Tumour markers in the clinical management of patients with small cell lung cancer

M. Hansen, H.H. Hansen*

Neoplastic cells produce and release several substances. Some of these substances are produced specifically by certain tumour types, making it possible to use these substances as tumour markers. The latter implies that they can be used in the histopathological classification and, provided the substances can be measured in blood or urine, also in the clinical management of patients, e.g. in screening, diagnosis, staging, prognostication, therapy monitoring, including evaluation of tumour response and early relapse. Well-known examples of clinically useful tumour markers are amines in carcinoids and pheochromocytomas, and the M-component in myeloma. In recent years, human chorionic gonadotrophin (HCG) and alpha fetoprotein have contributed significantly to the diagnosis and treatment of germ cell tumours, including testicular cancer.

For patients with lung cancer in general, carcinoembryonic antigen (CEA) was one of the first markers described. The concentration of this marker has been found to be related to the prognosis and tumour burden in groups of patients with small cell lung cancer (SCLC), but CEA has no significant predictive value for the individual patient.

Among the various histological cell types, SCLC has been known to produce a series of tumour makers compatible with the neuro-endocrine histological origin of SCLC from the amine precursor uptake and decarboxylation (APUD)-system. Already in 1928 a patient with small cell lung cancer was described with the ectopic Cushing syndrome a few years before Cushing described the syndrome related to his name in non-malignant cases [1].

Subsequently, it was recognized that endocrine syndromes, such as the ectopic Cushing syndrome and the Schwartz-Bartter syndrome (SIADH) in lung cancer were particularly related to SCLC [2, 3].

During the 1970's considerable progress was made in the cytostatic treatment of SCLC with a subsequent interest in identification of tumour markers in order to improve the clinical management of patients with SCLC. Initially, the hormonal peptides were investigated, and ACTH, ADH and calcitonin were classified as being special hormonal markers for SCLC. However, measurement of these markers was not found to contribute significantly to the clinical management of patients with SCLC [3].

Within the present decade, gastrin-releasing peptide (GRP), has often been found to be produced by SCLC cell lines [4]. This was initially identified as bombesin, which is an amphibian peptide of 14 amino acids. The bombesin-like immunoreactivity is due to the first 14 of the 27 amino acids in GRP. Cells with GRP are rare in the normal adult lung, but are regularly found in the fetal and infantile epithelium of the lung [5]. It is particularly noteworthy that SCLC is often equipped with receptors for GRP [6], which has a growth promoting activity in SCLC [7]. Accordingly, it has been suggested that GRP acts as an autocrine growth factor in SCLC.

Unfortunately, increased concentrations of GRP in the serum are rare [4, 8] due to its very short half-life. Recently, a radioimmunoassay for pro-GRP has been developed. Using this assay, elevated plasma concentrations were found in 72% of 71 SCLC patients [9]. Further clinical studies are at present in progress to define a possible role of pro-GRP as a clinically useful tumour marker in SCLC.

In addition to different hormonal peptides, some enzymes were also detected in the cell lines derived from SCLC tumours, i.e. the brain fractions of enolase and creatine kinase (CK), known as neuron-specific enolase (NSE) and CK BB. The latter enzyme has been noted to be elevated in about half of the patients with SCLC, particularly in patients with extensive disease, but a clinical role of this marker has not yet been defined.

In contrast, NSE has been extensively tested in SCLC [10]. It has been found to be elevated in about 70% of SCLC patients with values of 50% in patients with localized disease and 85% in extensive stage patients. Recently, it was also demonstrated that NSE may be an important prognostic factor [11, 12]. The relation to stage is also found in the individual patients, as it has preliminarily been observed that the concentration of NSE decreases with response and increases some weeks before the clinical recognition of relapse [13]. In patients with non-SCLC, NSE is found to be elevated in only 10–15%, and in this group of patients, the concentrations are almost always below 25 ng·ml⁻¹. Accordingly, NSE may be diagnostic for SCLC if the concentration is above this level, whereas at lower concentrations it is of no diagnostic value [14].

On the other hand, a recent publication observed that the demonstration of NSE in non-SCLC tumour tissue predicts a much better response to chemotherapy than has usually been noted in non-SCLC patients [15].
phenomenon should be further investigated, including a possible predictive value for response of an elevated serum NSE-concentration in non-SCLC.

In the future, NSE may be included as a tumour marker in the management of SCLC patients, but at least one more large prospective study is necessary for a more exact definition of its role in the routine clinic.

References