

## Views and news from Melbourne, the Sixth World Conference on Lung Cancer

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The Sixth World Conference on Lung Cancer was held in Melbourne, Australia, 10-14 November 1991, in the well-equipped World Conference Center, by the river Yarra. About 1,000 participants came from all over the world, and almost 700 abstracts were presented. The scientific and the social programme were both extremely stimulating and perfectly organized, thanks to D. Ball and the organizing committee, from the McCallum Cancer Center in Melbourne.

### Epidemiology

Among several epidemiology reports from different geographical localities, a few large series were presented. The prevalence of adenocarcinomas, as observed in the US has been confirmed in a large autopsy data base of almost 60,000 autopsies performed in Japan, this histological type being diagnosed in 35% of males and 55% of females of all lung cancer autopsies. The reason why squamous cell carcinoma is the most common histological type in European countries remains obscure. However, it is expected that in Europe a similar trend to that in the US and Japan will soon be visible, perhaps indicating a change in aetiological factors of lung cancer.

An epidemic of small cell lung cancer (SCLC) in women, in the coming 10 yrs, has been foreseen in the UK; this alarming report is based on analysis of the Mersey region data base (about 9,000 lung cancers), where SCLC represents 29% and 18% of lung cancers in women and men, respectively, but SCLC accounts for 35% of lung cancer cases in women <50 yrs of age.

### Chemoprevention

There is increasing interest in the field of chemoprevention. Initial findings of the large ATBC ( $\alpha$ -tocopherol and  $\beta$ -carotene) study have been presented. This chemoprevention study involves 29,000 male

smokers, 50-69 yrs of age, who were enrolled in a double-blind, placebo-controlled trial of  $\alpha$ -tocopherol 50 mg, plus  $\beta$ -carotene, 20 mg. The trial has now been under way for 6 yrs, and the intervention was shown to be very well tolerated, with 93% of enrolled subjects taking more than 90% of the allotted number of pills. The results of this study and the Euroscan study, which is testing N-acetylcysteine and vitamin A for prevention of a secondary tumour in patients radically treated for a lung or a head and neck cancer, are awaited in the coming years. Obviously, this type of study requires much longer observation times than any other clinical investigation in malignancy.

The mature results of a chemopreventive study of radically resected Stage I non-small cell lung cancer (NSCLC) have been presented by Pastorino *et al.* (Istituto Nazionale Tumori, Milan). The study involved 307 patients randomized to receive retinol palmitate 300,000 IU·day<sup>-1</sup> for 12 months or placebo. The compliance was good and there was a significant reduction of recurrence (33 vs 44%) and appearance of secondary tumours (14 vs 25 patients) in the chemopreventive arm, in comparison to the control arm. The 5 yr survival was, however, not yet significantly different in the two arms of the study (66 vs 57%). Coming as an additional link between current chemo-preventive attempts and basic research, an interesting report by Houle and Bradley (Montreal Cancer Institute, Canada), suggested a possible role for retinoic acid receptor- $\beta$  (RAR- $\beta$ ) as tumour suppressor gene in squamous cell lung carcinoma cells. This gene is located on 3p, which is very often lost in SCLC and NSCLC. Transfection of a normal RAR- $\beta$  gene is able to slow the growth and decrease the tumourigenicity of tumour cells which do not express this gene.

### Tumour markers

With increased application of molecular biology techniques, the use of molecular markers for early detection of tumours, including lung cancer, might shortly become feasible. The findings by Sundaresan and co-workers (Cambridge, UK), of 3p allelic losses and p53 mutations discovered in dysplastic bronchial epithelium samples, as well as in the paired

corresponding tumours, were exciting. New techniques are becoming readily available, e.g. the screening of point mutations can now be performed more quickly and reliably by the single strand conformation polymorphism technique. With this method p53 mutations have now been extensively screened by Japanese investigators. The presence of k-ras point mutations in adenocarcinomas have been confirmed in Hong Kong; as different base modifications were observed, this study also indicates that different carcinogens are possibly involved in the aetiology of lung cancer in Europe and the US, as compared to Oriental countries.

### Drug resistance

Several papers were presented on drug resistance. Whilst some reports confirmed the negligible role of MDR1 in the development of multidrug resistance in lung cancer, the important role of topoisomerase II has been reported by independent groups. Interestingly, topoisomerase II seems to be a marker of sensitivity not only to topoisomerase II inhibitors, but also to other unrelated drugs. In fact, lung cancer cell lines appear to fall either into a broadly sensitive or broadly resistant category: SCLC and NSCLC with neuroendocrine properties (15% of NSCLC cell lines) are in the sensitive group, whilst the majority of NSCLC and carcinoids belong to the resistant group. Therefore, topoisomerase II might find a clinical application as a marker of drug sensitivity in the future. However, several problems have still to be solved, pertaining to the relatively labour-intensive molecular biological techniques, which appear to lack sensitivity in lung tumour samples. As soon as reliable antibodies against topoisomerase II become available, immunohistochemistry would of course be an interesting development. Conflicting reports were given on the importance of glutathione-S-transferase- $\pi$  (GST- $\pi$ ) as a marker of resistance in NSCLC cell lines.

Neuroendocrine properties in NSCLC are present in about 30% of tumours and were positively correlated to nodal status in a study by Sundaresan and co-workers (UK). Neuroendocrine characteristics might be considered as a marker of a higher malignant behaviour in NSCLC, but also as a marker of sensitivity to chemotherapeutic drugs, as reported in cell lines and in retrospective and prospective clinical studies.

### Grading

The value of grading in the prognosis of NSCLC is still unclear. In a study of 368 resected NSCLC cases in Japan, investigating the prognostic value of grade of differentiation, a better degree of differentiation was correlated with fewer central localizations, smaller T, less nodal involvement, and more conservative operations in adenocarcinomas. This was not the case for squamous cell histologies.

### Imaging studies

A number of new imaging techniques are being devised; among noninvasive radiological techniques, positron emission tomography appears to be extremely accurate and might prove superior to computerized tomography (CT) and nuclear magnetic resonance (NMR), providing a 98% agreement with surgical staging of NSCLC undergoing resection. Several other imaging techniques are being developed, some employing radiolabeled monoclonal antibodies, also under investigation for therapeutic purposes. Scintigraphy with  $^{123}\text{I}$ -Tyr<sup>3</sup>-octreotide (a somatostatin analogue) visualized most SCLC investigated, as reported by Kho and co-workers (Rotterdam).

### Surgery

Although small studies and retrospective analyses often reported a possible impact of surgery on survival of SCLC, the results of the large intergroup study by Lung Cancer Study Group/European Organization for Research and Treatment of Cancer/Eastern Cooperative Oncology Group (LCSG/EORTC/ECOG) has substantially denied this effect. Three hundred and twenty eight patients responding after five cycles of CAV chemotherapy cyclophosphamide, adriamycin, vincristine were randomized between surgery or no surgery. Both arms received thoracic radiation. Forty four per cent of all patients were randomized (166 patients in total), with an 83% resection rate, 19% pathological complete remission, and 9% residual NSCLC. Survival curves of the two randomized arms were superimposable, with a 2 yr survival of 20%.

A large randomized study performed in Japan investigated the role of mediastinal lymphnode dissection in 230 NSCLC patients, who had negative preoperative mediastinoscopy. This study did not show any benefit in survival.

The cause of death of 309 T<sub>1</sub>N<sub>0</sub> resected NSCLC patients enrolled in a large LCSG study has been investigated. Forty three died of unrelated disease and 54 of tumour. Only in 20 patients, however, was the recurrent tumour a relapse of the primary lung cancer, whilst it was a new lung cancer in 18 and a non-lung cancer in 13. This study indicates the importance of secondary tumours in causing the death of patients who survive their initial lung cancer, and points to lung cancer as a major secondary malignancy in this patient population.

Another surgical study by the LCSG, reported by Ginsberg, investigated segmentectomy *versus* lobectomy in T<sub>1</sub>N<sub>0</sub> NSCLC in 247 randomized eligible patients. There was a significantly higher recurrence rate in the limited resection arm, although no difference in survival was apparent, with a follow-up of 2-8 yrs. It was, therefore, concluded that lobectomy should be the standard operation in these patients and more limited resection should only be performed in compromised patients.



### Radiation therapy

A randomized study by the Neutron Therapy Co-operative Working Group showed that fast neutron radiation might be of benefit in some favourable subgroups of patients with NSCLC, giving a longer survival than standard radiation techniques.

The timing of chest irradiation in SCLC with limited disease has been investigated in a randomized trial of the National Cancer Institute (NCI) Canada, in which 308 patients were randomized to receive radiotherapy either during the first or during the last cycle of chemotherapy. There was a clear advantage in survival of patients who received early radiation in comparison to late radiation (20 vs 15 months median survival time, respectively). The results of this study indirectly support the results of a large French trial in 434 limited disease SCLC patients who were randomized to late radiotherapy (after eight chemotherapy cycles) or no irradiation; this study did not demonstrate any advantage in giving radiation at a late stage. An ongoing study of the EORTC is comparing alternating radiochemotherapy with late radiotherapy.

### Chemotherapy

Recent developments in chemotherapy of lung cancer were worthy of notice, mainly due to the introduction of new effective drugs. Because the long-term results in SCLC treatment have not improved over at least the last 10 yrs, the length of chemotherapy remains an important question in this disease. The final analysis of an EORTC study on almost 700 patients, comparing 5 versus 12 cycles of combination chemotherapy, has definitely demonstrated the absence of survival benefit in giving more than 5 cycles; however, a difference in progression free survival has been observed in favour of the maintenance arm. This has been interpreted as mainly due to the persistent chemosensitive disease in patients who are treated with shorter chemotherapy. Preliminary results of another study by the Medical Research Council (MRC) showed no difference in survival between 3 and 6 cycles of chemotherapy.

In a study by South West Oncology Group, 358 NSCLC patients were randomized to low-dose cisplatin versus high-dose cisplatin with and without mitomycin C. This study could not demonstrate differences in response rate between the two doses of cisplatin (50 or 100 mg·m<sup>-2</sup> day 1 and 8), whilst there was a higher response rate in the combined arm which, however, did not influence the survival.

Interesting results have been obtained in 72 NSCLC randomized to receive either cisplatin-vindesine with or without verapamil, as reported by Milward and co-workers (Newcastle, UK). A higher response rate (21 vs 42%) and a longer survival (22 vs 40 weeks median) have been observed in the verapamil arm, in comparison to the chemotherapy alone arm. These results are difficult to interpret, because MDR1 expres-

sion is usually very low or undetectable in most lung tumours, unless verapamil works through a different mechanism than simple interference with p-glycoprotein. Another randomized study by a Scottish co-operative group failed to show any improvement from addition of verapamil to chemotherapy in 226 SCLC patients.

Testing new drugs in SCLC remains an issue of debate. It appears from pooled data from phase II trials published between 1970–1990, as reported by the Memorial group, that none of the active drugs would have been missed if tested only in previously treated patients, if the acceptable level of response rate had been decreased from 20 to 10%. This proposal might adequately solve the ethical issue concerning treatment-previously untreated patients who have a sensitive tumour, such as SCLC, with a single investigational agent. It might, however, appear more efficient to select previously treated patients who responded to prior chemotherapy and have been off-treatment for a few months. This is indeed the on-going strategy within the EORTC for testing new drugs in SCLC.

A number of new agents have shown promising activity in the last 2–3 yrs in SCLC and in NSCLC. Among these, 10-Ethyl-10-Deazaaminopterin (10-EDAM) achieved a 30% response rate in advanced untreated NSCLC, according to the Memorial Sloan Kettering experience. A somewhat lower response rate of around 13% has been obtained in a British study. The results of other active new drugs in NSCLC were reported: navelbine (29% response rate), fotemustine (16%), gemcitabine (26%), CPT-11 (34%), zeniplatin (21%). CPT-11, a derivative of camptothecin, a specific topoisomerase I inhibitor, also demonstrated activity in SCLC in a Japanese study, with a 39% response rate in 24 previously treated patients, including 2 out of 6 responses in patients refractory to prior chemotherapy. In a randomized comparison of VP16 and VM26 from the Finsen Institute (Copenhagen), both appeared to be highly active in untreated SCLC patients, with a slightly higher response rate in VM26 treated patients (79 vs 65%), but no difference in survival. The significant activity of VM26 was confirmed in SCLC patients with brain metastases, in an EORTC study, indicating its high effectiveness even in patients who had received VP16 in the past.

The use of intensive weekly chemotherapy has been compared in 291 SCLC patients to a 3 weekly schedule in a British study, without any advantage of the weekly regimen in terms of response rate and survival.

Several studies reported the use of colony stimulating factors in the attempt to prevent leucopenia-related complications and/or to increase the dose intensity of chemotherapy. Although a clear positive influence on leucopenia is obtained with granulocyte-colony stimulating factor (G-CSF) and granulocyte macrophage colony stimulating factor (GM-CSF), the levels of platelets do not appear to be positively affected, and they therefore become dose-limiting for attempts to further increase the dose of drugs. In a large SWOG

trial, GM-CSF was randomly administered to 176 limited disease SCLC patients, undergoing chemotherapy and concurrent irradiation. The study was prematurely interrupted because the frequency and severity of thrombocytopenia and pulmonary toxicity were significantly higher in the GM-CSF arm. No clear explanation was given, but a possible interaction with the concurrent chemoradiotherapy regimen was hypothesized by Bunn (Denver). This study cautions against the indiscriminate use of CSF (GM-CSF in particular).

In the field of supportive care the antiemetic prophylaxis has greatly improved since the introduction of ondansetron and other 5-HT<sub>3</sub> receptor antagonists. However, the use of ondansetron in combination with dexamethasone was significantly superior to ondansetron alone in the control of emesis induced by high-dose cisplatin, as reported by Tonato and co-workers (Perugia, Italy).

Neoadjuvant chemotherapy is a current topic in inoperable or borderline operable NSCLC. Several pilot or feasibility studies were reported, which agreed overall that with at least two cycles of cisplatin containing regimens a response in excess of 50% can be achieved in this selected group of patients, that the majority of patients can be radically resected, but that

pathologically confirmed complete responses are relatively few. The results of randomized studies are, therefore, awaited with interest. A randomized phase II study by the LCSG compared the MVP (mitomycin C, vinblastine, cisplatin) regimen with preoperative radiation in technically unresectable NSCLC. The overall response was low in both arms and the morbidity was substantial. On this basis, none of the treatments will be selected for further phase III trial of LCSG.

Arriagada and co-workers (Paris) updated the results of a study of 353 locoregionally advanced NSCLC patients randomized between radiation alone *versus* chemotherapy plus radiotherapy. There was a significant difference in survival and reduction of metastasis in favour of the combined arm. This finding was confirmed by a smaller Italian randomized study.

Interestingly, in an EORTC study, chronic oral administration of VP16 appeared effective in malignant pleural mesothelioma, with 6 out 13 responses.

#### References

Further information on the studies mentioned are reported in the Abstract Book of the Congress, published in *Lung Cancer*, Vol. 7 (Suppl.), 1991.