Medicine Section

Progastrin-releasing peptide – a useful and reliable biomarker in small cell lung cancer

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Abstract

In the last few years the biomarker progastrin-releasing peptide (ProGRP) has proved a useful and reliable laboratory parameter for differential diagnosis and treatment management of lung cancer. ProGRP displays high sensitivity and specificity for small cell lung cancer (SCLC) and is suitable for differentiating it from benign lung disease, lung cancer of non-small cell histology (NSCLC) and metastatic non-lung cancers. This distinction is of considerable practical relevance in view of the different treatment approaches in SCLC and NSCLC. Differential diagnostic classification of indeterminate pulmonary nodules can be further improved by combined use of a lung marker panel comprising ProGRP, NSE, CYFRA 21-1, CEA and SCCA. Serial ProGRP measurement during treatment and follow-up of SCLC provides important information about therapeutic response or tumour progression.
Lung cancer – a medical and social challenge

Lung cancer remains a formidable medical and health policy challenge. In Germany alone about 50,000 people a year develop lung cancer and over 42,000 die of it (1). With 1.35 million new cases and almost 1.2 million deaths a year, it is one of the most dangerous cancers worldwide (2). The close link between lung cancer and smoking is widely acknowledged and has prompted numerous anti-smoking campaigns.

One reason for the high mortality rate is the frequently late diagnosis of lung cancer. Symptoms often appear only at an advanced tumour stage, when therapeutic options are limited. Over 70% of lung cancers are not amenable to complete surgical removal and require systemic chemotherapy or radiotherapy (3-5). In addition, the treatment approach is quite different in different histological subgroups. While primary tumour resection is the primary goal for the common non-small cell subtype (NSCLC, approx. 80%), which includes adenocarcinoma and squamous cell carcinoma, this is not normally useful for the small cell subtype (SCLC, approx. 20%) owing to the tumour’s pattern of growth and spread. On the other hand, the malignant cells in the latter case respond very well to cytotoxic chemotherapy or radiotherapy, although the remissions thus achieved generally last for only a limited time before further tumour progression (3-5).

Diagnostic requirements

The significance of this for medical diagnostics is that in addition to the assessment of suspicious clinical and imaging signs of cancer, histological classification of a tissue sample is essential for further treatment planning. Although an unequivocal and accurate diagnosis is possible in many cases, there are often difficulties, for example if a high-quality biopsy cannot be taken or if different histopathological cell types are found within one tumour or in the presence of metastases. In these situations additional diagnostic tools can contribute to more reliable classification. A special role is played by biomarkers detectable in the blood, which sensitively reflect biochemical changes of malignancy. The test methods available today are generally highly sensitive, inexpensive, robust, readily reproducible and quick to perform, delivering quantitative results that undergo continuous quality control. Whether individually or as panels of multiple markers, these so-called “tumour markers” provide important information for differential diagnosis and prognostic evaluation before planned cancer treatment (6,7). It is important to bear in mind that the release of these markers into the bloodstream can vary according to tumour size or aggressiveness, so that very small or slow-growing tumours sometimes remain undetected (limited sensitivity), while in some cases slightly raised levels are also found in non-malignant disease (limited specificity). Despite these known limitations, “tumour marker” release patterns in particular are often very helpful in classifying equivocal findings (6,7).

The “tumour marker” constellation of cytokeratin-19 fragments (CYFRA 21-1), carcinoembryonic antigen (CEA), squamous cell carcinoma antigen (SCCA), neurone-specific enolase (NSE) and progastrin-releasing peptide (ProGRP) can be used in this way for differential diagnosis of a suspicious pulmonary nodule. In most cases this can distinguish between lung cancer and benign lung disease or non-lung cancer metastases (8). The expression and release pattern also often allows conclusions to be drawn about the underlying histology: Predominant expression of CYFRA 21-1 and CEA suggests non-small cell lung cancer, while strong SCCA
expression indicates squamous cell carcinoma. By contrast, marked release of ProGRP and/or NSE indicates with high probability the presence of small cell lung cancer (6-8).

**Progastrin-releasing peptide (ProGRP) as a biomarker for small cell lung cancer**

ProGRP is the precursor of gastrin-releasing peptide (GRP). This corresponds in mammals to the bombesin of amphibians, which has been used for years for histopathological classification of lung tissues. Because of the instability of GRP in blood, the more stable recombinant ProGRP [31-98] was developed as a serum marker. ProGRP consists of 125 amino acids; there are three different ProGRP isoforms with a common amino terminus and variable carboxy termini. GRP is thought to act as a neurotransmitter in the human nervous system and is also found in neuroendocrine cells of the gastrointestinal and respiratory tracts (6-8).

The ProGRP biomarker is released in particular by small cell lung cancer (SCLC) cells and is often already clearly raised in the serum of patients with a localised tumour (limited disease). Very high ProGRP concentrations have also been reported in the blood of patients with very rare medullary thyroid cancer. By contrast, it is not released to an appreciable extent in non-small cell lung cancer (NSCLC), other cancers or benign lung disease. These properties make ProGRP a highly sensitive and specific biomarker for SCLC (6,9,10).

For diagnostic classification of moderately raised ProGRP levels it is important to bear in mind that impaired renal function can lead in some cases to ProGRP blood concentrations up to about 300 pg/mL (6,11,12). In benign gastrointestinal or respiratory tract disease, on the other hand, only slightly elevated levels are occasionally observed (6,12). The 95th percentile for healthy subjects is 40-60 pg/mL, depending on the test employed. For some ProGRP tests better stability has been found in plasma than in serum (13), although in our experience this is not true of all tests.

**ProGRP in the differential diagnosis of small cell lung cancer**

In combination with CYFRA 21-1, CEA, SCCA and NSE, marked ProGRP and/or NSE release in the absence of SCCA release indicates with high probability the presence of small cell lung cancer. In particular, ProGRP levels above 300 pg/mL can be regarded as virtually diagnostic criteria, assuming normal renal function. In a large study, benign lung disease and lung metastases from other cancers showed merely levels below 100 pg/mL. With few exceptions – possibly due to tumours of mixed histology – ProGRP levels in NSCLC were below 300 pg/mL (8). At 95% specificity versus benign lung disease, diagnostic sensitivity in various studies ranged from 47 to 80% (10,14,15), exceeding that of NSE. Because of the different biological backgrounds of the two markers, ProGRP and NSE had additive sensitivity, meaning that use of both markers results in enhanced diagnostic accuracy (8,10,14).

ProGRP and NSE are also the two key markers for distinguishing between SCLC and NSCLC. In combinations with the other lung markers a sensitivity of over 80% was achievable at a specificity of 95% (8). As already mentioned, this classification is particularly important when planning further treatment steps (5).
ProGRP in the treatment management of small cell lung cancer

Several questions are relevant to treatment management:

1. Can ProGRP predict the patient’s response to planned therapy and/or prognosis before the start of treatment?
2. Do ProGRP kinetics during cytotoxic therapy permit reliable monitoring of treatment response or early detection of non-response?
3. Do ProGRP kinetics in the follow-up – i.e. post-treatment – setting permit early and reliable detection of cancer recurrence or progression?

Few studies have so far been conducted on these questions. No reliable evidence has yet been found that pretherapeutic ProGRP levels are of prognostic and/or predictive value (17-20). This is also consistent with observations of high ProGRP levels both in prognostically favourable early tumour stages and in advanced stages (8,14,16).

As with most tumour markers, continuously and strongly decreasing ProGRP levels during cytotoxic therapy are indicative of a good response, while constant or rising levels suggest poor treatment efficacy or tumour progression (20,21). It is noteworthy that ProGRP levels fall markedly during treatment in most patients, even those experiencing progression. The groups with absent (or only brief) response and subsequent progression are distinguishable at most by a somewhat smaller decrease, quickly followed by a renewed increase (22).

In a further study the response to treatment was evident from changes in ProGRP levels after only two cycles of chemotherapy – and more clearly so than with NSE. Moreover, these ProGRP kinetics had prognostic value for one-year patient survival (23). These results accord with our own experience, which likewise shows a high association between ProGRP levels after one and two cycles of first-line chemotherapy and therapeutic response. Combination with the markers NSE and CYFRA 21-1 further enhanced its value for biochemical staging (at the time of radiological follow-up after the second cycle). For early assessment of treatment response (after only one cycle), combination with the marker nucleosomes resulted in further enhancement (20).

Although these studies already suggest great potential for ProGRP for monitoring treatment in SCLC patients, further studies will be needed to define the ideal intervals for ProGRP determination and cutoff values or algorithms for assessing marker changes. On this basis ProGRP can then be deployed – perhaps in combination with other markers – in future treatment management strategies.

Conclusions

The new biomarker progastrin-releasing peptide (ProGRP) represents an informative and reliable laboratory parameter for small cell lung cancer. In combination with the tumour markers CYFRA 21-1, CEA, SCCA and NSE it enables sensitive and specific differential diagnosis of suspicious pulmonary nodules. Serial measurement of ProGRP permits early assessment of response to cytotoxic therapy or of tumour progression in SCLC. However, clinical influencing factors such as renal impairment should be taken into account when interpreting ProGRP results.
References


**Figure legend**

ProGRP, NSE and CYFRA 21-1 time courses in a patient with small cell lung cancer during and after combined first-line chemotherapy (CTx1) and radiotherapy (RTx) and sustained complete remission. ProGRP levels showed a rapid, complete and lasting fall to within the range of individual baseline values.
Figure legend

ProGRP, NSE and CYFRA 21-1 time courses in a patient with small cell lung cancer during first-line chemotherapy (CTx1). While partial remission was initially achieved, this was followed by tumour progression. ProGRP levels showed an initial marked fall, but soon began to rise again continuously.
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