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Perspectives and Commentaries

Current Status of Research into Small Cell Carcinoma of the Lung: Summary of the Second Workshop of the International Association for the Study of Lung Cancer (IASLC)*

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INTRODUCTION

SMALL cell carcinoma of the lung (SCCL) presents one of the most interesting challenges in oncology today. Although steadily increasing in incidence in many countries, especially in women, SCCL is the cell type amongst the four major histological types of lung cancer for which most progress has been made within the last decade — both with respect to clinical management and to an understanding of the biology of this disease.

These changes were reviewed in detail at the First International Workshop on Small Cell Carcinoma of the Lung arranged by the International Association for the Study of Lung Cancer (IASLC) in September 1981 in Ireland and reported in five subsequent publications which included recommendations for future areas of research [1-5]. A second workshop on SCCL was held in Scotland in September 1984 to re-evaluate the state of the art and to discuss the progress being made in understanding the problems posed by this specific form of lung cancer. This report is not intended to represent an official statement by the IASLC and does not necessarily represent the views of every participant but attempts to summarise the major issues discussed at the workshop. The 56 investigators participating in the meeting came from 19 countries in four continents. The programme included presentations on medical oncology, radiation therapy, pulmonary medicine and surgery, describing the management and complications of therapy, staging and prognostic factors, histopathological classifications and experimental studies of the biology of small cell carcinoma of the lung.

TREATMENT

Of the various treatment modalities, chemotherapy remains the mainstay of treatment while the adjuvant role of other treatment modalities is less well defined. With suitable combined drug regimens, partial or complete responses can be obtained in 70-90% of previously untreated patients, including 25-40% complete responses. Median survival in patients with disease that is clinically confined to one lung, the mediastinum and/or supraclavicular lymph nodes — ipsilateral or on both sides — is 13-15 months in most studies. In extensive disease with well-documented distant metastases the median survival is in the order of 9-11 months. Studies of more than 1000 patients from major centres in Europe and the U.S.A. show that survival for periods in excess of 5 yr after discontinuation of treatment is obtainable in 5-10% of all patients, including some who present with far advanced disease.

The most widely used drug combinations include three of the following four drugs; vincristine, doxorubicin, cyclophosphamide or VP 16-213. Among the various issues concerning chemotherapy for SCCL both the use of

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maintenance therapy and the concept of using alternating drug regimens with non-cross-resistant combinations were brought into focus. Several prospective randomised trials were presented on both issues, with somewhat conflicting results. In general there is a tendency to shorten the duration of treatment, limiting it to a period of 6–12 months and restricting it to patients who obtain a complete remission within the first 3 months of treatment. Over the past few years the concept of alternating regimens has gained considerable interest in the treatment of small cell carcinoma, the prime purpose being to provide different metabolic insults to a tumour characterised by heterogeneity, and to suppress the emergence of drug resistance. Compared with the other cell types of lung cancer and many solid tumours, SCCL has the advantage of being sensitive to a large number of cytotoxic agents with different mechanisms of action, thereby making it an ideal tumour for testing the hypothesis that Goldie and Coldman developed in pre-clinical models [6]. Some benefit from the use of alternating chemotherapy with non-cross-resistant regimens has been observed in at least two prospective randomised studies, while three other studies have been entirely negative. On the whole the results of alternating treatment have been somewhat disappointing, but to some extent this failure when compared with the continued use of the same regimen might be due to suboptimal design of alternating treatment programmes. Therefore, although the present trials with alternating drug combinations cannot be recommended as standard therapy, the concept is still likely to attract further attention in future comparative trials.

The concept of using highly intensive cytotoxic treatment usually combined with autologous bone marrow transplantation either as initial treatment or as late intensification was discussed. None of the data presented gave reason for therapeutic optimism using this particular approach.

Among the very many new cytotoxic agents tested in SCCL, only VM-26 and a new analogue of *cis*-platinum-JM8 (CBDCA) appeared to have significant activity.

The role of radiotherapy both with regard to prophylactic cranial irradiation and to the chest as an adjuvant to systemic treatment remains controversial. It is evident that prophylactic CNS irradiation (PCI) decreases the rate of clinical CNS relapse and it should be used mainly for patients achieving complete response. It is still questionable whether PCI prolongs median survival and concern was also raised about the later effects on neuropsychological function from PCI in long-term survivors. The optimal timing and dose of PCI remain a controversial area. Most centres are at present using 25–35 cGy in 8–14 fractions over 2–2.5 weeks. As for radiotherapy to the primary tumour, this definitely reduces the rate of local recurrence but is also associated with increased acute and chronic treatment morbidity. No major influence on median survival has yet been demonstrated and further maturation of data from current studies is necessary before more definite conclusions concerning long-term survival can be drawn. Again a number of questions were raised such as "What is the correct volume for locoregional radiotherapy?" "What is the radiation dose required?" "What is the optimal sequence and timing of radiation therapy in relationship to chemotherapy?" and also "How best to apply the use of CT scanning in radiotherapy planning?"

With respect to other modes of radiotherapy, such as hemi- and total-body irradiation, the use of radiosensitisers, hypothermia and neutrons, these still remain at an experimental level. Concerning surgery, radical surgical resection should still be attempted for the small fraction of patients (<5%) who are very thoroughly staged as having T_1 or T_2 NO, MO disease provided that the resection is followed by combination chemotherapy. Current studies are at present evaluating the role of surgery in patients obtaining complete remission after a few courses of combination chemotherapy.

Finally, the various complications occurring in connection with intensive treatment were reviewed. Concern was raised not only about the immediate complications in connection with the use of chemotherapy and radiotherapy but also about the late effects, where recent data suggest a rather high incidence of secondary leukaemia in patients achieving long-term survival, presumably secondary to the use of multiple alkylating agents.

PROGNOSTIC FACTORS AND STAGING

In the session on prognostic factors and staging, it was evident that the application of CT scanning had been expanded and was especially useful in delineating pulmonary and mediastinal structures, allowing for more accurate assessment of these anatomical regions. It is expected that this will have a major influence on the use of radiotherapy to this area, eliminating some of the toxic effects secondary to irradiating normal tissues, especially the oesophagus. For the detection of distant metastases the exact role of CT scanning remains unclear, and prospective studies are at present comparing CT scanning

with existing staging procedures. Employing other staging procedures, one prospective study indicated that ultrasonography of the liver with biopsy was superior to peritoneoscopy with liver biopsy, resulting in a higher diagnostic yield and fewer complications. It was stressed that it was important to obtain either cytological or histological proof of malignancy when evaluating these non-invasive procedures.

It was also emphasised that the intensity of staging procedures used at diagnosis would have an effect on the assessment of the results obtained in the various trials. More intensive staging will result in patients previously categorised as having limited disease (thereby a better prognosis) being reclassified to the group of patients with more extensive disease. This change, exclusively based on the intensity of staging procedures, will thereby result in improving relative results for both stage categories, but the overall results will of course remain constant.

The potential usefulness of various biomarkers such as ADH, ACTH and calcitonin was also reviewed. So far none of these markers alone or combined has been shown to be better or more sensitive than a careful clinical evaluation in following the clinical course of patients with SCCL. Exceptions to this might be the use of neuron-specific enolase and bombesin in the detection of CNS disease, particularly meningeal carcinomatosis.

HISTOPATHOLOGY

The morphological subclassifications of the WHO subdivision of small cell carcinoma into the oat cell subtype and the intermediate type were subjected to intensive discussion particularly as regards ultrastructure, immunohistochemical and biological characteristics. The relationship of the various subtypes to the clinical course was analysed. It was the consensus that the subtyping as defined by the WHO did not have any significant clinical application as no correlation was demonstrated between the subtypes and the clinical course reflected by survival, response rate, sensitivity to chemotherapy, radiotherapy, etc. It was therefore suggested that SCCL (WHOII) in the future should be classified as having three variants consisting of 'pure small cell', one which includes patients having both small and large cells in the specimen; this latter group has a worse prognosis when compared with pure small cell type and corresponds in the cell cultures to the type described as 'variant cell type'. Finally, the third variant is defined as combining small cell with elements from squamous and/or adenocarcinomas. A detailed concensus report is in preparation describing the present status of the histopathological features of SCCL.

EXPERIMENTAL STUDIES OF THE BIOLOGY OF SMALL CELL CARCINOMA OF THE LUNG

With respect to the biology of the disease, considerable advances have been made in the understanding of the biologic properties of SCCL. Firstly, investigators from many different laboratories are now able to culture successfully cell lines of SCCL using various media, either directly or following incoculation of fresh specimens into nude mice with subsequent culture of these heterotransplants. The cell lines have most frequently been obtained from metastatic sites, either in newly diagnosed patients or from patients who have relapsed after therapy, but a small proportion of cell lines have also been established from the primary tumour either at surgery or at bronchoscopy. Cell lines can now be established from approximately 75% of all tumour-containing specimens received in the laboratory. These cells are usually able to retain the histologic and biochemical properties from the patient's tumour despite multiple replications in cell cultures or serial transplantations in athymic nude mice. The cell lines of small cell carcinomas can be separated into either the classic cell line or variant lines. The former is characterised by tight spherical aggregates, a doubling time of more than 50 hr and low colony-forming efficiency, of 1-5%, while the latter grows with much looser aggregates of floating cells, has a faster doubling time (<30 hr) and higher colony-forming efficiency, and usually has more distinct nucleoli. The classic line corresponds clinically to the pure small cell carcinoma of the lung and expresses also the usual APUD properties of SCCL such as containing high levels of BB-isoenzymes of creatinine kinase, l-dopadecarboxylase, bombesin and neuron-specific enolase, with the presence of many dense granules. In contrast, the variant lines do not usually have granules and have a low content of l-dopadecarboxylase and bombesin. However, data using different techniques including immunohistochemistry reactions were also presented, challenging this rather sharp distinction. Some of these polypeptides have also been demonstrated in other major histologic types of lung cancer such as large cell and squamous cell carcinomas.

Noteworthy was the observation that, using serum-free cloning assays, the peptide hormones such as bombesin, gastrin-releasing peptide and arginine vasopressin stimulate clonal growth. It is conceivable that a number of these peptides act as autocrine growth factors.

The ability to establish SCCL in culture has provoked several investigations on drug radiotherapy and sensitivity testing of human small cell cancer. At present, none of the various systems exploited has produced convincing results useful in the selection of the most appropriate drugs or in the use of radiotherapy.

With respect to other biologic properties of SCCL, the heterogeneity of the tumour (based on the determination of DNA-content using flow cytometric DNA-analysis) was again stressed, with at least 20% of the specimens analysed showing more than a single aneuploid clonal cell. The previously reported specific chromosome alterations, characteristic for small cell carcinoma with deletion of the short arm of chromosome 3P, were questioned both by American and European investigators. However, all agreed that major chromosome abnormalities were observed in specimens from SCCL.

The topic of monoclonal antibodies was reviewed extensively with a study showing that monoclonal antibodies can now be produced that react with various types of human lung cancer, including a variety of small cell carcinoma cells, further emphasising the heterogeneity of these tumours. It was evident that none of the monoclonal antibodies was specific, e.g. many of them shared the properties with antibodies for monocytes. Further refinements of the techniques used are necessary before they can be applied to clinical use. However, clinical data were presented suggesting the usefulness of monoclonal antibodies in the detection of SCCL in cytologic specimens such as pleural fluid and bone marrow.

Overall, despite the high initial response to various forms of non-surgical therapy, the cure rate for patients with SCCL remains distressingly low. The impression from this workshop was that after a period of rapid progress in the 1970s, therapeutic results appear to have reached a plateau over the last 3-4 yr. In addition to taking every opportunity to emphasise the preventative measures which might avoid this dreadful disease, it is to be hoped that the existing advances now being obtained in the knowledge of the biology of SCCL will result over the next few years in similarly encouraging therapeutic gains.

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