The ESO has made (and will continue to make) every possible effort to keep its scientific independence of any non-medical influence while being well aware of the considerable importance of technology in cancer medicine. Moreover, the importance of industrial research is acknowledged and ESO collaborates very positively with it, e.g. by inviting researchers from companies to teach in courses and seminars.

As a final comment, even if 1992 is to be the year of Europe, this does not mean that one should stop looking to America; their system of promoting the education of doctors by both periodical controls and fiscal incentives (i.e. Continuing Medical Education) has proved to be an effective and certainly a positive move when compared to the lack of any kind of initiative in this field on the part of most European countries. Will we one day see a European Medical Association willing to review the infinite number of congresses, workshops and meetings and to make a distinction between truly scientific and educational events and those which resemble tourism and business events? Nothing against such happenings, provided they do not abuse the name of scientific eduction.

The ESO is much indebted to the hundreds of oncologists, general practitioners, nurses, secretaries and health professionals in general who have so enthusiastically offered their knowledge to update and train their colleagues in this decade. It has been a great pleasure and honour to have had them with us, and we hope to be able to continue to provide the medical community with our services for many years to come.

Alberto Costa
ESO, Director

Controversies in the Management of Lung Cancer 23–25 September 1991, Venice, Italy European School of Oncology Meeting Report

TO REVIEW the current controversies in the management of lung cancer, an international panel of experts in cell biology, radiotherapy, surgery, medical oncology and pulmonary medicine gave presentations at a meeting of the European School of Oncology entitled "Controversies in the Management of Lung Cancer" and held 23–25 September 1991, Venice, Italy.

Dr Desmond Carney (Mater Misercordae Hospital, Dublin, Ireland) presented an overview of lung cancer biology. There has been an explosion in our understanding of the cell biology of lung cancer made possible in part by the availability of human lung cancer cell lines representing each histological type of lung cancer including squamous carcinoma, adenocarcinoma and its bronchoalveolar subtype, large cell carcinoma, and small cell carcinoma (SCLC). Small cell carcinoma cell lines grow in serum-free chemically defined media with hydrocortisone, insulin, transferrin, oestradiol and selenium. The cells grow as floating aggregates which are tightly adherent ('classic' cell lines) or loosely adherent ('variant' cell lines). The SCLC cell lines have a number of neuroendocrine properties including: (1) production of dopa-decarboxylase, creatine-kinase BB isoenzyme, chromogranin A, polypeptide hormones (including bombesin/gastrin releasing peptide, arginine vasopressin, calcitonin, somatostatin and others); (2) the presence of neurosecutory granules; and (3) cell surface antigens including neural cell adhesion molecule (NCAM, cluster 1), neuron-specific enolase (NSE), Leu-7, and others. Recently, it has been appreciated that 20–30% of tumours classified as non-small cell carcinomas (NSCLC) by pathologists have neuroendocrine features. These endocrine NSCLC tumors have a slightly higher response rate to chemotherapy than non-endocrine NSCLC tumours. All lung cancers have epithelial properties and differentiation toward various cell types may change *in vitro* or *in vivo*, suggesting a common stem cell origin.

The majority of non-small cell lung cancer (NSCLC) cells express EGF receptors and respond to EGF, NGF and TGF-alpha with proliferation. Interference with this pathway could lead to new methods of treatment and prevention. Trials of anti-EGF receptor antibodies were reviewed. Neuropeptides such as GRP, AVP, etc., are growth factors for SCLC and to a lesser extent for NSCLC. They induce signal transduction by activation of phospholipase C, protein kinase C, liberation of inositol trisphosphate (IP3), intracellular calcium and ultimately transcription of genes including those involved in proliferation. Interference with multiple peptide receptors or the signal pathway open up new therapeutic possibilities.

A small proportion of lung cancers express amplified or mutated oncogenes. In SCLC, 10–25% of cases have amplification of one of the *myc* family of oncogenes (*c-myc*, *L-myc*, *N-myc*) which may be associated with an aggressive course. In adenocarcinoma, about 25% of cases have a mutated K-ras oncogene which is also associated with a poor prognosis. There is an association of overexpression of *erb*-B and the EGF receptor, especially in NSCLC. Transfection of *ras* genes into SCLC tumours causes loss of neuroendocrine features.

Suppressor oncogenes play a more important role in lung cancer. Virtually all SCLC tumours have a loss of one or more oncogenes in the region 3p14-23. Virtually all also have mutations in the p53 oncogene on 17p and most have abnormalities of retinoblastoma protein. In NSCLC, nearly all tumours also have p53 mutations, the majority have 3p loss and many have retinoblastoma protein abnormalities.

Dr Robert Ginsberg (Department of Thoracic Surgery, Memorial Sloan-Kettering Cancer Center, New York, USA) discussed the role of surgery in small cell lung cancer. Dr Ginsberg concluded that surgery is indicated in peripheral clinical stage I small cell lung cancer and if this histology is confirmed at operation, post-operative chemotherapy is recommended. Every attempt should be made during the surgical procedure to effect a complete resection. However, when more locally advanced stage II and III small cell lung cancer is identified preoperatively, there is no evidence, as yet, to recommend the addition of surgery to conventional chemo/radiation therapy. The role of neoadjuvant chemotherapy and radiation followed by surgery should be considered to be experimental. A randomised trial has been conducted by the Lung Cancer Study Group and preliminary results show no benefit for adding surgery after chemotherapy and radiation therapy.

Dr Paul Bunn (Division of Medical Oncology, University of Colorado Cancer Center, Denver, Colorado, USA) summarised results of chemotherapy as a surgical adjuvant approach for operable stages and as a preoperative neoadjuvant therapy in inoperable Stages IIIA and IIIB NSCLC. There is evidence that post-operative chemotherapy improves survival in Stage II and IIIA NSCLC but not in Stage I. Additional trials with platinum based chemotherapy are necessary and are ongoing in the USA.

For patients with regional but inoperable stages (some IIIa and IIIb NSCLC), experimental approaches have included the combined use of chemotherapy and radiotherapy and the neoadjuvant use of these agents before surgery. In the USA,

radiotherapy alone has been the most commonly used treatment even though randomised trials have not shown survival benefit. The median survival in most radiotherapy trials is about 10 months with 5% of patients surviving 5 years. In the past years there have been several randomised trials showing improvement in both median survival and late survival with combined therapy employing cisplatin based chemotherapy. Several randomised trials with cisplatin based chemotherapy with or without radiotherapy also showed a survival advantage compared with best supportive care. There were several randomised trials employing non-cisplatin based chemotherapy showing no survival advantage for chemotherapy in this setting. Thus, many physicians consider cisplatin based chemotherapy to be an integral part of the therapy of NSCLC patients with inoperable stage IIIa and IIIb.

About two-thirds of patients with stage IIIa and IIIb NSCLC have an objective response to cisplatin based chemotherapy with or without radiotherapy. Recent phase II trials have evaluated the role of surgery in these selected responding patients. These phase II studies establish that this can be done with acceptable surgical mortality (average about 6%) and with favourable early results. In most, but not all series, about 50% of all patients have a complete surgical resection, about 10–20% have no tumour in the operative specimen (pathological complete remission) and the median survival exceeds 12 months. It is too early to determine precise 5-year survival rates, but these may be in the range of 15%. Randomised phase III trials are needed to precisely define the role of surgery.

In stage IV NSCLC, the role of chemotherapy has been controversial. Combination chemotherapy produces responses in about one-third of patients. This clearly benefits symptomatic patients. Chemotherapy rarely benefits patients with poor performance status. Recent studies have established that both cisplatin and carboplatin are active in NSCLC. Several randomised trials showed that platinum based chemotherapy improved survival compared with best supportive care. The improvement was modest with an average increase of 8–12 weeks at the median. A Canadian study showed that this improvement was cost effective because patients receiving chemotherapy required less radiotherapy and days in hospital than the patients receiving "best supportive care". Other active agents include ifosfamide, high dose epirubin, lipid soluble antifols, vinca alkaloids, topoisoamerase I inhibitors (camptothecins) and possibly taxol. These agents need further testing alone and in combination with other agents.

Dr Peter Postmus (Department of Pulmonary Diseases, University Hospital, Groningen, The Netherlands) discussed the staging and chemotherapy of small cell lung cancer. After establishing diagnosis, extensive staging is only indicated if these patients are treated in a clinical trial or if there are additional therapeutic possibilities, such as radiotherapy of the primary or surgery as part of the treatment. Staging procedures normally used are physical examination, blood cell counts, renal and liver function tests, computed tomography (CT) of thorax and upper abdomen or magnetic resonance imaging, CT of brain, bone marrow biopsy and isotope bone scan. Complete restaging is only indicated in clinical trials and if prophylactic cranial irradiation is given to complete responders.

Chemotherapy is the cornerstone of therapy for small cell lung cancer. Most regimens consist of cyclophosphamide, doxorubicin, vincristine, etoposide and cisplatin in combinations of 2 or 3 drugs. Short-term treatment—3 to 4 months—is considered sufficient, since maintenance therapy had no impact on survival. The value of the frequently used alternating regimen is not proven. Overall, therapy will result in limited disease patients in a median survival of $\geq$ 14 months with 10–15% disease free after 2.5 years. Median survival of $\geq$ 8 months is reached in extensive stage patients with very few long-term survivors. Groups of patients for whom no standard therapy is available are patients over 70 years of age and patients with a poor performance status (ECOG-4). Elderly patients will benefit from a simple oral regimen with etoposide with minimal toxicity, whereas patients with ECOG-4 may not benefit at all from any treatment. For patients with brain metastases, chemotherapy was found to be an effective palliative treatment, probably as effective as whole brain radiotherapy. Patients with tumour relapse or progression shortly after the induction therapy ($\leq$ 3 months) are almost all resistant for the initially used drugs and need treatment with other drugs, whereas the patients progressing at a later stage have a good chance to respond again to the initially used drugs. Improvement of therapy is still needed to improve the outcome of these patients. Adding haematopoietic growth factors might reduce toxicity and allow higher doses of chemotherapy or more intensive treatment. The routine use of such growth factors should be considered as investigational since doses of etoposide and cisplatin, which are as effective as any other agents, rarely produced severe myelosuppression. The search for effective new drugs should be continued.

Dr Andrew Turrisi (Department of Radiation Oncology, University of Michigan, Ann Arbor, Michigan, USA) discussed the role of radiation therapy (RT) in lung cancer. In non-small cell lung cancer, standard radiotherapy alone, at doses of 60 Gy, produced poor results: 1-year survivals of approximately 40–50%; 2-year survivals of approximately 10–20%; and 5-year survivals of approximately 5%. The addition of regional lymphatics to the radiation port does not influence survival appreciably. Studies of altered fractionation, both hyperfractionation and accelerated fractionation, have shown promising results in pilot studies. In addition, numerous pilot studies adding chemotherapy to chest radiotherapy suggest the combination may provide superior survival results, particularly with combinations employing cisplatin based chemotherapy. For example, the Cancer and Acute Leukemia Group B (CALGB) studies showed that two cycles of vinblastine and cisplatin prior to radiation therapy was superior to radiation therapy alone. Most, but not all, combination trials employing cisplatin based chemotherapy show improved survival outcome for the combination. Another method of delivering concurrent platinum and radiation is to employ daily cisplatin as a 'radiosensitiser'. Studies of the SWOG and the EORTC in Europe show benefit for this approach and confirmatory trials are underway. There are plans for future trials to evaluate the role of reduced volume radiation, and dose escalation trials starting at 60 Gy.

Radiation therapy has a definite role in small cell lung cancer. In limited stage small cell lung cancer, a meta-analysis of the world's literature of randomised trials shows a small survival benefit for the addition of chest radiotherapy to chemotherapy. This is especially important because chemotherapy alone results in a high local failure rate. Even the best combined modality treatments using cisplatin and etoposide chemotherapy with chest radiotherapy still show significant local failure rates. Twice daily radiation fractions may exponentially kill tumour cells which express a shoulder in radiotherapy killing curves. This is especially important in variant small cell lung cancer which shows a significant shoulder in *in vitro* studies. In a study from

the University of Pennsylvania and the Eastern Cooperative Oncology group, the strategy of twice daily radiotherapy with cisplatin and etoposide produced excellent results with a response rate of greater than 90%. However, patients with mixed histology had a low response rate and a high local failure rate. A randomised trial comparing once daily with twice daily radiotherapy is being conducted in the United States by the Eastern Cooperative Oncology Group and other groups.

The role of prophylactic cranial irradiation (PCI) in small cell lung cancer remains controversial. Most feel that if used, it should be reserved for patients experiencing a complete remission on systemic chemotherapy and the PCI should be given at the completion of all chemotherapy. The major advantage of PCI is that it was shown to reduce subsequent brain metastases. The disadvantages are that there may be central nervous system toxicity and a survival advantage has not been proven. At the present time, randomised trials are being conducted in both the United States and Europe.

For both small cell lung cancer and non-small cell lung cancer, improved radiotherapy techniques with reduced volumes appeared to improve results and reduce toxicity. Increasing the number of fractionations and combining chemotherapy with radiation appears to improve the local control rate in both small cell and non-small cell lung cancers. Additional studies of different methods of combining chemotherapy and radiation therapy are in progress.

Dr James F. Bishop (Department of Hematology and Medical Oncology, Peter MacCallum Cancer Institute, Melbourne, Australia) discussed future directions in the therapy of lung cancer. Substantial improvements in the treatment of small cell lung cancer (SCLC) have only resulted in cure rates which are similar to those for non-small cell lung cancer (about 15%). New treatment directions are: (1) new anti-cancer drugs; (2) dose escalation; (3) the use of haemapoietic growth factors; (4) new methods of combining drugs and radiation; (5) new radiotherapy schedules, and (6) the future role of chemoprevention with new agents against new targets identified by molecular genetics.

Etoposide is a very active drug in SCLC which is clearly schedule dependent. New schedules using continuous oral etoposide have shown excellent activity. Carboplatin is active in SCLC and the combination carboplatin and etoposide is clearly active, well tolerated by older patients and has less non-haematological toxicity than cisplatin and etoposide. The major toxicity of the combination is myelosuppression, which may be modified by cytokines. Other newer agents with activity in lung cancer include ifosfamide and epirubicin. There has recently been some methodology developed to allow early evaluation of new drugs in untreated SCLC. Haemopoietic growth factors now under study in lung cancer include granulocyte–macrophage colony stimulating factor (GM-CSF), granulocyte colony stimulating factor (G-CSF), and interleukin-3 (IL-3). GM-CSF given with carboplatin + etoposide is best given at 5 to 10 μg/kg on days 4 to 11 after chemotherapy which includes etoposide on days 1–3. However, even at this optimal schedule of GM-CSF, this cytokine cannot protect the patient against neutropenia and thrombocytopenia which occurs with double dose chemotherapy.

Another use of GM-CSF or G-CSF is to reduce febrile neutropenic episodes. Growth factors may also be able to allow rapid recovery neutrophils in patients presenting with febrile neutropenic episodes. Future roles of haemopoietic growth factors will be to allow rapid recovery following autologous stem cell transplantation either with peripheral stem cell or bone marrow harvest.

These approaches may allow more extensive evaluation of high dose chemotherapy, with some of the new agents, in lung cancer. In limited SCLC, new programs using concurrent radiation, particulary with cisplatin and etoposide, have produced encouraging results. The optimal drugs, doses and schedules for drug–radiation interaction in SCLC and NSCLC require further study. Novel radiotherapy schedules using multiple daily radiation fractions, and accelerated hyperfractionation hold promise for future improvement in outcome. An area of importance for the future is that of chemoprevention. The identification of a genetic cascade in the evolution of colon cancer has suggested a similar phenomenon may occur in other cancers such as lung cancer. If new targets can be identified in the evolution of lung cancer, new compounds may be able to prevent the evolution of premalignant conditions to invasive lung cancer.

Acknowledgement—This Task Force was sponsored by a generous grant from Bristol-Myers.

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EORTC Invasive Fungal Infections Cooperative Group

A new EORTC Cooperative Group devoted to invasive fungal infections in cancer patients has been recently created. The name of the group is "EORTC Invasive Fungal Infections Cooperative Group". The officers of this group are, Chairman: F. Meunier, Secretary: P. Martino, Treasurer: I. Varthalitis.

The aims of the group will be to conduct, develop, coordinate and stimulate clinical studies for the diagnosis, prevention and treatment of invasive fungal infections in cancer patients. Epidemiological studies including the incidence of various fungal pathogens, the creation of a register of fungemia occurring in cancer patients as well as cost benefit studies will also be encouraged.

Several projects are presently being activated including a therapeutic trial of oropharyngeal candidiasis, and autopsy survey and a study of fungal infections occurring in patients undergoing bone marrow transplantation.

If you are interested in becoming a member of the EORTC Invasive Fungal Infections Cooperative Group, please contact F. Meunier, Avenue E. Mounier 83/Bte 11, 1200 Brussels, Belgium, Tel: 32 (2) 774 16 30, Fax: 32 (2) 771 20 04.