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Lung cancer biomarkers – Where we are and what we need

Petra Stieber* and Stefan Holdenrieder
Institute of Clinical Chemistry, University Hospital of Munich-Grosshadern, Munich, Germany

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Lung cancer is at present and will be in future a major problem for societies throughout the world [6, 10]. Although national anti-smoking campaigns may have some effects in the western industrialized world, the aging of the societies there as well as the growing societies in the less developed world and air pollution problems like in China will contribute to a rising incidence of lung cancers [5,7,13]. Whether and how screening projects will lead to an earlier detection of lung cancer is still an open question. Therefore further diagnostic and therapeutic efforts are needed to meet this tremendous challenge.

Circulating biomarkers are valuable and informative tools in the management of lung cancer disease [11]. Although they are not helpful in the asymptomatic stage for screening purposes – at least not by a single investigation – they have shown great potential in supporting differential diagnosis, estimating prognosis, monitoring the therapy response and the early detection of recurrent disease [2,4,9,12]:

- Histological subtyping is particularly important for patients with poor performance status or with peripheral tumors when biopsies can not be performed successfully. Further biomarkers indicate mixed tumor histologies which is highly relevant for therapy planning [9].
- Estimating prognosis will become even more important in the future when more therapeutic alternatives are available and survival of some patient subgroups is improved. The selection of individual patients for specific treatment strategies will then depend not only on clinical characteristics but also on tumor biology which is mirrored in the release of tumor related biomarkers into the blood [4,16].
- The monitoring of therapies has been outside the focus for many years because the panel of alternatives was quite limitted. However, as more effective cytotoxic drugs and targetted therapies are available, it is of great importance to modify the treatment early if it had shown to be ineffective. During systemic therapies but also during the development of recurrent disease, tumor activity can be estimated with imaging methods only with a certain delay. However, biochemical changes in the blood indicate early the potentially increasing tumor activity. Therefore circulating biomarkers are very valuable for these follow-up investigations [2].
- Following the argument that biomarkers detect early the recurrence of disease, they may trigger further intensive diagnostics and earlier and potentially more effective treatments of lung cancer patients.

If these assumptions on the value of biomarkers are true they are expected to be part of the standard diagnostic workup of lung cancer patients and be present in all relevant guidelines for thoracic oncologists – all

*Corresponding author: Petra Stieber, MD, University Hospital Munich-Grosshadern, Institute of Clinical Chemistry, Marchioninistr. 15, D- 81377 Munich, Germany. Tel.: +49 89 7095 3115; Fax: +49 89 7095 6298; E-mail: Petra.Stieber@med.uni-muenchen.de.

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Table 1
Recent guidelines for the use of biomarkers in lung cancer (adapted from 14)

Marker (s)	Application	ASCO	ACS	EGTM 1999	NACB 2006**
CYFRA 21-1	For differential diagnosis	NR	NR	Yes, for NSCLC	Yes, for NSCLC
	For prognosis	NR	NR	NR	Yes, in NSCLC
	For post-operative surveillance	NR	NR	Yes, in all NSCLC and SCLC	Yes, in NSCLC
	For monitoring therapy in advanced disease	NR	NR	Yes, in all NSCLC and SCLC	Yes, in NSCLC
	For detection of recurrent disease	NR	NR	Yes, in all NSCLC and SCLC	Yes, in NSCLC
CEA	For differential diagnosis	NR	NR	Yes, for NSCLC	Yes, for NSCLC
	For prognosis	NR	NR	NR	NR
	For post-operative surveillance	NR	NR	Yes, in adenocarcinoma	Yes, in NSCLC
	For monitoring therapy in advanced disease	NR	NR	Yes, in adenocarcinoma	Yes, in NSCLC
	For detection of recurrent disease	NR	NR	Yes, in adenocarcinoma	Yes, in NSCLC
NSE	For differential diagnosis	NR	NR	Yes, for SCLC	Yes, for SCLC
	For prognosis	NR	NR	NR	NR
	For post-operative surveillance	NR	NR	Yes, in SCLC	Yes, in SCLC
	For monitoring therapy in advanced disease	NR	NR	Yes, in SCLC	Yes, in SCLC
	For detection of recurrent disease	NR	NR	Yes, in SCLC	Yes, in SCLC
ProGRP	For differential diagnosis	NR	NR	NR	Yes, for SCLC
	For prognosis	NR	NR	NR	NR
	For post-operative surveillance	NR	NR	NR	Yes, in SCLC
	For monitoring therapy in advanced disease	NR	NR	NR	Yes, in SCLC
	For detection of recurrent disease	NR	NR	NR	Yes, in SCLC

ASCO, American Society of Clinical Oncology; ACS, American Cancer Society; EGTM, European Group on Tumor Markers; NACB, National Academy of Clinical Biochemistry; NR, no recommendation published, NSE, neuron specific enolase; CEA, carcino embryonic antigen; CYFRA 21-1, cytokeratin 19 fragments; ProGRP, progastrin-releasing peptide; SCLC; small cell lung cancer; NSCLC; non-small cell lung cancer.

the more as most lung cancer markers have been investigated systematically for more than 15 years and the frequency of an increased release of these biomarkers due to lung cancer is much higher than for most other cancers where biomarkers are recommended since many years. However, neither in the recommendations of the American Society of Cinical Oncology (ASCO), nor of the American Cancer Society (ACS) biomarkers are listed as a part of any of the diagnostic or prognostic procedures in lung cancer patients (3, Table 1). The first society to recommend the biomarkers CYFRA 21-1, CEA and NSE for the management of lung cancer patients was the European Group on Tumor Markers (EGTM) in 1999 [1]. In the new version of the guidelines of the National Academy of Clinical Biochemistry (NACB), which is soon to be published, these markers and additionally ProGRP are recommended for the use in differential diagnosis, prognosis, post-operative surveillance, monitoring therapy in advanced disease and detection of recurrent disease in different histological subtypes [14].

Why are the abundant results of studies and the rich clinical experience of so many experts in the field so poorly recognized by official societies? Are the facts on biomarkers only fiction or is there a basic problem of confidence in the information by circulating biomarkers?

There may be a bundge of reasons for this situation:

- Tumor related biomarkers have been regarded by many physicians as tumor specific in the past and in addition to be related to a certain kind of tumor like colorectal cancer or ovarian cancer. Thus expectations especially for the early diagnosis of cancer have been high – and the desillusion was great after it became obvious that due to the lack of tumor- and organspecificity it will be difficult to establish primary diagnosis especially in asymptomatic patients.
- Especially the implementation of reference limits or cut off values for these non-tumor specific but physiological blood components has led to a continuous misunderstanding and misuse of tumor markers. Biomarker levels higher than the reference range have been and still are interpreted as "tumor positive", whereas values within the reference range have been regarded as "normal". Up to now it is not understood and respected that it is a question of the increased release of a biomarker based upon the individual baseline level of a single healthy individual before the tumor develops.
- The knowledge on the release of biomarkers by different benign and malignant diseases has been quite limited. If a marker was known to be a lung marker, it was investigated only in lung diseases. Only step by step it has been revealed that for example CYFRA 21-1 may also have applications in breast, ovarian and pancreatic cancer as well.

– Serial biomarker results have been interpreted as kinetics irrespective of the change of the laboratory or of the methods leading to clinically highly meaningful misinterpretations.
– Influencing factors such as renal or hepatic diseases have not been respected in the biomarker interpretation.
– The relevance of the release *and* non-release of biomarkers in "patterns" is being explored now especially in cancers with mixed histologies such as the lung, or in cancers of unknown primaries. Therefore, "negative" biomarker information (low resp. very low value levels) can be highly important as well.
– The concept of individual baseline values has been recognized only since the last years. Following this procedure, repeated measurement of biomarker levels after primary therapy enables the identification of the individual baseline values. During the further follow-up, the interpretation of the biomarkers rely only on the changes of marker levels from this baseline values irrespective whether they are within or outside the reference range.

All those shortcomings in the handling and interpretation of tumor-related biomarkers and the desillusion about unsatisfactory results may have contributed to an often very emotional rejection of biomarkers in the clinical routine setting. Further a plentitude of studies on this topic with poor quality, on single new markers without comparison to known markers, the non-comparability of the results in terms of different assays used and different statistical evaluations applied, has led to a confusion of many who are not deeply involved in the matter [8,17]. The companies themselves have had only limited interest in harmonization of the assays and particularly in standardized, prospective biomarker trials that could have shown their relevance e.g. in monitoring systemic disease or post-operative surveillance of cancer patients.

However, this is exactly what we need and especially what the patients need. After it becomes clear which role biomarkers play for the diagnosis and the estimation of prognosis, the wide and open field of the biomarker application in future is the follow-up of cancer patients during their disease. Many questions are ahead:

– How can we best stratify patients for the most effective therapies?
– How can we monitor those therapies with high accuracy? Which are the approriate time intervals? What thresholds of biomarker changes are reliable and clinically meaningful? Can we spare costs for imaging investigations by appliying step wise diagnostic exams?
– Can we already estimate the therapy response at the very beginning of chemo- or radiotherapy, e.g. after only one application? Which panel of biomarkers and which criteria (time points of measurements, extent of increaes or decreases) are necessary to achieve a high specificity for non-response? Can we help to improve the individual management of disease?
– How can we follow patients after the primary therapy? Which biomarker would be the most relevant ones? How often should we control them? Again, what thresholds of biomarker changes are reliable and clinically meaningful? Which criteria indicate a certainty in the clinical interpretation of recurrent disease? This is highly relevant, as false positive results would provoke unnecessary stress situations for the patients and potentially harmful and invasive investigations.

On the other hand is an earlier detection of recurrent disease only useful if it leads to therapeutic consequences in terms of an earlier application of potentially more effective therapies. To show that such a strategy can prolong the patient survival requires large, prospective, randomized intervention trials which are a huge logistic and financial challenge to meet. To be able to perform those studies physicians are needed who want to treat a patient with recurrent disease earlier in an asymptomatic stage and by consequence often more frequently even if the patient will finally not survive. A step from passive caring which means treatment if needed (symptoms) to an active caring which means treatment before needed (no symptoms) is necessary. However, as our experiences with a prospective surveillance and intervention study with more than 600 breast cancer patients [15] show, this way of intensive diagnostic follow-up combined with early therapeutic interventions supports the patients to cope with their disease and enables many patients – also in the metastasized stage – to live with the tumor disease at a high life quality which often lasts for many years.

It is clear that the biology of lung cancer and in particular of non-small cell lung cancer has its own peculiarities and will have to be investigated in its own way. Nevertheless, we have already today a panel of powerful tools with circulating biomarker at hand that could be very valuable if it is used in a well defined way (Table 2). With all the new and promising diag-

Table 2
Recommendations for use of markers according to histologies of lung cancer and application forms according the National Academy of Clinical Biochemistry (NACB, 14)

Histology	Before therapy	Post-therapy follow-up
Unknown	CYFRA 21-1, CEA, NSE, ProGRP	After surgery: following histology In advanced disease: using the leading marker
Adenocarcinoma	CYFRA 21-1 and CEA	CYFRA 21-1 and/or CEA
Squamous cell carcinoma	CYFRA 21-1 and CEA (and SCCA)	CYFRA 21-1 and/or CEA
Large cell carcinoma	CYFRA 21-1 and CEA	CYFRA 21-1 and/or CEA
Small cell carcinoma	NSE and ProGRP	NSE and/or ProGRP

NSE, neuron specific enolase; CEA, carcino embryonic antigen; CYFRA 21-1, cytokeratin 19 fragments; ProGRP, progastrin-releasing peptide. SCCA, squamous cancer cell antigen.

nostic techniques on the horizon, the clinical questions remain the same and should be answered thorougfully, patiently and with high competence to pave the patients a way to deal always better with this – hopefully more and more only chronical – disease.

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