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Perspectives and Commentaries

Tumor Markers in Small Cell Lung Cancer

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CLINICIANS have for years been looking for specific laboratory tests which can be used either to detect malignant disorders or to monitor cancer patients during treatment. Major success has only been achieved in rare disease entities such as, for example, germ cell tumors and medullary thyroid carcinoma; on the other hand the value of developing such tests has also clearly been demonstrated in the latter malignancies and beta-HCG, alpha-fetoprotein and calcitonin play today an important role in the successful management of these tumors.

The occurrence of paraendocrine syndromes in patients with small cell lung cancer (SCLC) was established as early as 1928 by Brown describing a case with small cell lung cancer and non-pituitary adrenal cortical hyperactivity [1]. The nature of this relationship was not definitely clarified until the early 1960s when Meador *et al.* demonstrated an ACTH-like substance in five tumors with concomitantly decreased ACTH content in the pituitary [2]. The term 'ectopic ACTH' was shortly afterwards used by Liddle *et al.* [3] and since then more than a dozen substances have been identified as being synthesized or strongly suspected of being synthesized in the lung. Most of these substances are polypeptides, but some are arachidonic acid metabolites and others again are biogenic amines.

The most frequently detected markers in SCLC are the polypeptides ACTH, ADH and calcitonin [4], which are all biomarkers revealing the histogenetic relationship between SCLC and bronchogenic carcinoids to the pulmonary APUD (amine content and/or amine precursor uptake and amino acid decarboxylation) cells. Evidence of this relationship has also been documented with the frequent histochemical and biochemical identification both in SCLC tumor tissue and in cultured cells of polypeptides or enzymes such as bombesin, dopa-decarboxylase, neuron specific enolase and creatinine kinase BB isoenzyme. With the development of this large panel of biomarkers in SCLC, it is to be expected that major impact could be achieved in (a) screening and early diagnosis, (b) clinical staging, (c) prognostication, for example, by subgrouping of various types of SCLC including mixed histologic types, (d) monitoring response to therapy including detection of subclinical disease and early relapse, (e) further characterization of various biological features of SCLC, especially of histogenetic origin, (f) *in vivo* or *in vitro* drug sensitivity testing either against established tumor cell lines from SCLC or SCLC tumors transplanted to nude mice.

Ideally, to fulfill these tasks the following conditions have to be met, as pointed out by Hansen in 1981 [4]: (a) the hormones must be produced by the tumor cells in the primary tumor and in the metastases, (b) the secretion and elimination rate must be almost constant in order to establish a relation between the quantity of the tumor cells and the peripheral values, (c) production secretion of ectopic hormones in tumor cells developing resistance must be the same as in the primarily sensitive cells in order to use ectopic hormones as markers for the progression of an initially responding tumor. Finally, in order to be useful as monitors during therapy the chemotherapeutic agents themselves must be without influence on the production and secretion of hormonal substances in non-affected tumor cells. Unfortunately none of the hormonal substances examined hitherto in SCLC have

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been found to fulfill the above criteria to a useful level.

Since 1981 the topic of ectopic hormones in lung cancer has been extensively reviewed at international conferences in Washington D.C., U.S.A. and Marburg, West Germany, in 1982 and 1984, respectively [5, 6]. Also a series of articles has appeared in the literature, including a recent publication in the *European Journal of Clinical Oncology*, dealing with serum ferritin in SCLC [7]. The latter is hampered by inclusion of relatively few patients (39 with SCLC) precluding firm statements especially concerning the value of serum ferritin as being of prognostic value. The methodological problems have also recently been elucidated by Gall *et al.* [8], who examined sera for 10 substances from 171 patient with advanced lung cancer, 110 normal persons and 123 subjects with benign respiratory diseases. The 10 substances included: ferritin, lipid bound sialic acid, total sialic acid, beta 2 microglobulins, lipotropin, the alpha and beta subunits of human chorionic gonadotropin, calcitonin, parathyroid hormone and carcinoembryonic antigen (CEA). Individual markers were studied and also combinations of markers were sorted to discriminate lung cancer patients from normals and from patients with benign lung disease. The best discrimination rules were obtained for a combination of CEA and total sialic acid which was better than CEA alone. When those two substances were used combined and designed to have 95% specificity, the sensitivity for discriminating advanced lung cancer from normal controls was 54% compared to 52% for discriminating advanced lung cancer from controls with benign respiratory disease. Overall the results from the study were thus disappointing and the need for the identification of other markers was clearly demonstrated.

Within the last two years the polypeptide called bombesin or its mammalian counterpart, gastrin-releasing peptide (GRP), and the enzymes neuron-specific enolase (NSE) and BB isoenzyme of creatinine kinase (CK-BB) have been tested intensively in SCLC. These markers are all produced or identified in SCLC. Among these the fast degradation of bombesin in plasma limits the value of this product as a useful clinical marker at present. Among the two other substances in six studies NSE has been found to be elevated on an average of 65% in 397 SCLC patients, while NSC was elevated in only 14% of 190 patients with non-small cell lung cancer [9].

Other recent investigations have revealed that the usefulness of NSE in monitoring the patients during therapy is somewhat limited at present. A certain correlation of the rates of the decline in the concentrations of plasma NSE to the initial response rates plus relapse rates has been established in three major studies [10–12], but not to a level where it has so much impact on the clinical decision making that it can be recommended for common clinical use.

A special area where biomarkers in SCLC appear to play an important diagnostic role is in the detection of meningeal carcinomatosis [13]. The diagnostic accuracy of combining the CK-BB and bombesin have been tested in 17 patients with meningeal carcinomatosis. None of these patients had normal CSF levels of both markers. 82% of patients with meningeal carcinomatosis had both markers elevated, and 93% of patients with both markers elevated had meningeal carcinomatosis.

With respect to NSE and calcitonin, NSE is found to have the highest overall detection in CSF from patients with CNS metastases, 95% for meningeal carcinomatose and 54% for parenchymal metastases. However, a substantial number of patients without CNS metastases have also had elevated NSE. Calcitonin by itself does not appear to add further information as a diagnostic tool as all patients with meningeal carcinomatosis and elevated CSF calcitonin also had detectable CSF bombesin in the above mentioned study.

As both creatinine kinase BB and bombesin are also produced in normal brain tumor tissue, one cannot exclude the possibility that their presence in the CSF arises from necrotizing brain tissue rather than from tumor cells and further evaluation of these markers in the CSF including CSF from other solid tumors than SCLC must be analyzed before the final impact on the value of these methods in the detection of CNS metastases in general and meningeal carcinomatosis can be judged specifically.

In the meantime the production of monoclonal antibodies to a series of these markers with a high specificity may conceivably improve the diagnostic accuracy of these markers including the detection of the various amino acid sequences within the polypeptide molecules, which are more consistently produced by SCLC cells.

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