did not affect the survival. SIADH, one of the most frequently observed paraneoplastic syndromes (Seute et al. 2004), is usually accompanied with hyponatremia. However, correlation of SIADH due to malignancies with the prognosis is not clear and the results of previous studies are controversial. Harper et al. (1982) showed that the survival of SCLC patients developing SIADH was shorter than the others, especially in patients with LD-SCLC. They hypothesized that SIADH was associated with the tumors acquiring drug resistance quickly. In the Vanderbilt experience, however, no relationship was observed between the presence of SIADH and response to chemotherapy or overall survival (List et al. 1986).

Ectopic production of AVP by SCLC cells is considered to play a causal role in the development of

hyponatremia, but a third of SCLC patients with hyponatremia had no evidence of AVP secretion (Kamoi et al. 1987; Bliss Jr et al. 1990; Johnson et al. 1997). In this study, a fifth of the SCLC patients with hyponatremia had almost no AVP secretion, and there were several cases with normal serum-sodium levels despite elevation of serum AVP level (Johnson et al. 1997). SCLC is frequently associated with paraneoplastic syndromes because of its neuroendocrine properties (Mason et al. 1997; Dropcho 1995; Ganz et al. 1987). The neuroendocrine properties are also considered to be responsible for metastatic activity (Seute et al. 2004), which suggests that neuroendocrine properties affect the prognosis of SCLC. In our study, high serum AVP level was the variable significantly affecting survival, which indicates that serum AVP level may reflect the degree of neuroendocrine properties. The correlation of serum LDH level with disease extent has been previously reported (Sagman et al. 1991; Kawahara et al. 1997; Cerny et al. 1987; Byhardt et al. 1986). On the other hand, Ganz et al. (1987) demonstrated a significant correlation between disease activity and serum LDH in the serial monitoring of response to therapy in patients with SCLC. Furthermore, Albain et al. (1990) also demonstrated that a normal LDH was the most important predictor of favorable survival in ED patients. Thus, elevated levels of serum LDH may reflect not only disease extent but also tumor bulk. In our study, the serum AVP level was significantly correlated with the serum LDH level ($P = 0.046$) (Table 5), which suggests that serum AVP level might correlate with tumor bulk. Three of the six cases with high AVP level were not accompanied with hyponatremia. Accordingly, the serum AVP level may become the better indicator of tumor bulk and prognosis than serum-sodium level.

Table 5 The characteristics of patients according to serum AVP level (>6.3 pg/ml vs. ≤6.3 pg/ml)

	Number of patients of AVP (<6.3 pg/ml)	Number of patients of AVP (≥6.3 pg/ml)	(*χ^2-test) *P*-value
Total	28	6	
LDH			
Normal	12	0	**0.0462**
High	16	6	
NSE (ng/ml)			
<10	4	1	0.8812
≥10	24	5	
CEA (ng/ml)			
<5.0	13	3	0.8736
≥5.0	15	3	

The present study suggests that the serum level of AVP is more useful for predicting prognosis than serum-sodium level. We can apply this marker for the subclassification of SCLC. However, the present study had several limitations, because all the analyses were performed retrospectively. Well-designed prospective trials are warranted.

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