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.

Key Words: Paraneoplastic Cushing's syndrome, Small-cell lung cancer, Survival.

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.

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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%),

TABLE 1. Patient Characteristics

			Type of Paraneoplastic Syndrome		
	All Patients	**No Paraneoplastic Syndrome**	**Paraneoplastic Cushing's Syndrome**	**Other Paraneoplastic Syndrome**	**Syndrome of Inappropriate Secretion of Antidiuretic Hormone Alone**
	n = 383 (%)	*n* = 304 (%)	*n* = 23 (%)	*n* = 56 (%)	*n* = 46 (%)
Sex					
Female	85 (22.2)	69 (22.7)	7 (30.4)	9 (16.1)	7 (15.2)
Male	298 (77.8)	235 (77.3)	16 (69.5)	47 (83.9)	39 (84.8)
Age					
Mean (SD)	63.9 (10.6)	63.8 (10.5)	60.7 (13.8)	66.1 (9.7)	65.9 (10)
Median (q1; q3)	64 (56; 72)	64 (56; 71)	62 (51; 71)	67 (56–76)	67 (55; 76)
<60	136 (35.5)	107 (35.2)	10 (43.5)	19 (33.9)	16 (34.8)
≥60	247 (64.5)	197 (64.8)	13 (56.5)	37 (66.1)	30 (65.2)
Minimum–maximum	29–88	34–88	29–84	48–83	48–83
Professional exposure					
Asbestos	62 (17.4)	46 (16.3)	3 (13)	13 (23.2)	11 (23.9)
Other	70 (19.7)	56 (19.9)	5 (21.7)	9 (16.1)	8 (17.4)
Tobacco					
Smokers	349 (91.1)	278 (91.4)	21 (91.3)	50 (89.3)	42 (91.3)
Nonsmokers	11 (2.9)	7 (2.3)	2 (8.7)	2 (3.6)	1 (2.2)
Unknown status	23 (6)	19 (6.2)		4 (7.1)	3 (6.5)
Pack-years					
Mean (SD)	46.9 (26.6)	47.4 (26.1)	39.4 (19.1)	47.6 (31.3)	49.3 (32.1)
Median (q1; q3)	40 (30; 60)	40 (30; 60)	40 (30; 50)	45 (25; 60)	42.5 (25; 60)
Weight gain					
+10 kg	1 (0.3)		1 (4.3)		
Weight: loss					
<10%	287 (74.9)	242 (79.6)	11 (47.8)	34 (60.7)	31 (67.4)
≥10%	80 (20.9)	50 (16.4)	11 (47.8)	19 (33.9)	13 (28.3)
ND	15 (3.9)	12 (3.9)		3 (5.3)	2 (4.3)
Charlson score					
<4	179 (46.7)	145 (47.7)	11 (47.8)	23 (41.1)	19 (41.3)
≥4	204 (53.3)	159 (52.3)	12 (52.2)	33 (58.9)	27 (58.7)
Cancer history					
Yes	63 (16.4)	45 (14.8)	4 (17.4)	14 (26)	10 (21.7)
World Health Organization performance status					
0–1	200 (52.4)	170 (56.1)	6 (26.1)	24 (42.8)	21 (45.7)
2	126 (33)	95 (31.4)	12 (52.2)	19 (33.9)	14 (30.4)
3–4	56 (14.7)	38 (12.5)	5 (21.7)	13 (23.2)	11 (23.9)
ND	1 (0.3)	1 (0.3)			
Stage					
1–3A	79 (20.6)	69 (22.9)	2 (8.7)	8 (14.3)	4 (8.7)
3B, 4	301 (78.6)	232 (77.1)	21 (91.3)	48 (85.7)	42 (91.3)
Missing	3 (0.8)	3 (1.0)			
Disease extension					
Limited disease	163 (42.6)	141 (46.4)	4 (17.4)	18 (32.4)	12 (26.1)
ED	219 (57.2)	162 (53.3)	19 (82.6)	38 (67.8)	34 (73.9)
ND	1 (0.3)	1 (0.3)			
ED: metastatic sites at diagnosis					
≤2	162 (74)	123 (75.9)	7 (36.8)	32 (57.1)	29 (85.3)
>2	57 (26)	39 (24.1)	12 (63.2)	6 (10.7)	5 (14.7)
Histology					
SCLC classical	346 (90.3)	274 (90.1)	20 (87)	52 (92.8)	43 (93.5)
SCLC composite	37 (9.7)	30 (9.9)	3 (13)	4 (7.1)	3 (6.5)

ND, not documented; ED, extensive disease; SCLC, small-cell lung cancer.

TABLE 2. Treatments: First and Second Lines

				With Paraneoplastic Syndrome		
		All Patients	**No Paraneoplastic Syndrome**	**Paraneoplastic Cushing's Syndrome**	**Other Paraneoplastic Syndrome**	**Syndrome of Inappropriate Secretion of Antidiuretic Hormone Alone**
		n = 383	*n = 304*	*n = 23*	*n = 56*	*n = 46*
First-line treatments						
Treatments with chemotherapy	Chemotherapy	369 (96.3)	294 (96.7)	21 (91.3)	54 (96.4)	44 (95.6)
	With curative surgery	25 (6.5)	25 (8.2)			
	With radiotherapy	106 (27.7)	95 (31.2)	3 (13.0)	8 (14.3)	6 (13)
Treatments without chemotherapy	Surgery alone	1 (0.3)		1 (4.3)		
	Radiotherapy alone	3 (0.8)	3 (0.1)			
	Palliative care	10 (2.6)	7 (2.3)	1 (4.3)	2 (3.6)	2 (4.3)
	All treatments without chemotherapy	14 (3.6)	10 (3.3)	2 (8.7)	2 (3.6)	2 (4.3)
Chemotherapy response	First line	369	294	21	54	44
	ORR (CR + PR)	259 (70.2)	209 (71.1)	10 (47.6)	40 (74.1)	32 (72.7)
	Stable	34 (9.2)	24 (8.2)	6 (28.6)	4 (7.4)	4 (9.1)
	Progression	49 (13.3)	41 (13.9)	1 (4.8)	7 (12.9)	6 (13.6)
	NE	21 (5.7)	14 (4.8))	4 (19)	3 (5.5)	2 (4.5)
	ND	6 (1.6)	6 (2)			
Sensitivity to first line	Refractory	85 (23)	66 (22.4)	7 (33.3)	12 (22.2)	11 (25)
	Resistant	86 (23.3)	63 (21.4)	5 (23.8)	18 (33.3)	14 (31.8)
	Sensitive	168 (45.5)	143 (48.6)	4 (19)	21 (38.9)	17 (38.6)
	NE	24 (6.5)	16 (5.4)	5 (23.8)	3 (5.5)	2 (4.5)
	ND	6 (1.6)	6 (2)			
Relapse		287	227	17	43	36
World Health Organization performance status (at relapse)	0–1	110 (38.3)	99 (43.6)	2 (11.8)	9 (20.9)	9 (25)
	2	92 (32)	72 (31.7)	4 (23.5)	16 (37.2)	15 (41.7)
	3–4	68 (23.7)	43 (18.9)	9 (52.9)	16 (37.2)	12 (33.3)
	ND	17 (5.9)	13 (5.7)	2 (11.8)	2 (4.6)	
Local recurrence	Yes	190 (66.2)	149 (65.6)	10 (58.8)	31 (72.1)	27 (75)
	ND	5 (1.7)	3 (1.3)	1 (5.9)	1 (2.3)	1
Metastatic recurrence	Yes	199 (69.3)	154 (67.8)	16 (94.1)	29 (67.4)	23 (63.9)
	ND	5 (1.7)	3 (1.3)	1 (5.9)	1 (2.3)	1
Evolving sites	≤2	234 (81.5)	189 (83.3)	9 (52.9)	36 (83.7)	29 (80.6)
	>2	48 (16.7)	35 (15.4)	7 (41.2)	6 (13.9)	6 (16.7)
	ND	5 (1.7)	3 (1.3)	1 (5.9)	1 (2.3)	1 (2.8)
Second-line treatments	Chemotherapy	208 (72.5)	166 (73.1)	10 (58.8)	32 (74.4)	29 (80.5)
Chemotherapy: response to second line	ORR (CR + PR)	79 (38)	71 (42.8)	0	8 (25)	8 (27.6)
	Stable	35 (16.8)	27 (16.3)	2 (20)	6 (18.7)	4 (13.8)
	Progression	85 (40.9)	60 (36.1)	7 (70)	18 (56.2)	17 (58.6)
	NE	6 (2.9)	5 (3)	1 (10)		
	ND	3 (1.4)	3 (1.8)			
Other treatments 2	Radiotherapy	18	17		1	
	Palliative care	58 (20.2)	42 (18.5)	6 (35.3)	10 (23.2)	7 (19.4)
	ND	3	2	1		
Death	No	34 (8.9)	27 (8.9)	1 (4.3)	6 (10.7)	4 (8.7)
	Yes	349 (91.1)	277 (91.1)	22 (95.7)	50 (89.3)	42 (91.3)
Causes of death	Cancer	310 (88.8)	247 (89.2)	18 (81.8)	45 (90)	38 (90.5)
	Iatrogenic complications	23 (6.6)	16 (5.8)	2 (9.1)	5 (10)	4 (9.5)
	Other	16 (4.6)	14 (5.1)	2 (9.1)		

ORR, objective response rate; CR, complete response; PR, partial response; NE, not evaluable; ND, not documented.

TABLE 3. Cushing's Syndrome: Clinical and Biological Signs

Clinical signs	n^a	n (%)
	Hypertension (23)	13 (56.5)
	Edemas (21)	11 (52.4)
	Myopathy (20)	11 (55)
	Obesity (23)	4 (17.4)
	Cachexy (23)	14 (60.9)
	Bowel disorder (22)	5 (22.7)
	Cutaneous disorder (15)	4 (26.7)
	Neurological disorder (17)	3 (17.6)
	Heart rate disorder (22)	3 (13.6)
Complications		
Infection	All (23)	20 (86.9)
	Of which: serious sepsis (20)	9 (45)
	Of which: opportunistic (20)	4 (20)
Digestive perforation	23	3 (13)
Cardiac	23	2 (8.7)
Treatment for Cushing's		
	Yes	15 (65.2)
	No	8 (34.8)
Treatment response	n = 15	
	Complete (15)	1 (6.7)
	Partial (15)	12 (80)
	No response (15)	2 (13.3)
Death: secondary causes	n = 22	
	Cardiac	2 (9.1)
	Infectious	10 (45.5)
Biological signs (normal values), n = no. of tested subjects	Mean (SD), median (q1; q3)	↑ High; ↓ low (%); → normal
Blood cortisol level nmol/liter (150–400), n =22	1934.5 (966.8), 2011 (1129; 2553)	↑ 20 (95.2); → 1 (4.5)
Cortisoluria nmol/24 hr (38–208), n = 11	3199.5 (2843), 2344 (1377; 6045)	↑ 11 (100)
ACTH (2–13 pmol/liter), n = 13	59.6 (64.8), 46 (13.3; 73.8)	↑10 (77); ↓ 1; → 2
Glycemia mmol/liter (3.8–5.8), n = 23	10.4 (6.8), 7.9 (7.2; 10.4)	↑ 22 (95.6); → 1
Kalemia mmol/liter (3.5–5.0), n = 23	2.6 (0.6), 2.6 (2.2; 2.8)	↓22 (95.6); → 1
Bicarbonates mmol/liter (24–32), n = 23	34.4 (6.2), 35 (29; 39)	↑ 17 (73.9); → 6
Lymphocytes G/liter (0.8–3.6), n = 23	1 (1.4), 0.5 (0.4; 1)	↓ 15 (65.2); → 7; ↑ 1

^{a}No. of patients tested or concerned.

jeopardizing the vital prognosis in nearly half the cases (11 of 20 or 55%). Fifteen patients (65.2%) had received specific treatment for Cushing's syndrome, but eight untreated patients died prematurely (mean survival, 17.5 days); the majority of these patients had been diagnosed at relapse (5 of 8). Among those responsive to treatment for Cushing's syndrome, 11 of 13 (84.6%) had presented the syndrome at diagnosis of SCLC. Most patients (21 of 23 or 91.3%) received chemotherapy. The ORR was low (10 of 21 or 47.6%). Sensitivity to the first-line chemotherapy was poor (4 responders/21 treated or 19%), and no response was obtained on second-line treatment. At the time of relapse, 13 of 17 patients (76.4%) had a WHO-PS more than or equal to 2, and seven (41%) had more than two sites with disease progression. Death, mostly related to tumor progression (18 of 22 or 81.8%), was hastened by septic complications still present in almost half the cases (10 of 22 or 45.5%) at the time of death.

Comparison with Other Groups

There was no difference between the groups in terms of sex and age. Almost all patients were heavy smokers (>40 pack yr) (Tables 1 and 2 and Supplementary Table 5, Supplementary Digital Content, http://links.lww.com/JTO/A533).

Presentation at diagnosis

1. A comparison of the 79 patients with a paraneoplastic syndrome with the 304 NoPS patients showed them more likely to present factors indicative of poor prognosis including weight loss of more than or equal to 10% (38% versus 16.4%, $p \leq 0.001$), high WHO-PS score 2 to 4 in 62.0% versus 43.7% ($p = 0.004$), greater disease diffusion at diagnosis in ED: 72.1% versus 53.3% ($p = 0.003$), and attenuated sensitivity to first-line chemotherapy of 33.3% versus 48.6% ($p = 0.01$).

2. A comparison of the CushingPS with OtherPS and NoPS patients confirmed the accumulation of factors linked to severity, with the most significant differences concerning weight loss of more than or equal to 10%: 47.8% versus 33.9% versus 16.4% ($p \leq 0.001$), WHO-PS score 2 to 4: 73.9% versus 57.1% versus 43.7% ($p = 0.006$), more ED: 82.6% versus 67.8% versus 53.3% ($p = 0.005$), with more than two metastatic sites: 63.2% versus 15.8% and 24.1% ($p \leq 0.001$), lower objective response to the first-line chemotherapy: 47.6% versus 74.1% and 71.1% ($p = 0.04$), and a reduced sensitivity to chemotherapy: 19% versus 38.9% versus 48.6% ($p = 0.007$).

3. Comparison of the CushingPS group with the "SIADH only" subgroup confirmed that this is the most severely affected group in terms of major tumor extension (>2 metastatic sites) with 63.2% versus 14.7% ($p \leq 0.001$).

4. Comparison of the CushingPS group with the subgroup of patients "NoSP and WHO-PS 3–4" (Supplementary Table 5, Supplementary Digital Content, http://links.lww.com/JTO/A533) indicated that they are equivalent in terms of weight loss, extent of tumor diffusion, objective response, and sensitivity to first-line chemotherapy. The CushingPS group was always recognizable by particularly diffuse forms at diagnosis (>2 metastatic sites) with 63.2% versus 31.2% ($p = 0.03$).

At relapse
1. The comparison of the CushingPS group and NoPS group showed an increase in factors of severity in terms of WHO-PS score 2–4: 76.5% versus 50.6% ($p = 0.01$).

2. The comparison of the CushingPS group with OtherPS and NoPS groups showed more tumor diffusion (>2 evolving sites): 41.2% versus 13.9% versus 15.4% ($p \leq 0.001$) and lack of response to the second-line chemotherapy: 0% versus 25% versus 42.8% ($p = 0.005$).

Survival

At the last follow-up point (March 11, 2013), 349 patients (91.1%) had died. The median follow-up of the 34 patients still alive was 41.9 months. The median survival for the entire group was 11.8 months (Table 4, Fig. 1, and Supplementary Table 6, Supplementary Digital Content, http://links.lww.com/JTO/A533).

The median survival for NoPS was 13.1 versus 8.1 months for those with a paraneoplastic syndrome ($p \leq 0.001$). The CushingPS group had poorer survival compared with OtherPS group (6.6 versus 9.2 mo, $p = 0.02$) and SIADH only patients (6.6 versus 8.5 mo, $p = 0.04$). Their survival was comparable to that of patients "NoPS with WHO-PS 3–4," median 6.6 months versus 3.3 months ($p = 0.69$). Patients presenting Cushing's syndrome at SCLC diagnosis had a median survival of 4.8 months.

When Cushing's syndrome was diagnosed at relapse, the survival of these patients (all now deceased) was particularly poor with death within an average of 27.3 days of this diagnosis. For patients deceased (22 of 23), those with Cushing's syndrome controlled by treatment survived an average of 298 days (from the diagnosis of cancer) and 243 days (from diagnosis of Cushing's syndrome) compared with 110 and 18 days, respectively, for those for whom Cushing's syndrome was untreated or uncontrolled (both Kruskal–Wallis $p \leq 0.001$) and whom had mainly been diagnosed at relapse.

Multivariate Analysis

1. The logistic regression (Table 5) looking at the impact of Cushing's syndrome on the sensitivity to first-line chemotherapy was done with the subgroup of 15 patients presenting Cushing's syndrome at SCLC diagnosis. Of these, 14 of 15 patients (93.3%) had WHO-PS 2 to 4, an ED, and received chemotherapy; seven of 14 (50%) achieved an ORR and two of 14 (14.3%) were sensitive (Supplementary Table 4, Supplementary Digital Content, http://links.lww.com/JTO/A533). Predictors of negative response to first-line chemotherapy were a WHO-PS 3 and 4, odds ratio (OR) 3.25 ($p = 0.02$); extended disease, OR 4.3 ($p \leq 0.001$); and composite histology, OR 4.86 ($p = 0.001$).

2. The multivariate Cox model (Table 5) looked at the impact of Cushing's syndrome on the risk of death and considered the whole group (23 patients). The risk factors for death were Cushing's syndrome: hazard ratio (HR), 2.31 ($p \leq 0.001$); Charlson score more than or equal to 4: HR, 1.71 ($p \leq 0.001$); WHO-PS more than or equal to 2: for WHO-PS = 2: HR, 1.44 ($p = 0.004$) and WHO-PS 3–4: HR, 2.65 ($p \leq 0.001$); and ED: HR, 3.05 ($p \leq 0.001$). A classical SCLC histology after 119 days was a protective factor: HR, 0.52 ($p = 0.001$).

DISCUSSION

CushingPS in a context of lung cancer is seen in cases of neuroendocrine tumors whose malignancy ranges from that of carcinoid tumors to SCLC, the most severe form.[10,14,21–23] In the 1990s, historical case studies and small cohort studies permitted us to highlight the extreme severity of this syndrome when associated with SCLC, showing the dominance of ED, with infectious complications making perilous any administration of chemotherapy, and the short survival of patients.[11,12,15–17,24–26] Our group of patients was consistent with the initial descriptions. Detailed analysis from patient presentation to diagnosis allowed us to observe the particularly diffuse spread of the disease, defined as metastasis to at least two other organs. The magnitude of weight loss, alteration of performance status, and poor response to first-line chemotherapy surpassed all other groups and made this the most severe of all paraneoplastic syndromes. Finally, the profile of these patients at presentation and the disease progression was similar to that of patients with poor performance status[3,4] but without paraneoplastic syndrome.

CushingPS and SCLC reinforce each other's deleterious effects. The immunodepression that accompanies cancerous states is amplified by that induced by the hypercorticism, leading to severe infectious complications, usually opportunistic. Metabolic disorders (hypokalemia, metabolic alkalosis, diabetes) with their own clinical consequences considerably

TABLE 4. Survival

	n	*p*	Median (mo) (95% Confidence Interval)	Alive at 1 yr, *n* (%)	Alive at 2 yr, *n* (%)	Alive at 5 yr, *n* (%)
All patients	383		11.8 (10.6–13.1)	191 (49)	92 (23)	41 (8)
Limited disease	163	<10³	20.7 (17.2–25.4)	122 (75)	74 (44)	32 (16)
Extensive disease	219		8.3 (7.6–8.9)	69 (31)	18 (6)	9 (1)
No PS	304	0.0002	13.1 (11.2–14.9)	164 (54)	80 (25)	33 (8)
All PS	79		8.1 (6.7–11.1)	27 (33)	12 (13)	8 (7)
Cushing' PS (at diagnosis)	15		4.8 (0.3–12.1)	5 (33)	0	0
Cushing' PS (all patients)	23	0.02	6.6 (3.2–11.4)	6 (24)	0	0
Other PS	56		9.2 (7.0–11.9)	21 (37)	21 (18)	7 (9)
Syndrome of inappropriate secretion of antidiuretic hormone alone	46	0.04[a]	8.5 (6.8–11.9)	16 (34)	9 (18)	5 (6)
No PS and World Health Organization performance status 3–4	38	0.69[b]	3.3 (1.5–7.0)	8 (21)	1 (2.6)	0

[a]Cushing' PS (all patients) vs syndrome of inappropriate secretion of antidiuretic hormone alone.
[b]Cushing' PS (all patients) vs no PS and World Health Organization performance status 3–4.
PS, paraneoplastic syndrome.

aggravate the worsening of the general state of health brought about by the rapid development of SCLC.

The occurrence of a paraneoplastic syndrome is directly linked to the tumor bulk. In our cohort, 72% of patients presenting a paraneoplastic syndrome of whatever type had ED at diagnosis. Our study suggests that in such cases, Cushing's syndrome is often found when the tumor bulk is particularly large and thus heterogeneous, with three or more organs affected by metastasis. This heterogeneity could explain the increased risk of the emergence of cellular clones with abnormal hormonal activity. When Cushing's syndrome was diagnosed, 22 of 23 patients (95.6%) had ED. This observation is in line with the study by Shepherd et al.[12] and individual case reports.[11,17,24]

If the diagnosis of Cushing's syndrome when it occurs alone is a complex diagnostic challenge,[22,27] the presence of

SCLC, with its noisy symptoms, can readily help to associate the two pathologies. Simple biological parameters such as hypokalemia and/or hyperglycemia and/or lymphopenia and metabolic alkalosis, accessible from the initial assessment of known SCLC, can suggest CushingPS and the need to assay plasma cortisol at 8 and 24 hours cortisoluria to confirm the diagnosis, even when Cushing's syndrome on its own would have little clinical expression.

Many authors stress the need to control the hypercorticism by specific treatment before chemotherapy to prevent infectious complications that are facilitated by glucocorticoid-induced immunosuppression and chemotherapy-induced agranulocytosis despite the use of leukocyte growth factors.[11,12,15,17,26] Some authors advocate systematic antifungal treatment[15] in view of the risk of the infectious complications that are
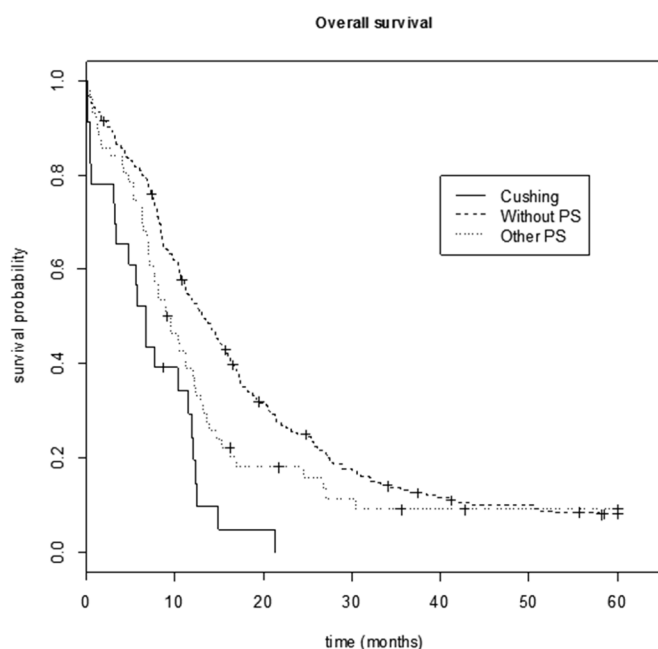

FIGURE 1. Survival curve of the three groups: Cushing: Cushing's paraneoplastic syndrome, *n* = 23; other PS, other paraneoplastic syndrome, *n* = 56; without PS: no paraneoplastic syndrome, *n* = 304 (log-rank *p* < 0.0001). PS, paraneoplastic syndrome.

TABLE 5. Multivariate Analysis

Logistic regression: sensitivity to first-line chemotherapy			
Variable	**Odds ratio**	**95% CI**	***p***
Cushing's syndrome at diagnosis: (15 patients)	2.75	0.54–13.99	0.22
Pack years >40	1.70	1.02–2.83	0.04
WHO-PS: 2	1.59	0.90–2.81	0.69
WHO-PS: 3–4	3.25	1.42–7.45	0.02
Extensive disease	4.33	2.57–7.28	<0.0001
Composite histology	4.86	1.88–12.57	0.001
Cox multivariate model: risk of death[a]			
Variable	**Hazard ratio**	**95% CI**	***p***
Time dependent Cushing's syndrome (23 patients)	2.31	1.47–3.64	0.0003
Classical SCLC before 120 days	1.15	0.42–3.19	0.79
Classical SCLC after 119 days	0.52	0.35–0.78	0.001
Charlson score ≥4	1.71	1.37–2.13	<0.0001
WHO-PS: 2	1.44	1.12–1.84	0.004
WHO-PS: 3–4	2.65	1.89–3.72	<0.0001
Extensive disease	3.05	2.39–3.91	<0.0001
Chemotherapy: yes	0.20	0.11–0.36	<0.0001

[a]Time in days.
CI, confidence interval; WHO-PS, World Health Organization performance status; SCLC, small-cell lung cancer.

correlated with elevated plasma cortisol levels.[15,25] In terms of the antitumor treatment, the objective response to first-line chemotherapy was diminished. This finding is in line with small series studies[12,16,26] and is stressed in individual case reports.[11,17,24] In our univariate analysis, we showed that a reduced ORR was specific to Cushing's syndrome patients compared with other groups. Furthermore, in univariate analysis the sensitivity to first-line chemotherapy was poor, compared to when Cushing's syndrome was absent. It was similar to that of WHO-PS 3–4 patients without a paraneoplastic syndrome. In multivariate analysis, while Cushing's syndrome itself did not appear as a specifically pejorative factor for sensitivity to first-line chemotherapy, we believe that it is synonymous with high WHO-PS and ED. Nevertheless, it clearly seems to be a specific risk factor for death. At relapse, none of the 10 CushingPS patients who received second-line chemotherapy gained any benefit, compared with NoPS patients where a 42.8% ORR was obtained (*p* = 0.006, Fisher's two-sided test). This result is explained by the very poor condition of patients with CushingPS in relapse (high WHO-PS and extensive tumor diffusion) and is linked to their poor response to the first-line treatment. This is in line with recent reappraisals of second-line chemotherapy for SCLC, which highlight the poor response at second line of patients who were refractory or resistant to first-line treatment.[7–9] Many studies agree that there should be greater emphasis on early palliative care in conjunction with antitumor treatments to improve the quality of life and survival of patients with advanced lung cancers.[28–32] This is also true for patients with cancers of various origins who are no longer receiving antitumor treatment.[33] The deleterious effect of chemotherapy administered at the end of life has already been demonstrated and is particularly useless in patients with performance status 3 and 4. Not only does it have no positive effect on the disease, but it aggravates the discomfort of patients and impedes the administration of affirmative palliative action.[34,35]

Proposals

All these considerations lead us to propose screening for CushingPS by cortisolemia at 8 AM and/or assay of cortisoluria more than 24 hours in patients with SCLC or ED with unexplained hypokalemia and/or hyperglycemia and/or lymphopenia. The earliest possible diagnosis will allow the establishment of specific treatment before chemotherapy. In cases with a diagnosis of SCLC when Cushing' syndrome is already established, it seems logical to renounce giving chemotherapy (temporarily or permanently) to patients with uncontrolled cortisolemia, with performance status 3 or 4, who already present infectious complications and/or who are too old. At relapse, the finding of Cushing's syndrome must shift the focus to palliative care. A second line should only be discussed on a case-by-case basis by a multidisciplinary review group.

Limitations

In this study, we considered paraneoplastic syndromes diagnosed throughout SCLC evolution to define the groups of patients. Although this is an unusual method, it allowed us to constitute independent groups, where each patient was attributed to a single group. Our study has the limitation of being monocentric; however, this guaranteed consistency in data collection and clinical practice. The small number of patients with Cushing's syndrome has forced us to restrict our comparisons to the most relevant parameters.

CONCLUSION

In SCLC, patients Cushing's syndrome is the most severe form of paraneoplastic syndrome. Its presence is related to particularly extensive tumors in patients who have poor performance status and excessive weight loss. Their objective response to first-line chemotherapy is impaired and is nonexistent to second-line chemotherapy, leading us to propose an early introduction of palliative care accompanying the first-line treatment and palliative care only at relapse.

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