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A Preliminary Evaluation of Calcitonin and PDN-21 as Tumor Markers for Lung Cancer

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Immunoreactive calcitonin (iCT) can be ectopically secreted by lung cancer cells and has been proposed as a tumor marker for bronchial neoplasms. Since PDN-21 (katacalcin or the carboxyl-terminal flanking peptide of the calcitonin gene) and CT are cosecreted in normal subjects and in patients with medullary thyroid carcinoma (MTC), we sought to determine the potential utility of PDN-21 as a tumor marker for lung cancer. We measured carcinoembryonic antigen (CEA), neuron-specific enolase (NSE), iCT, and PDN-21 in 119 to 378 healthy subjects, 88 to 91 patients with benign pulmonary diseases, and 249 patients with advanced lung cancer (108 small cell lung cancers and 141 other forms). Tumor marker specificity was satisfactory: the percentage of increased values (greater than the 95th percentile of normal subjects) in patients with benign pulmonary diseases varied from 9% (NSE, PDN-21) to 12% (CEA). PDN-21 was a more sensitive marker for lung cancer than iCT: the percentage of increased values was 44% for PDN-21 versus 19% for iCT, and 51% versus 23% for the subgroup of patients with small cell lung cancer (SCLC). PDN-21 concentrations were increased in 69 (34%) of 202 patients with a normal iCT level, whereas iCT concentrations were increased in only six (4%) of 139 patients with a normal PDN-21 level. However, markedly elevated concentrations of the two markers generally occurred in the same patients and the correlation between the two markers was significant ($r = 0.60; P < 0.01$). PDN-21 provided complementary information to that from the classical markers NSE and CEA. PDN-21 was thus elevated in seven (47%) of 16 patients with SCLC and a normal NSE level, and in 19 (30%) of 63 patients with non-SCLC and a normal CEA level. Immunodilution curves of sera with elevated concentrations of PDN-21 were strictly parallel to the standard curve, suggesting that the assay essentially measured authentic PDN-21. These preliminary results suggest that PDN-21 and possibly other CT gene products are worthwhile in further biologic and clinical investigations in lung cancer. (Henry Ford Hosp Med J 1989;37:190-3)

Several authors have reported increases in circulating calcitonin (CT) in various other cancers than medullary thyroid carcinoma (MTC), particularly in lung cancer (1-3). The secreted forms are generally larger than monomeric CT (4), and it is thus more adequate to speak of immunoreactive CT (iCT). The frequency of elevated values varies much between studies but has been higher than 50% in some series of patients with small cell lung cancer (SCLC) (3). Measurement of iCT could be useful for monitoring the tumor mass in SCLC (5), but reported series are small and do not include valid comparisons with classical tumor markers.

PDN-21 (katacalcin or the carboxyl-terminal flanking peptide of the calcitonin gene) derives from the same precursor as CT and is cosecreted with CT in healthy subjects and in patients with MTC (6,7). In our studies of tumor markers for lung cancer (8,9), we investigated the possibility that this cosecretion might be present in other cancers than MTC and that PDN-21 might be a potentially useful tumor marker for lung cancer.

Methods

Assays

The four evaluated markers were measured by commercially available radioimmunoassays: carcinoembryonic antigen (CEA) and neuron-specific enolase (NSE) (Pharmacia Inc, Uppsala, Sweden), iCT (INCStar, Stillwater, MN), and PDN-21 (Medgenix Diagnostics, Fleurus, Belgium). The assays' detection limits were 40 pg/mL for iCT and 7 pg/mL for PDN-21, and undetectable values were assigned levels of 20 pg/mL for iCT and 3.5 pg/mL for PDN-21.

Subjects

Normal values were determined in 377 healthy subjects for iCT (251 males and 126 females; median age 43 years, range 18

\*Submitted for publication: October 24, 1989.
\*Accepted for publication: November 20, 1989.
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to 84 years) and in 119 for PDN-21 (82 males and 37 females; median age 42 years, range 18 to 64 years). We defined the upper limits of normal values as the 95th percentiles determined in these groups, i.e., 123 pg/mL for iCT and 15.7 pg/mL for PDN-21. The 95th percentiles for CEA and NSE were 7.5 ng/mL (n = 316) and 11.0 ng/mL (n = 378), respectively.

Tumor marker specificity was determined in 88 patients with various benign pulmonary diseases (9) (54 males and 34 females; median age 63 years, range 19 to 87 years). Tumor markers were evaluated in 249 patients with advanced lung cancer (214 males and 35 females; median age 59 years, range 35 to 77 years). Of these patients, 210 had never been treated before and 39 had recurrent disease after previous antineoplastic therapy (radiotherapy [n = 13], chemotherapy [n = 9], surgery [n = 4], or combined modalities [n = 13]). Tumor types were as follows: 108 SCLC and 141 non-SCLC (NSCLC) including 80 squamous cell lung cancers, 39 adenocarcinomata, 12 large cell lung cancers, and 10 other forms.

### Results

Serum CEA concentrations were elevated in 12% of the patients with benign pulmonary diseases, compared to 10% for iCT and 9% for NSE or PDN-21. In this population, the 95th percentiles were 12.5 ng/mL for CEA, 183 pg/mL for iCT, 11.6 ng/mL for NSE, and 24 pg/mL for PDN-21.

Individual values of iCT and PDN-21 measured in the three groups of patients with benign pulmonary diseases, SCLC, or NSCLC are depicted in Figs 1 and 2, respectively. The data are summarized in Table 1. Serum iCT levels were increased in 19% of the patients with lung cancer compared with increases in PDN-21 levels in 44% of the patients. In the subgroup of patients with SCLC, iCT concentrations were increased in 23% of the patients compared to 51% for PDN-21.

As shown in Table 2, PDN-21 and iCT were frequently not increased in the same patients. PDN-21 concentrations were elevated in 69 (34%) of 202 patients with a normal iCT level, whereas iCT concentrations were increased in only six (4%) of 139 patients with a normal PDN-21 level. However, as shown in Fig 3, markedly elevated values of the two markers generally occurred in the same patients. Even though the low values of iCT and PDN-21 did not correlate, the correlation gradually improved as values increased (Fig 3; r = 0.60, P < 0.01).

Not surprisingly, NSE was the most sensitive marker in patients with SCLC (83% had elevated values) whereas CEA was the most sensitive marker for NSCLC (50% had elevated values). However, PDN-21 provided some complementary information to that from the classical tumor markers. PDN-21 was increased in seven (47%) of 16 patients with SCLC and normal NSE levels, and in 19 (30%) of 63 patients with NSCLC and normal CEA levels.

In preliminary experiments investigating the possible immunoheterogeneity of circulating PDN-21, immunodilution curves of three sera from patients with elevated immunoreactive PDN-21 levels were found to be parallel to the standard curve (Fig 4).

### Discussion

Many tumor markers have been investigated in lung cancer, particularly in SCLC where ectopic secretion of various en-
enzymes or hormones is frequently observed (10). The secretion of hormones such as CT suggests a histogenetic relationship between SCLC and the pulmonary neuroendocrine cells (10,11). NSE is currently considered to be the best clinical marker for SCLC and is increasingly used to monitor the therapy of this type of lung cancer (12). Our study confirms that NSE levels are increased in over 75% of the patients with SCLC. NSCLC are a heterogeneous group of tumors that progress more slowly and are less chemo sensitive than SCLC. Despite the increasing number of available markers, CEA remains the "gold standard" for all NSCLC even though it has limited clinical value (13).

Our data indicate that PDN-21 is a new tumor marker for lung cancer. Its specificity was very satisfactory and its sensitivity was far better than iCT measurement. This increased sensitivity appeared to be mainly due to the lower limit of normal values. Even though the concentrations of iCT and PDN-21 were frequently not increased in the same patients, the correlation between the two markers was good for markedly elevated values. Exceptions, however, were noted in the cosecretion of the two peptides which has been reported for MTC (7). This suggests an abnormal processing of CT gene products in some patients with cancers other than MTC, but further studies are necessary before firm conclusions can be made on this important point.

Circulating CT is immunochromically heterogeneous, particularly in cancer patients (4). The use of extraction techniques is necessary to study correctly CT physiology or CT deficiency conditions (17,18). It has also been necessary to measure PDN-21 after serum extraction to demonstrate its cosecretion with CT in normal subjects (6), but little is known about the possible immunochemical heterogeneity of circulating PDN-21. The nature of secreted immunoreactive PDN-21 by lung cancer cells remains to be determined, but the strict parallelism of the immunodilution curves to the standard curve suggests that authentic PDN-21 has been measured. The use of monoclonal antibodies to measure CT monomer, PDN-21, and other CT gene products should be useful in defining better the exact nature of the secreted peptides (19).

Although its clinical value remains to be proven, PDN-21 appeared to provide complementary information to NSE and CEA, the classical tumor markers for SCLC and NSCLC, respectively. Our study supports the theory that NSCLC can have similar neuroendocrine biological properties as SCLC. Concentrations of NSE were increased in 43% (data not shown) and PDN-21 in 39% of our patients with NSCLC. Other authors have also reported elevations of endocrine-related markers in substantial proportions of patients with NSCLC (14,15). These biochemical observations are corroborated by histologic descriptions of neuroendocrine differentiation of some NSCLC (16). The prognostic or therapeutic importance of such neuroendocrine characteristics remains to be determined, but these studies could lead to a new classification of lung cancers which would no longer be based on sole histologic criteria but also on biological properties possibly leading to different therapeutic approaches.

These preliminary data show that PDN-21 is a new tumor marker for lung cancer which is more sensitive than iCT. Moreover, PDN-21 may provide complementary information to the classical tumor markers CEA and NSE. This work also supports the concept of neuroendocrine differentiation in a as yet undefined subgroup of patients with NSCLC and raises some interesting questions about the processing of CT gene products in other cancers than MTC.

Table 2
Comparison of Immunoreactive calcitonin (iCT) and PDN-21 in Patients with Lung Cancer

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*P < 0.0001.  †P < 0.0005.
The correlation between serum concentrations of PDN-21 and iCT in patients with lung cancer ($y = 214 + 0.83x; r^2 = 0.60; P < 0.01$). For clarity, normal values of both markers have been withdrawn from panel A and are shown in panel B.

**Acknowledgments**

The authors are grateful to Ms. A. Collet for secretarial assistance.

This work has been supported in part by a grant from Foundation Lefevre and from Association Beige contre le Cancer, Brussels, Belgium.

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