

ORIGINAL ARTICLE

Syndrome of Inappropriate Antidiuretic Hormone Secretion: A Poor Prognosis in Small-cell Lung Cancer

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Received for publication July 1, 2015; accepted December 9, 2015 (ARCMED-D-15-00490).

Background and Aims. Small cell lung cancer (SCLC) is frequently associated with syndrome of inappropriate antidiuretic hormone (SIADH) secretion. In this study we investigated the prognostic value of SIADH in Chinese patients with SCLC.

Methods. We prospectively studied a total of 385 patients with SCLC diagnosed in our institution. The relationship between the SIADH and treatment outcomes including progression-free survival (PFS) and overall survival (OS) were analyzed. Univariate analysis and Cox multivariate analyses were used for statistical analyses. PFS and OS curves were drawn using Kaplan-Meier method.

Results. The median PFS and OS in patients with SIADH was 6.7 months (95% confidence interval [CI]: 4.3–9.1) and 11.6 months (95% CI: 7.4–15.7), respectively. The corresponding PFS and OS in SCLC without SIADH was 9.2 months (95% CI: 8.6–9.8) and 19.2 months (95% CI: 16.5–21.9), respectively; the difference between groups was statistically significant ($p = 0.007$ and $p = 0.000$, respectively). The association of SIADH with poor PFS ($p = 0.000$) and OS ($p = 0.002$) retained its statistical significance after adjusting for potential confounding variables. In addition, PFS ($p = 0.000$) and OS ($p = 0.000$) of SIADH patients with plasma sodium <125 mmol/L or without plasma sodium recovery to normal level are both shorter than in patients without SIADH. OS in SIADH patients with plasma sodium recovery time to normal level is also shorter than patients without SIADH ($p = 0.03$).

Conclusions. SIADH is a common occurrence in patients with SCLC and is associated with poor prognosis for SCLC in Chinese patients. © 2016 IMSS. Published by Elsevier Inc.

Key Words: Small cell lung cancer, Syndrome of Inappropriate Antidiuretic Hormone secretion (SIADH).

Introduction

Lung cancer is the most common cancer by incidence and a leading cause of cancer-related deaths worldwide according to GLOBOCAN 2012 (1). Small cell lung cancer (SCLC) is a highly malignant form of lung cancer and accounts for up to 15–20% of all newly diagnosed cases of lung cancer (2,3). SCLC is a neuroendocrine tumor of the lung and is associated with paracrine and paraneoplastic syndromes.

Syndrome of inappropriate antidiuretic hormone (SIADH) is a well-recognized paraneoplastic syndrome associated with SCLC caused by ectopic secretion of antidiuretic hormone. Antidiuretic hormone is central to the maintenance of plasma osmolality by acting on the collecting duct of the kidneys to effect conservation of water. Several prospective and retrospective studies in addition to case series and reports have assessed the prognostic impact of SIADH in SCLC (4–6). However, much of this evidence has come from either SCLC case series or findings based on univariate analyses. Some studies (4–6) have demonstrated a poorer prognosis in SCLC patients with SIADH than those without the syndrome. However, other studies such as that by Hainsworth et al. (7) found no such

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difference in survival between 18 patients with SIADH and 250 SCLC patients without SIADH. Tai et al. (8) studied SIADH in limited stage SCLC and found that the response to treatment was not different. They reported a non-significant trend towards poorer 5-year overall survival and cause-specific survival.

Race has an important influence on survival of lung cancer patients; lung cancer is particularly more common in China (9,10). In addition to race, several other variables including sex, age, clinical stage, and performance status may influence the prognosis (11–14). To date, very few studies have investigated the potential effect of confounding factors. In particular, the prognostic value of SIADH in SCLC and its incidence in the Chinese context has not been investigated. In this study, we sought to focus on both extensive and limited stage SCLC in the era of modern treatment to study the role of SIADH as an independent prognostic factor in SCLC.

Materials and Methods

Study Population

All patients who underwent treatment for SCLC at the Department of Cancer Center at the First Hospital of Jilin University between July 2008 and June 2014 served as the study population. Criteria for inclusion in the study included: a) age > 18 years; b) primary SCLC confirmed by pathology or cytology; and c) no prior chemotherapy. Exclusion criteria were: a) hyponatremia not due to SIADH; b) secondary (metastatic) lung cancer from other sites; c) multiple co-existing primary cancers. Patients were prospectively observed for tumor response and survival outcomes. Clinical staging was divided into limited disease stage and extensive disease stage using the criteria as previously described (15). The study was approved by the institutional ethics committee of the First Hospital of Jilin University. Criteria to define SIADH were serum sodium < 135 mmol/L associated with serum hypoosmolality (< 275 mOsm/kg), continued urinary excretion of sodium (urine sodium > 25 mEq/L), less than maximally dilute urine (urine osmolality > serum), serum glucose < 250 mg/dL, serum albumin > 3.0 gm/dL, and normal renal (serum creatinine < 1.5 mg/dL), adrenal, and thyroid function in a non-edematous patient. Tests of endocrine function included either a normal morning serum cortisol or appropriate response to cortrosyn stimulation and a normal serum level of thyroxine or thyroid-stimulating hormone. Patients receiving diuretics or other medications known to cause hyponatremia were excluded according to the study by List et al. (16).

Treatment Regimen

Chemotherapy. All patients received four to six cycles of etoposide plus platinum doublet first-line chemotherapy.

Cisplatin (25 mg/m² body surface area) day 1 to day 3 or carboplatin (AUC 5) day 1 was administered in combination with etoposide (100 mg/m² body surface area) on day 1 to day 3, every 3 weeks. All subsequent lines of chemotherapy were recorded until the patient died or cases were censored for this analysis.

Radiotherapy. For limited stage patients, 54 Gy external radiotherapy was administered after the third cycle of chemotherapy. In patients who achieved complete remission (CR), prophylactic cranial irradiation was administered. For extensive stage patients, palliative radiotherapy was administered if required.

Symptomatic and Supportive Treatment. SIADH was managed with sodium-free fluid restriction (< 1000 mL per day) and supplemental sodium in cases of symptomatic hyponatremia (17). In addition, all patients had access to standard supportive care.

Response to Treatment. Response to treatment was evaluated after every two cycles with computed tomography. Complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) were assessed according to RECIST 1.0 (18). Numerator for calculating the disease control rate included CR, PR and SD, whereas for calculating for overall response rate the numerator included only those patients who had a CR and PR.

Follow-up Regimen. After treatment completion, all patients in both groups were followed-up every 2–3 months. The primary end point was progression-free survival (PFS) time and overall survival (OS) time. PFS was defined as the time from the start of the first-line chemotherapy until the time of disease progression or death from any cause. OS was defined as the time from the start of first-line chemotherapy until death due to any cause.

Statistical Analysis

Differences between groups (SIADH vs. non-SIADH) were statistically analyzed using χ^2 test for categorical variables. PFS and OS curves were plotted by Kaplan-Meier method. Kaplan-Meier curves of the two groups were compared using a log-rank test. Cox multivariate analysis was performed to determine the impact of using a backward/forward stepwise method for the selection of the covariates. The proportional hazards assumptions underlying the Cox models were verified by examining plots of Schoenfeld residuals against time. Confidence intervals (CI) at 95% for hazard rates (HR) were calculated. All analyses were conducted using SPSS software (v.19.0); *p* value < 0.05 was considered statistically significant.

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