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GONADAL ENDOCRINE DYSFUNCTION IN PATIENTS WITH LUNG CANCER: RELATION TO RESPONSIVENESS TO CHEMOTHERAPY, RESPIRATORY FUNCTION AND PERFORMANCE STATUS

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Summary—Male lung cancer patients with poor performance status [Eastern Cooperative Oncology Group (ECOG) index 3–4] have an endocrinological dysfunction as assessed by serum testosterone and sex hormone-binding globulin (SHBG) levels. Patients who respond to therapy regain normal free testosterone levels within 12 weeks post chemotherapy, whereas non-responders continue to exhibit subnormal levels. The perturbations of endocrinological variables in patients with lung cancer is not due to development of hypoxia, as patients with respiratory failure maintain a significantly lower testosterone level compared to cancer patients. The development of a deficiency in total testosterone concentrations in lung cancer patients is correlated to their performance status, and not to the presence of metastatic disease. The mechanisms responsible for the endocrinological dysfunction in patients with lung cancer remain unknown.

INTRODUCTION

Hypothalamic–pituitary–gonadal axis failure may be a result of a variety of pathological conditions in several organ systems. Of these, diseases of the airways contribute significantly to endocrine sexual dysfunction in humans. Chronic hypoxic pulmonary disease is associated with low total serum testosterone [1–5] as well as azoospermia and impotence in males [3, 4]. Low total serum testosterone levels have also been found in male patients with lung cancer [6], and we have previously reported data demonstrating reduced free testosterone levels in lung cancer patients during cyclic chemotherapy [7]. It is noteworthy that the endocrinological variables may be indistinguishable in subjects with either primary pulmonary malignancies or hypoxia [1].

In patients with lung cancer, the mechanism underlying the endocrine dysfunction has remained elusive. Possible explanations include metastatic disease [8, 9], nutritional imbalance [9], unknown pulmonary pathology [10], enhanced expression of steroid receptors in pulmonary tissue [11], or combinations thereof, which together may constitute the "fatigue" syndrome [12, 13].

In addition, glucocorticoid therapy may induce decreased testosterone levels in patients with chronic lung disease [14–17], as well as in healthy male subjects [14]. To our knowledge, no comprehensive studies have attempted to relate the endocrinological dysfunction accompanying lung cancer to these putative causative factors.

The present study was focused on whether the endocrinological perturbations in chemotherapy-treated lung cancer patients were persistent, and if these changes were related to hypoxia, corticosteroid therapy, or the presence of metastases. Our results suggest that the relationship between low testosterone levels and primary pulmonary cancer may be more complex than hitherto perceived.

MATERIALS AND METHODS

Transiency of endocrinological changes

Informed consent was obtained from all patients. In this part of the study, 12 consecutive male patients, age 46–69 years (mean 63 years), with bronchial carcinoma took part. Nine

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Table 1. Characteristics of patients

Group	No. of patients	Age (mean)	Diagnosis	Steroids	pO_2 (kPa)	FEV_1 (%)
A	11	44–67(59)	COPD[a]	–	8.7 ± 0.4	43.0 ± 3.9
B	9	59–70(63)	COPD	+	8.2 ± 0.5	33.1 ± 5.3
C	10	54–69(60)	CA[b]	–	10.0 ± 0.3*	70.0 ± 1.5*

[a]Chronic obstructive pulmonary disease; [b]cancer of the lung; and *significantly different ($P < 0.05$) from A and B.

Twenty patients had COPD, of which 9 were on steroid therapy. The lung cancer patients had limited disease, but a poor performance status (ECOG 3–4). Arterial pO_2 and percentage of expected FEV_1 (forced expiratory volume in 1 s) are given as means ± SEM.

patients with non-small cell lung cancer received cisplatin (70 mg/m^2 i.v.) and etoposide (100 mg/m^2 i.v. on day 1, 200 mg/m^2 p.o. on days 2 and 3) every third week for 3 or 4 cycles. Three patients with small cell lung cancer received VAC (vincristine 2 mg i.v., doxorubicin 50 mg/m^2 i.v. and cyclophosphamide 1,000 mg/m^2 i.v.) every third week for 5 cycles. All patients were within the limits of Eastern Cooperative Oncology Group (ECOG) index 0–2 (staging done by one physician), with normal hematological, liver and kidney functions at the time of inclusion. Liver scans in all patients, and bone scans in patients with small cell lung cancer, revealed no metastases. Interviews and clinical examination gave no indications of endocrine dysfunction in any of the patients prior to therapy, and all patients claimed to have normal sexual function. A simplified metyrapone test [18], performed in all patients prior to therapy, gave no indication of adrenal dysfunction. Blood samples were drawn on the day of starting the first chemotherapy cycle, and were repeated at the same time of the day every third week, for 3 ($n = 8$) or 4 ($n = 4$) consecutive treatments. The same procedure was repeated 12 weeks after discontinuing chemotherapy. All patients were eligible for evaluation.

Endocrinological function in hypoxia and lung cancer

Twenty male patients with chronic obstructive pulmonary disease (COPD) (group A and B) and 10 male patients with bronchial carcinoma (group C) were included in this part of the study. Patient characteristics are given in Table 1. Eleven of 20 patients with COPD received no corticosteroid therapy (group A), whereas 9 patients received oral corticosteroid medication (group B). The lung cancer patients were without metastasis and had near normal lung function. None of the cancer patients were undergoing radio- or chemotherapy, nor were they given corticosteroid treatment. Patients in all three groups had poor performance status (ECOG 3–4).

Endocrinological function and performance status

Three groups of male patients with recently diagnosed non-small cell lung cancer took part (group D–F). Patient characteristics are shown in Table 2. None of the patients had a history of previous malignant disease. The presence of liver metastasis as determined by ultrasound examinations were excluded in all subjects, and none had clinical or laboratory signs of hypoxia. In the presence of localized tumor, operability was evaluated by CT scanning. At the time of the study, no patient received corticosteroid medication, and none had previously been subjected to radio- or chemotherapy.

Blood samples

Venous blood samples were drawn at 8 a.m. Serum was immediately separated by centrifugation at 2000 *g* for 10 min, and the samples frozen at −20°C until analysis.

Analytical procedures

Endocrinological variables were measured by commercially available assay kits. Sex hormone-binding globulin (SHBG): Farmos Diagnostica,

Table 2. Characteristics of patients

Group	No. of patients	Age (mean)	Performance status		Metastases
			ECOG[a] 0–2	ECOG 3–4	
D	12	46–69(63)	+	–	–
E	10	51–69(64)	+	–	+
F	10	54–69(60)	–	+	–

[a]Performance status classification according to the WHO.

All subjects had non-small cell lung cancer with no signs of hypoxia, and had not received steroid treatment or chemo- or radiotherapy at the time of investigation.

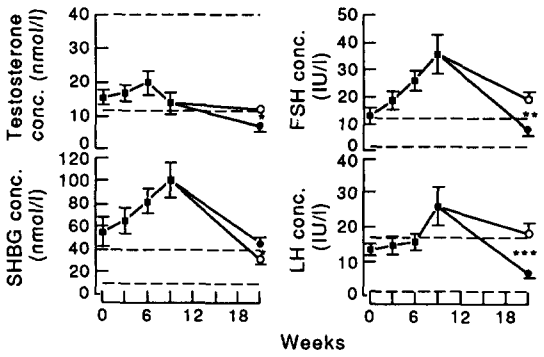

Fig. 1. Serum levels of total testosterone (upper left), SHBG (lower left), FSH (upper right) and LH (lower right) in lung cancer patients ($n = 12$) during chemotherapy (■) and in those found to respond (○, $n = 7$) and not to respond (●, $n = 5$) to the treatment. Patients were evaluated 12 weeks after cessation of chemotherapy. The asterixes indicate significant differences in hormone levels between responders and non-responders 12 weeks post chemotherapy (*$P < 0.02$, **$P < 0.006$, ***$P < 0.003$). Data are given as means ± SEM, and the dashed lines define the normal ranges.

Turku, Finland; testosterone: R.S.L., Carson, CA, U.S.A.; and FSH and LH: Amersham International plc, Bucks., U.K.

Statistical analysis

Statistical computations were performed by the non-parametric Mann–Whitney U-test (Microstat©, Ecosoft Inc., Indianapolis, IN, U.S.A.), or by one-way analysis of variance and estimation of least significant distance (Statgraphics©, STSC, Rockville, MD, U.S.A.) using microcomputer programs. Statistical significant differences were defined as $P < 0.05$. Values are expressed as mean ± SEM.

RESULTS

Transiency of endocrinological changes

Serum testosterone, FSH, LH and SHBG levels are given in Fig. 1. Twelve weeks after cessation of chemotherapy, 7 patients had achieved complete or partial remission, and maintained their initial performance status (responders). The other 5 patients demonstrated progressive disease with a decline in performance status to WHO index 3–4 (non-responders). Twelve weeks after cessation of chemotherapy, the non-responders showed a reduction in testosterone, FSH and LH levels with significantly (Mann–Whitney U-test) lower values compared to the responders (Fig. 1). The SHBG levels declined to the largest extent in the therapy-responsive patients and were significantly lower 12 weeks after termination of chemotherapy, as compared to the non-responders.

Endocrinological function in hypoxia and lung cancer

The results are summarized in Table 3. By analysis of variance, the mean total serum testosterone level was significantly lower in the lung cancer patients (3.4 nmol/l, mean), which had a near normal lung function, than in patients with severe COPD (10.9 and 6.5 mmol/l, means), displaying pathologically low pO_2 and FEV_1 values (Table 1). The serum testosterone levels were below normal range in all three groups. There were no significant differences between the groups as to serum concentrations of SHBG, FSH and LH. All groups demonstrated FSH and LH levels within the normal range, whereas the SHBG levels were elevated.

Endocrinological function and performance status

The results of the endocrinological assays are shown in Table 4. Statistical calculations (analysis of variance) showed significantly decreased levels of testosterone in group F as compared to the other two groups. In addition, the serum testosterone levels in group F, 3.4 ± 0.8 nmol/l (mean ± SEM), were below the normal range. There were no significant differences between the groups with respect to SHBG and FSH levels. The difference in LH levels between groups D and F was significant. LH concentrations were within the normal range, whereas FSH levels were slightly above the normal range in groups D and E. SHBG levels were elevated in groups D and F. As shown in Fig. 2, there

Table 3. Endocrinological variables in patients with CPOD without (A) or with (B) steroid treatment and patients with lung cancer (C) prior to onset of therapy

	Normal range	A ($n = 11$)	B ($n = 9$)	C ($n = 10$)
Testosterone (nmol/l)	12–40	10.9 ± 1.2	6.5 ± 0.6*	3.4 ± 0.8**
FSH (IU/l)	2–12	9.6 ± 2.5	10.8 ± 3.3	9.0 ± 2.5
LH (IU/l)	2–17	7.6 ± 0.8	7.3 ± 1.9	8.6 ± 1.9
SHBG (nmol/l)	10–40	58.7 ± 5.5	40.6 ± 4.4	47.3 ± 8.2

*Significantly ($P < 0.05$) smaller than A, **significantly ($P < 0.05$) smaller than B.
Concentrations are given as means ± SEM.

Table 4. Endocrinological variables in subgroups of patients with non-small cell lung cancer prior to onset of therapy

	Normal range	D ($n = 12$)	E ($n = 10$)	F ($n = 10$)
Testosterone (nmol/l)	12–40	15.6 ± 2.2	13.0 ± 0.6	3.4 ± 0.8*
FSH (IU/l)	2–12	12.8 ± 3.0	13.8 ± 2.6	9.0 ± 2.5
LH (IU/l)	2–17	13.6 ± 1.6	11.3 ± 1.8	8.6 ± 1.9**
SHBG (nmol/l)	10–40	54.8 ± 13.0	37.5 ± 5.1	47.3 ± 8.2

*Significantly ($P < 0.05$) smaller than D and E, **significantly ($P < 0.05$) smaller than D. Concentrations are given as means ± SEM.

was a negative correlation between testosterone levels and ECOG performance status in patients with no signs of metastases ($r = 0.82$).

DISCUSSION

We have previously demonstrated a fall in free testosterone levels, apparent as increases in SHBG concentrations, during cyclic chemotherapy in lung cancer patients [7]. Testosterone is approximately 98% bound in serum, with SHBG as the primary binding protein, and fluctuations in SHBG levels may thus significantly alter the concentrations of the unbound, and presumably active, testosterone in blood [19]. Other investigators have reported unchanged testosterone concentrations, consistent with a preserved Leydig cell function in these patients [20–27]. Permanent or prolonged dysfunction of the Leydig cells has, however, been described after chemotherapy, either alone or in combination with radiotherapy [28, 29].

The initial part of the present study was conducted to evaluate the gonadal hormonal function 12 weeks after cessation of chemotherapy in patients with lung cancer. Following the termination of chemotherapy, the non-responders showed a significant reduction in total serum testosterone, SHBG, FSH and LH concentrations (Fig. 1). In this group, the reduction in SHBG levels were smaller than the decline in total testosterone, suggesting a substantial reduction in unbound and endogenously active testosterone. The high pretreatment levels of SHBG and the moderately increased FSH levels may reflect relatively low free testosterone. Together, these findings indicate that non-responding patients with lung cancer suffer from gonadal endocrine dysfunction [30]. On the other hand, the data demonstrate that responding patients who maintain their initial performance status have normal levels of gonadal endocrine hormones as assayed at 12 weeks after the last cycle of chemotherapy. Thus, the initial perturbations of endocrine function are reversible in therapy-responsive patients.

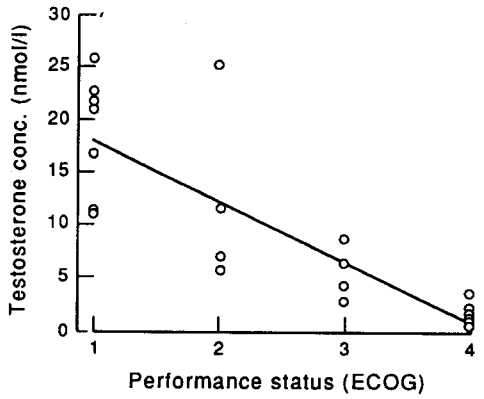

Fig. 2. Correlation between total serum testosterone concentrations and ECOG performance status in lung cancer patients without metastatic disease ($r = 0.82$).

It has previously been shown that male patients with severe COPD have a marked reduction in total serum testosterone [1–5]. Despite low serum testosterone levels in the COPD patients examined, the LH and FSH levels remained normal, indicative of an involvement of the hypothalamic–pituitary axis [31] (Table 3). The significantly lower testosterone levels in COPD patients receiving corticosteroid treatment (group B) compared to those not (group A) may be due to an additional suppressive effect exerted by steroid medication. Corticosteroid therapy has been shown to induce primary testicular failure normally accompanied by elevation of FSH and LH levels [14–17]. As FEV_1 and pO_2 levels were somewhat lower in group B than in group A, a combined suppressive action of steroids and hypoxia may account for the significant lower serum testosterone levels in group B. Unexpectedly, the group of lung cancer patients (group C) demonstrated serum testosterone levels significantly lower than the COPD patients in groups A and B (Table 3). Patients in group C had normal lung function parameters and were not on corticosteroid therapy. Hence, hypoxia and steroid treatment can be ruled out as agents causing the gonadal endocrine dysfunction in these patients.

Low serum total testosterone in patients with malignant disease has previously been ascribed to the presence of metastases [8]. Since patients with metastatic disease were excluded from this

part of the study, other mechanisms must be involved in the observed gonadal endocrine dysfunction.

The impact of patient performance status on endocrinological function was studied in non-hypoxic patients not receiving steroid therapy, thus enabling the exclusion of these complicating factors in the assessment of the results. Normal serum testosterone concentrations were measured in patients with relatively good performance status, i.e. ECOG 0–2, irrespective of the presence of metastatic disease. However, substantial and significant decreases in testosterone levels were apparent in patients with non-metastatic disease and poor performance status (Table 4), and subsequent analyses revealed a negative correlation between testosterone concentrations and ECOG performance status in patients with no sign of metastatic disease (Fig. 2). The similar SHBG levels in all three groups suggest that the decline in testosterone levels in one group of patients may be of physiological significance. A decrease in total testosterone levels, unaccompanied by a concomitant decline in the concentration of its high-affinity binding protein, suggests a functional testosterone deficiency in lung cancer patients with poor performance status, but without metstases [19]. We have not been able to confirm previous suggestions that low testosterone levels in these patients are due to the presence of metastatic disease [8, 9]. However, in these studies, the contributive effects of the performance status, possible hypoxia, or administration of corticosteroids have not been taken into account. In accordance with our results, it has been reported that weight loss and general malaise may correlate with decreased gonadal hormone function, and in particular low serum testosterone levels, in patients with disseminated cancers [9].

In summary, male lung cancer patients with poor performance status (ECOG 3–4) have an endocrinological dysfunction as assessed by testosterone and SHBG levels (Tables 3 and 4, Figs 1 and 2). Patients who respond to therapy regain normal free testosterone levels within 12 weeks post chemotherapy, whereas non-responders exhibit subnormal levels. The perturbations of endocrinological parameters in patients with lung cancer is not due to development of hypoxia, as patients in respiratory failure maintain a significantly higher testosterone level compared to cancer patients (Table 3). Finally, low testosterone concentrations in these patients is correlated to their performance status, and not to the presence of metastatic disease (Fig. 2).

The underlying mechanism for the persistent gonadal endocrine dysfunction in therapy-resistant patients with lung cancer remains unknown. Other investigators have suggested that the presence of tumor tissue alone may cause low serum testosterone [10]. In this context, the secretion of endogeneous active substances by the cancer cells has been postulated [10]. As inhibin has been found to exert inhibitory feedback on gonadotropin production [32], such agents may have inhibin-like characteristics. Furthermore, secretion of endogenously active compounds by the primary tumor tissue may affect endocrinological regulation [11] by mechanisms which, at least to some degree, could depend on tumor bulk. However, the material does not permit the exclusion of a comparatively poorer nutritional status, which by itself may account for the endocrinological dysfunction in the lung cancer patients [9]. The 'fatigue' syndrome, which has been associated with gonadal endocrine dysfunction, may well also be present in patients with locally advanced bronchial carcinoma [13, 31]. It is further probable that our findings may be reproduced in patients with other forms of cancer with poor performance status.

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