*Table 1. Molecular characterisation of chromosomal translocations in acute myeloid leukaemias*

| Disease subtype | % of all AML | Chromosomal translocation | Fusion product | Reference |
|---|---|---|---|---|
| 1. Differentiated myeloid (FAB AML M2) | 5–20 | t(8;21)(q22;q22) | CBFα (AMLI)-ETO | 2 |
| 2. Myelomonocytic with eosinophilia (M4Eo) | 8 | inv (16)(p13;p32) | CBFβ-MYH 11 | 3 |
| 3. Promyelocytic | 10 | t(15;17)(q24;q21) | PML-RARα | 4, 5 |
| (M3/M3v) | Rare | t(11;17)(q23.1;q21) | PLZF-RARα | 6 |
| 4. AML with basophilia | 1–2 | t(6;9)(p23;q34) | DEK-CAN | 7 |

Fusion products deriving from translocation in AML generally represent the fusion of two transcription factors. Exceptions are MYH11 (smooth muscle myosin heavy chain) and RARα (retinoic acid receptor-α). PML, promyelocytic leukaemia gene; PLZF, promyelocytic zinc finger gene. Note that the frequency of the t(8;21) varies with geographical location.

PML/RARα fusion, a condition analogous to chronic myeloid leukaemias which lack cytogenetically the t(9;22)(q34;q11), but have molecular evidence for BCR-ABL fusion [8]. Since clinical efficacy of ATRA depends on the expression of the PML/RARα gene, evidence for this fusion product should be sought in all cases where such therapy is being considered.

The efficacy of ATRA in APL is a most exciting development. Much remains to be learnt, both clinically and scientifically. Might other forms of retinoic acid produce more durable CRs? Most importantly, do patients treated with ATRA fare as well as those treated with chemotherapy alone? (APL is one of the "best" subgroups of AML with regard to outcome.) Finally, given the experience in APL, do other translocations in other malignancies involve other RAR genes of which there are several, and if so, can the same approach to therapy be adopted?

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Pergamon

*European Journal of Cancer* Vol. 30A, No. 5, pp. 574–576, 1994
Elsevier Science Ltd
Printed in Great Britain

0959-8049(93)E0127-P

# Serum Neurone-specific Enolase and Other Neuroendocrine Markers in Lung Cancer

J.A. Ledermann

SMALL CELL lung cancer (SCLC) can be distinguished from other types of lung cancer by its morphology, biological behaviour and chemosensitivity. Neuroendocrine differentiation is consistent, although not a specific feature of SCLC, and different patterns of neuroendocrine expression can be found in 'classic' and 'variant' subtypes of SCLC lines [1]. This raises the possibility that neuroendocrine markers might identify biological properties of SCLC which could provide useful clinical information.

Neurone-specific enolase (NSE), a neuronal form of the glycolytic enzyme enolase consistently found in SCLC lines, is a secreted biochemical marker of neuroendocrine tumours and SCLC [2]. The neuronal form of the enzyme contains either alpha-gamma or gamma-gamma subunits, and raised levels of NSE are found in the serum of 66–81% of patients with SCLC [3–5]. The detection of raised levels of NSE in serum correlates with its presence in tissue [6]. Elevated levels of other neuroendo-

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Received 22 Feb. 1994; accepted 2 Mar. 1994.

crine markers, such as creatine phosphokinase BB [7] or chromogranin A [8], may also be found in serum. Recently, another neuroendocrine marker, the cluster 1 antigen NCAM (neural cell adhesion molecule), has been added to the list. NCAM is present in high concentrations on the surface of SCLC [9]. There are several isoforms of NCAM, including a secreted product, and all of these may be found in SCLC tumours. NCAM levels are frequently elevated in the serum of patients with SCLC [10, 11].

Ideally, serum tumour markers should be diagnostic, correlate with disease extent, predict prognosis and influence therapeutic decisions. Only the embryonic tumour markers produced by germ cell malignancies fulfil all these criteria. Early detection of lung cancer is important as it may identify potentially curable disease, but so far there are no satisfactory screening methods. Attempts to screen for lung cancer by combining the results of measurements of four tumour markers, carcinoembryonic antigen, CA-50, tumour-specific trypsin inhibitor and NSE have not yielded encouraging results [12]. A diagnosis of lung cancer can usually be obtained by examination of sputum cytology, bronchoscopy or radiologically guided needle biopsy. Measurement of serum tumour markers may be useful when lung cancer is suspected but the diagnosis is uncertain. Bergman and colleagues [13] measured NSE, carcinoembryonic antigen and CA-50 in 168 patients with lung cancer and 102 patients with non-malignant chest conditions. Combining the results in a multivariate analysis, the diagnostic sensitivity of the tumour marker assays for lung cancer was 57% with a positive predictive value of 95%. In 22% of cases, a firm diagnosis of lung cancer was made more than 1 month after tumour markers were assayed. It is in this group that serodiagnosis could be most useful, but only half of these patients had previously had raised levels of tumour markers.

Therapeutic decisions in SCLC are usually made on the basis of complex and often costly staging procedures. These identify patients with widespread disease who have a worse prognosis. Serum NSE levels are generally higher in patients with 'extensive' compared with 'limited' stage disease [3, 4, 14, 15]. This is true for other neuroendocrine tumour markers, such as NCAM which correlates with NSE levels [10, 11]. However, measurement of serum NSE levels has not been shown to be able to predict reliably the presence of 'extensive' disease [16]. Furthermore, simple biochemical measurements and patient performance score provide an accurate prediction of prognosis [17], and these tests can be used to select patients who might benefit from more intensive treatment regimens. In a recent series, where serum NSE, chromogranin A and lactate dehydrogenase were measured in patients with SCLC NSE, performance status and serum albumin were shown by multivariate analysis to be the best independent predictors of survival. Twenty-five per cent of patients with NSE levels below twice the upper limit of normal, a Karnofsky score greater than 80 and a serum albumin greater than 35 g/l were alive at 2 years [5]. Jørgensen and colleagues [18] have shown in a multivariate analysis that disease-free survival was significantly prolonged in patients with 'limited' disease, those attaining a complete remission and those with pretreatment serum levels of NSE $\leq$ 12.5 ng/ml. Using a Cox regression analysis, they demonstrated that the probability of a complete response was related to disease extent but not NSE levels. However, NSE levels and the type of response were independent predictors of the duration of response. When examined as a continuous variable, NSE levels appear to relate to survival, with a reduction of approximately 10% in median survival of patients with 'limited' disease for each 5 ng/ml incremental rise in NSE [19]. Drawing conclusions from all these studies, it seems that if complex staging is not performed to assess disease extent, pretreatment NSE levels might be useful in predicting disease-free survival.

As patients respond to treatment, levels of NSE fall; they are usually normal in patients in complete remission and often rise at relapse [3, 4]. Thus, NSE mirrors tumour bulk quite well, but in longitudinal studies, follow-up measurement of NSE has not been shown to be useful in predicting relapse [20, 21].

The neuroendocrine phenotype can also be demonstrated in some cases of non-small cell lung cancer (NSCLC), particularly adenocarcinoma, where features of neuroendocrine differentiation are found in 20–30% of cases [22–24]. Approximately 20% of patients with NSCLC have raised serum NSE levels [4]. There is some evidence that the presence of these markers may influence chemosensitivity or the metastatic potential of tumours. Two retrospective studies have shown an increased response rate to chemotherapy in patients with tumours expressing NSE [25, 26]. Serum NSE correlates with levels of lactate dehydrogenase, and both have been shown to be predictors of chemosensitivity [27]. However, studies have not shown that neuroendocrine differentiation, as an independent variable, is associated with a better or worse survival [24, 26, 28].

The literature on serum NSE in lung cancer is now quite extensive. The presence of neuroendocrine differentiation is used most often to support a diagnosis of SCLC. The reasons for the consistent expression of the neuroendocrine phenotype in this tumour and its association in some NSCLC remains enigmatic, but of great interest to researchers studying the biology of lung cancer. Measurement of NSE levels in NSCLC cannot be regarded as useful in routine clinical practice. However, in SCLC, knowledge of serum NSE values may help to predict recurrence-free survival.


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*European Journal of Cancer* Vol. 30A, No. 5, pp. 576–577, 1994
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0959–8049/94 $7.00+0.00

0959–8049(93) E0080-A

# Radiosensitivity Testing of Normal Tissues: a Way to Optimise Radiotherapy?

**P. Lambin and P. Lawton**

IN THIS issue, Floyd and Cassoni (pp. 615–620) assessed the reliability of a lymphocyte micronucleus assay to determine the radiosensitivity of individual patients. Levels of radiation-induced micronuclei were measured following exposures of up to 4 Gy X-rays. The variation between individuals was greater than between repeat experiments on the same individual and, in accordance with the literature, they found that cord blood lymphocytes were generally more radiosensitive than normal lymphocytes. The authors conclude that the lymphocyte micronucleus assay could have some predictive capacity for the determination of individual radiosensitivity. Unfortunately, it is difficult to be certain as to whether or not the conclusions of Floyd and Cassoni are generally valid. Lymphocytes are a heterogeneous cell population, especially with regard to the proportion of lymphocytes subtypes. Furthermore, they die after irradiation both by reproductive death and by apoptosis, in contrast to the majority of cell types which die mainly by a reproductive death. Despite these limitations, this is an important study. We urgently need a reliable assay for predicting the radiosensitivity of normal tissues before radiotherapy is commenced. In order to achieve this, it is essential to understand the relationship between the *in vitro* radiosensitivity of different cell types and the clinical response to radiotherapy.

*A subpopulation of radiosensitive patients*

There is evidence to suggest that both tumours and normal tissues show interindividual differences in intrinsic radiosensitivity. In 1975, Taylor and colleagues noted a correlation between the cellular radiosensitivity of skin fibroblasts and severe reactions to radiotherapy in an individual with the genetic disorder ataxia teleangiectasia (AT) [1]. There have now been a number of published retrospective studies of individuals showing severe reactions to radiotherapy where cultured fibroblasts have shown excessive *in vitro* radiosensitivity [2–4].

AT is a rare genetic disorder but it has been estimated that about 1% of the population are carriers for the AT gene. These

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Received 23 Nov. 1993; accepted 9 Dec. 1993.