Prognostic Impact of Paraneoplastic Cushing's Syndrome in Small-Cell Lung Cancer

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Introduction: Paraneoplastic Cushing's syndrome (CushingPS) in small-cell lung cancer is rare but severe.

Methods: We studied 383 patients with small-cell lung cancer diagnosed between 1998 and 2012. Among them, 23 patients had CushingPS, 56 had other paraneoplastic syndrome (OtherPS), and 304 had no paraneoplastic syndrome (NoPS).

Results: After comparison of the three groups, we observed that CushingPS patients had more extensive disease: 82.6% versus 67.8% versus 53.3% ($p = 0.005$), respectively, with more than two metastatic sites: 63.2% versus 15.8% and 24.1% ($p \leq 0.001$), a higher World Health Organization performance status (2–4): 73.9% versus 57.1% versus 43.7% ($p = 0.006$), greater weight loss (≥10%): 47.8% versus 33.9% versus 16.4% ($p \leq 0.001$), reduced objective response to first-line treatment: 47.6% versus 74.1% versus 71.1% ($p = 0.04$), and poorer sensitivity to first-line treatment: 19% versus 38.9% versus 48.6% ($p = 0.01$). NoPS patients, with World Health Organization performance status of 3–4, had extensive disease at diagnosis, with response, sensitivity to first-line treatment, and survival similar to the CushingPS group. At relapse, the CushingPS group had no objective response to second-line treatment versus 25% versus 42.8% in OtherPS and NoPS groups, respectively ($p = 0.005$). The median survival of CushingPS patients was 6.6 months versus 9.2 months for OtherPS and 13.1 months for NoPS patients ($p \leq 0.001$). CushingPS is a prognostic factor of death (hazard ratio, 2.31; $p \leq 0.001$).

Conclusion: CushingPS is the worst form of the paraneoplastic syndromes with particularly extensive tumors. Reduced objective response and sensitivity to first-line treatment and no response to second-line treatment suggest starting palliative care early at first line and exclusively at relapse.

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Among lung cancers, the proportion of small-cell lung cancers (SCLC) has decreased over the last 30 years,[1–5] falling from 17.26% to 12.95% between 1986 and 2002 in the United States.[2] In our institution, it has dropped from 22.5% of all lung cancers in 1982 to 10% in 2011. Changes in smoking habits may explain this evolution. SCLC is notorious because of its early metastatic spread and its initial but transient sensitivity to chemotherapy.[6] The standard first-line treatment is a platinum–etoposide combination, with radiotherapy for intrathoracic forms. The survival rate at 5 years remains low at approximately 10% for limited forms, with only modest improvement over the last 30 years.[2,3,7] Prognostic factors that strongly affect survival are the initial extent of the tumor,[2,3,7] the World Health Organization performance status (WHO-PS), sensitivity to first-line chemotherapy,[7–9] and the presence, or not, of a paraneoplastic syndrome, particularly Cushing's syndrome.[7,10,11] Paraneoplastic syndromes are present in 20% to 40% of cases.[4,12,13] The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is the principal one, whereas Cushing's syndrome is present in 1% to 5.5% of cases.[11,14–16] Cushing's syndrome is characterized mainly by the inappropriate secretion of adreno corticotropic hormone (ACTH), responsible for clinical and biological hypercorticism making the SCLC particularly severe.[10–12,15–17] Other paraneoplastic syndromes are mostly neurological (mainly Lambert–Eaton myasthenia).

In this 14-year retrospective study, we analyzed the impact of paraneoplastic Cushing's syndrome (CushingPS) in SCLC in terms of presentation, response to treatment, and survival, compared with other SCLC patients. We attempt to suggest the treatment strategy to be adopted at the different stages of the disease.

PATIENTS AND METHODS

Population

We registered all patients with SCLC, confirmed by cytology or histology, presenting at Grenoble University Hospital between January 1998 and June 2012.

Data Collected

We recorded the patient's age, sex, tobacco consumption, pack-years, occupational exposure, other history of cancer, changes in weight, WHO-PS, and Charlson comorbidity score.[18] We collected their medical characteristics at diagnosis including stage (Union for International Cancer Control classification 1998, 2003, 2007), histology (pure or composite SCLC according to the World Health Organization Systematized Nomenclature of Medicine classification),[19] and whether the disease was limited (LD) or extensive (ED). For patients with an ED, the tumor bulk was accounted for by dividing the patients into those with ≤ 2 organs affected and those with > 2 organs affected by tumor metastasis. Patients who had a paraneoplastic syndrome at SCLC diagnosis, and those who developed one in the course of their disease, were divided into two categories: paraneoplastic Cushing's syndrome (CushingPS) and other paraneoplastic syndrome (OtherPS), and compared to those without paraneoplastic syndrome (NoPS).

Cushing's syndrome was defined as an excess of corticosteroid production with or without clinical signs. At least two of the following criteria were required: elevated plasma cortisol level (>550 nmol/liter), persistent spontaneous hypokalemia (potassium level <3.2 mmol/liter), hyperglycemia (>5.8 mmol/liter) without prior history of diabetes, elevated plasma ACTH level (>15 pmol/liter), and 24-hour urinary cortisol level more than 300 nmol/liter.

The details of the first two lines of treatment were collected. For patients treated with chemotherapy, tumor responses were graded as complete response, partial response, stable disease, or progressive disease, using the Response Evaluation Criteria in Solid Tumours criteria.[20] An objective response rate (ORR) was considered complete response + partial response. Sensitive patients were those with an objective response 3 months after completing their first-line chemotherapy. Resistant patients were those with an objective response lasting less than 3 months. Refractory patients had no objective response to their first-line chemotherapy.[4,7,8]

The first relapse was described in terms of date, sites, number of evolving sites (≤2 or >2) WHO-PS, and treatments.

Survival was measured from the start of the first treatment. For patients in palliative care, this is the date of the multidisciplinary decision to initiate palliative care. Last follow-up or death and vital status at the last day of the study (date point) were recorded, as well as causes of death. No patient was lost to follow-up.

Statistical Analysis

Data are expressed as *n* (%) for qualitative variables and mean ± SD and median (first–third quartile) for quantitative variables. Standard survival curves were established using the method of Kaplan–Meyer and compared using the log-rank test. To assess the impact of Cushing's syndrome on outcomes, we first computed a logistic regression with susceptibility to the first-line chemotherapy as the outcome variable and introducing Cushing's syndrome at diagnosis. Then, to assess the impact of Cushing's syndrome on prognosis, we performed a Cox regression and introduced Cushing's syndrome as a time-dependent covariate adjusted on other prognostic factors. Proportionality assumptions of the prognostic factors were tested using graphical methods and taken into account if needed. Variables meeting the *p* value of 0.20 criteria in the univariate analysis were proposed to a selection procedure and were maintained in the multivariate model when the *p* value remained less than 5%. Age was not proposed because it is taken into account in the Charlson score. The stage and the associated treatments were not included because they are highly correlated with the disease form. All tests were two-sided and a *p* value of less than 0.05 was considered statistically significant. Mean survival was compared using a Kruskal–Wallis test. Statistical analyses were performed using SAS 9.13 (Cary, NC).

RESULTS

During the studied period, 407 SCLC cases were identified. Among them:

- Three hundred four patients had no paraneoplastic syndrome (NoPS).
- Twenty-three patients had Cushing's syndrome (CushingPS), 15 at diagnosis and eight at first relapse.
- Fifty-six patients had other forms of paraneoplastic syndrome (OtherPS) including 46 with SIADH (42 at diagnosis and four at relapse), four with neuromuscular (three with Lambert–Eaton myasthenia and one case of myelitis), three with hypercalcemia (without bone metastases), two with osteoarticular, and one with disseminated intravascular coagulation.
- Twenty-four patients (5.9%) with no information about paraneoplastic syndrome were excluded.

Thus, this study concerned 383 patients.

Patients with SIADH formed a subgroup of OtherPS. To place the CushingPS group on a scale of severity, we compared them with a subgroup of NoPS patients having a WHO-PS of 3–4 (38 of 304).

Characteristics of Patients with Cushing's Syndrome

These patients, mostly with ED (19 of 23 or 82.6%) with more than two metastatic sites (12 of 19 or 63.2%), were in poor general condition with WHO-PS 2 to 4 (17 of 23 or 74%) (Tables 1–3 and Supplementary Tables 1–4, Supplementary Digital Content 1, http://links.lww.com/JTO/A533). Nearly half of them had lost more than or equal to 10% of their baseline weight (11 of 23, 47.8%). More than half presented cachexia, edema, hypertension, and/or muscle weakness. Hyperglycemia and hypokalemia were practically continual (21 of 23 or 91.3%), whereas metabolic alkalosis and lymphopenia affected the majority of them (69.6% and 65.2%, respectively), the latter contributing to their immunosuppression. Plasma cortisol levels (median, 1934.5 nmol/liter), ACTH (median, 59.6 pmol/liter), and cortisoluria over 24 hours (median, 3199.5 nmol/24 hr) supported the diagnosis. One patient, with a very characteristic clinical profile, was kept in the study, although she died before the hormone assays.

Cushing's syndrome progression was marked by almost constant infectious complications (20 of 23 or 86.9%),