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Perspectives and Commentaries

Immunohistology of Lung Cancer

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(A COMMENT ON: Berendsen HH, de Leij L, Poppema S, Postmus PE, Sluiter HJ, The H. Simultaneous standard light microscopy and immunohistology on bronchoscopically procured lung cancer specimens. *Eur J Cancer Clin Oncol* 1988, **24**, 915–922.)

IN RECENT YEARS the advent of monoclonal antibody technology has greatly facilitated our ability to diagnose, detect and treat a variety of human malignancies, including lung cancer. Over the past decade in excess of 60 monoclonal antibodies generated against lung cancer-associated antibodies have been characterized and evaluated for their reactivity with both cell lines and fresh biopsy specimens of lung cancer, and a variety of other normal and malignant cells [1]. Until recently, because of their lack of relative specificity and, more importantly, the problem of antigenic and biologic heterogeneity within lung cancer, the widespread use of monoclonal antibodies in the diagnosis, staging and treatment of lung cancer patients has been limited.

The application of monoclonal antibodies in the clinical management of patients dictates that these antibodies be selected on the basis of specificity testing. Antibodies should be selected on the basis of their pattern of reactivity with both normal and malignant tissues, in studies which include a broad range of normal and pathologic conditions. If such detailed studies are not carried out, then an unacceptable number of false-positive determinations may occur.

In an attempt to consolidate the patterns of reactivity of these many different monoclonal antibodies generated, in particular those generated against small cell lung cancer (SCLC)-associated antigens, a recent international workshop on lung cancer antigens evaluated the reactivity of numerous (>50) monoclonal antibodies raised against lung cancer-associated antigens [1]. Antibodies, characterized by individual investigators, were tested for reactivity on both normal and malignant tissues of various types (both fresh and paraffin blocks) and on panels of lung and non-lung human cell lines. In these studies both the tissue specificity of each antibody was evaluated, in addition to the intensity and heterogeneity of reactivity within a given tissue. The reaction of these antibodies in most centres where studies were carried out were determined by immunohistochemical techniques.

An analysis of the reactions revealed that approx. 60% of the monoclonal antibodies submitted to this workshop could be classified into six 'SCLC' clusters. Thus, these studies demonstrated that many individually generated monoclonal antibodies react with a similar antigen in tumour cells, and that some antibodies were highly specific for neuro-endocrine tumours, including SCLC, while others demonstrated cross-reactivity with many epithelial cells. The results of this workshop clearly demonstrated the importance of evaluating many different monoclonal antibodies against a similar panel of tumours and non-malignant tissues so that those antibodies with greater specificity could be identified, further characterized and tested in clinical trials.

While lung cancer-derived monoclonal antibodies potentially may be of value in both diagnostic imaging and target-directed cytotoxic therapy, most studies have reported on the use of these antibodies in the typing of lung cancers and in the detection of tumour cells in metastatic sites, in particular bone marrow. The use of monoclonal antibodies in the immunohistology of lung cancer has several important clinical applications: (1) as

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an aid to the classification of the cell type present (e.g. SCLC vs. NSCLC); (2) in determining the specific phenotype of the tumour cells (e.g. endocrine or non-endocrine) and (3) in evaluating the pattern and intensity of reactivity of cells with individual and panels of monoclonal antibodies. The results of these studies may have a major impact on therapy selection, in predicting prognosis and responsiveness to cytotoxic therapies.

Historically, lung cancers have been classified as SCLC and non-SCLC. While such distinctions were important on a biological, therapeutic and prognostic basis, they were also based on the belief that SCLC was of neuro-endocrine origin while NSCLC was of ectodermal origin. Such a notion is no longer tenable based on many studies which have shown that both SCLC and NSCLC are of ectodermal origin, and indeed may be derived from a common stem cell [2].

This hypothesis is based on data demonstrating that both SCLC and NSCLC frequently share common epithelial antigens and cytokeratins, may express or lack neuro-endocrine markers (e.g. L-dopa decarboxylase), and may share a specific cytogenetic abnormality—a deletion on the short arm of chromosome 3 [3–6]. The implications of a common stem cell with the possible expression of surface antigens and other markers by both SCLC and NSCLC will have both benefits and create problems in the immunohistology of lung cancer. Because the exact diagnosis may require more than morphological assessment, there will be an urgent need to establish a panel of antibodies which can clarify or confirm the diagnosis. However, because of the heterogeneity that will exist in all lung tumours, tests with multiple antibodies will be required if a firm diagnosis is to be made [7].

Much work has been published demonstrating the complex heterogeneity in SCLC cells in the expression of biomarkers, growth behaviour and oncogene expression, and the relationship of these to clinical behaviour [2, 8]. It is clear that SCLC represents a spectrum of different diseases with different biological properties and treatment responses [2]. Preliminary data suggests the need to evaluate these biomarkers (L-dopa, CK-BB, NSE etc.) in prospective clinical trials. However, in many instances, particularly in SCLC, insufficient material is obtained for such biochemical analysis. The report by Berendsen *et al.* is an important demonstration of how much the tumour can be characterized with detailed monoclonal antibody studies on specimens obtained at bronchoscopy [9]. This study, like others, clearly demonstrates the importance of fixation procedures on antigen expression. In addition to this study, the same group have shown an important correlation between the presence or absence of neuro-endocrine antigens, and chemotherapy-resistant SCLC [10–12].

While the importance of this observation cannot be overstressed, much greater numbers of patients must be evaluated in clinical trials before such assessments can be put to wide-scale use.

Several studies have reported on the use of monoclonal antibodies in the detection of SCLC tumour cells in bone marrow specimens [13, 14]. In some studies SCLC cells were identified in up to 75% of specimens including many specimens considered pathologically negative for SCLC cells. Moreover SCLC cells were identified in 50% of cases considered to have limited stage disease [13]. While the finding of such cells may have some impact on therapy selection (e.g. autologous bone marrow transplantation), recent reports have shown that the detection of metastatic SCLC cells using monoclonal antibodies has a significant impact on patient prognosis [14]. Further large-scale trials are required to evaluate the value of immune-detection of tumour cells in SCLC patients.

SUMMARY

Over the past decade the use of monoclonal antibodies has greatly advanced our knowledge of the biological properties and heterogeneity that exist within human tumours, and in particular in lung cancer. Early studies suggested that both the lack of specificity of individual antibodies and heterogeneity in antigenic expression would limit their widespread application in clinical practice. However, improvements in antibody selection techniques and a greater understanding of the epitopes detected with these antibodies have slowly led to the development of antibodies with improved specificity. While preliminary studies of the immunohistology of lung cancer suggest that these antibodies may be of value in histologic typing, predicting chemosensitivity and detecting bone marrow metastases, larger clinical trials are required before immunohistology becomes standard clinical practice in lung cancer studies.

With such studies it is likely that the role of lung cancer immunohistology will become better defined. It is also certain through our greater understanding of lung cancer biology and heterogeneity that monoclonal antibodies will in the future play a major role in imaging diagnostic techniques, and in specific targeted therapies where antibodies directed against autocrine growth factors or their receptors, oncogene protein products, or conjugated with pharmacologic agents may replace the highly toxic, non-specific chemotherapeutic approaches of today [15].

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