



### Report

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The main objective of the ESMO International Symposium (EIS) on Chest Tumors, which recently took place in Geneva, was to provide a state-of-the-art approach to lung cancer in its different stages as well as to discuss other more rare tumors, i.e. malignant pleural mesothelioma, thymic malignancies and chest wall tumors. The meeting established a quality benchmark for a multidisciplinary approach by providing a forum for surgeons, radiation oncologists and medical oncologists to focus on how each specialty's contribution can improve cancer management and minimize negative aspects. There were approximately 600 participants from Europe, Asia and Africa. Besides lectures on the state-of-the-art of diagnosis and treatment, there were several patient case reports of diverse presentations of lung cancer, where the different general management issues and research questions were discussed.

After a brief introduction of the aims of the meeting by P. Kosmidis and G. Giaccone, Chair of the Scientific Committee, the meeting started with a discussion of the emerging data on smoking and smoking cessation as a way to prevent lung cancer. D.W. Bettcher, acting Director of the World Health Organization (WHO) Tobacco Free Initiative, focused on the use of campaigns against smoking and recent legislation against tobacco companies, in particular in Europe but also in emerging areas of the world, where the tobacco companies have recently been moving their assets.

C. La Vecchia presented some novel data on the epidemiology of lung cancer, particularly regarding the rise of lung cancer in women and the potential role of anti-smoking policies in deterring young women from smoking. It appears that women are more susceptible to

the carcinogenic damage caused by several carcinogenic chemical entities present in tobacco smoke. Whereas in men the incidences of lung cancer have started to decline in most areas of the western world. In countries such as the United States, lung cancer has surpassed breast cancer as the first cancer killer in women.

R. Stahel introduced the emerging data on the molecular changes that are characteristic of lung cancer and in particular he focused on a few for which molecular targeted treatments are presently available, or are being developed. Among these, he discussed the use of molecules that target several different pathways in the apoptosis machinery. He also discussed a number of receptor tyrosine kinases for which drugs have been developed or could be developed, given that these kinases are frequently altered in lung cancer. In particular he discussed the HER family of receptor tyrosine kinases and c-met.

W. Gullick extensively reviewed the biology of the epidermal growth factor receptor (EGFR), specifically the biology of the mutations and amplification of the gene as responsible for the sensitivity to EGFR tyrosine kinase inhibitors. Mutations in the ATP-binding site have been recognized as major alterations responsible for the induction of dramatic response in patients with lung cancer bearing these mutations. Two major types of mutations have been described: deletions in exon 19 and point mutations in exon 21. These are sensitizing mutations. More rare mutations have been described in other areas of the ATP-binding site, and a well known resistant mutation, the T790M point mutation in exon 20 has also been characterized recently. Among the sensitizing mutations, apparently the deletion mutants in exon 19 are those that confer the highest sensitivity to inhibitors of EGFR and also have a better prognosis for the patients, whereas the exon 21 point mutations have a less positive impact.

There were major sessions devoted to the staging and treatment of non-small cell lung cancer (NSCLC). In the staging session, K. Turnoy explained a number of novel, non-invasive, technologies that can help stage preoperative patients, especially concerning the presence of mediastinal lymph nodes, which themselves are difficult or impossible to sample by mediastinoscopy. Esophageal ultrasound (EUS) and endobronchial ultrasound (EBUS) were addressed as potentially complementary methods to more accurately stage patients with lung cancer where the preoperative

work-up may require extensive investigation of the mediastinal structures.

D. Lardinois described the surgical staging procedures that are necessary in adequately staging patients with lung cancer, in particular the indications of mediastinoscopy in patients with suspicion of mediastinal involvement.

E. Comans demonstrated the use of [<sup>18</sup>F] fluoro-2-deoxy-d-glucose positron emission tomography (FDG-PET) in the staging of patients with lung cancer, and in particular its use to show extra-thoracic disease and to help stage the mediastinum. Preoperative FDG-PET has become the standard pre-operative procedure in several countries, such as The Netherlands, and this procedure is presently being replaced by PET-CT machines, which allow a more precise definition of anatomical structures than independent PET and computer tomography (CT) scanners.

R. van Klaveren reported on several studies that have been published with the use of screening procedures for high-risk individuals (heavy smokers). In particular, he described the most recent studies that used low-dose spiral CT scans to screen patients for lung cancer. Results of randomized studies are still awaited, as the results of non-randomized studies, albeit encouraging, cannot be taken as a proof of a decrease in mortality introduced by screening techniques.

In a keynote lecture, P. Goldstraw reported on the attempts to develop a revised TNM classification. The International Association for the Study of Lung Cancer (IASLC) has sponsored a large staging project, which has examined 81,495 patients surgically treated between 1990 and 2000, 59% from Europe, 8% from Australia, 20% from North America and 13% from Asia. This is definitely a much larger effort than the one that led to the previous TNM staging systems and undoubtedly will give more confidence on correct prognostic classifications of patients. In particular the new classification, which will probably be fully released only in 2009, will have some changes related especially to the definition of T3 lesions, satellite lesions in the lung and there will be a novel mapping of the nodal staging system. The goal of this great effort performed on this large number of patients is to come to a better grouping of patients with different presentations into more adequate categories. In previous editions of this classification, certain categories of patients

were represented by a handful of cancer patients and therefore the precision of that classification for some subcategories was imprecise.

The treatment of early non-small-cell lung cancer (NSCLC) was discussed with particular focus of the adjuvant treatment of radically resected patients. E. Vallieres and C. Le Pechoux respectively discussed adjuvant chemotherapy and adjuvant radiotherapy. Adjuvant chemotherapy has become standard treatment in patients with radically resected stage II and III disease. This has been based on several very large randomized studies that concluded that cisplatin-based chemotherapy (cisplatin-vinorelbine is the regimen with the strongest evidence) improves survival by 4-5% at 5 years. For stage IB the evidence is somewhat weaker.

Adjuvant radiotherapy is no longer routine because meta-analyses have shown potential detrimental effects in early disease. Most likely, some of this negative effect was due to the use of obsolete machines. In N2 disease adjuvant radiotherapy may still have a limited role, and studies are being set up to answer this question. Adjuvant radiotherapy has a definite role in the treatment of patients where residual tumor is left after surgery. R. Stephens addressed the potential impact of treatment of early lung cancer on general health status and quality of life, a subject not well covered so far. It would appear that patients with lung cancer who underwent a major surgical resection have a poorer health status as compared to other tumor types.

F. Barlesi reviewed the use of neo-adjuvant chemotherapy in early lung cancer. There is only one adequately powered French randomized study that demonstrated advantage in time to progression but not overall survival by giving neo-adjuvant chemotherapy in radically resectable disease. Studies in stage III disease indicate that chemoradiotherapy has a higher complete response rate, but is more toxic than chemotherapy alone and there is no clear indication of superiority in terms of survival. The local treatment after neo-adjuvant therapy does not necessarily have to be surgery, as a large EORTC study demonstrated similar survival with radical radiotherapy, as presented by J. van Meerbeek.

Novel radiotherapy techniques were discussed by S. Senan, in particular in the treatment of stage III NSCLC and W. Weder evaluated the use of surgery in these patients, discussing also patients who are

borderline operable at start or inoperable and are brought to surgery after induction therapy. In this light the treatment of superior sulcus tumors with chemoradiation has become standard before surgery.

Treatment of advanced NSCLC underwent major developments in the last few years, mainly due to the introduction of targeted therapies. C. Gridelli summarized where we stand in terms of chemotherapy treatment. Standard doublet platinum-based chemotherapy remains the backbone treatment of first-line patients with advanced NSCLC (stage IIIB with pleural effusion and stage IV). There are no major differences in outcome among the several doublets. The addition of bevacizumab has however improved survival in one large randomized study and therefore the introduction of this monoclonal antibody against vascular endothelial growth factor (VEGF) has become standard in patients with non-squamous histology in the US. In Europe this drug is still not approved for this indication.

L. Paz-Ares discussed the 3 major options for second-line treatment, namely docetaxel, pemetrexed and erlotinib and R. Rosell explained novel ways of trying to understand which patients would benefit most from particular forms of chemotherapy, based on the molecular profile of the tumor. In particular, advances have been made in understanding the role of DNA repair enzymes, such as ERCC1 and BRCA1, which are involved in repair of DNA damage induced by platinum compounds. G. Giaccone addressed the issue of how targeted therapies, including bevacizumab, have had a major impact in the treatment of advanced NSCLC. In this context he clearly stated that EGFR tyrosine kinase inhibitors are to be used in patients who are selected on the basis of clinical characteristics (never-smokers, adenocarcinoma, women, Asian) or even better on the basis of presence of EGFR mutations and/or amplification. No markers are presently available for selection of angiogenesis inhibitors, and the selection presently performed for treatment with bevacizumab is based only on the exclusion of patients with squamous cell histology, brain metastases and significant hemoptysis. These exclusions are due to safety reasons, in that patients with these characteristics are known to be at a higher risk of bevacizumab-induced bleeding.

Treatment of neuroendocrine tumors of the lung were discussed in a separate session, where P. Kosmidis summarized the experience of systemic chemotherapy

in the treatment of small-cell lung cancer (SCLC), and C. Faivre-Finn discussed radiotherapy in limited stage SCLC. Essentially no substantial improvement in survival has been obtained in the past 2 decades in treating SCLC with chemotherapy and novel agents are now being investigated in this disease. Among the novel agents some are chemotherapeutics, such as amrubicin, but many are targeted agents. Radiotherapy has a major recognized role in the treatment of patients with limited disease, where chest radiotherapy given early and concomitant with chemotherapy has better survival than sequential chemotherapy followed by radiotherapy. Prophylactic cranial irradiation also has a recognized role in that it increases survival in patients who have a complete or near complete response to systemic treatment. M. Mueller discussed the treatment of carcinoids, which remains surgical in most cases.

The last session included the presentation of treatment of rare chest tumors. P. Baas provided a comprehensive report on novel approaches to pleural mesothelioma, including new drugs such as pemetrexed, vorinostat and bevacizumab, as well as multidisciplinary approaches. P. van Schil approached the treatment of thymic malignancies, in particular the surgical treatment of this interesting disease, and P. Macchiarini illustrated the surgical approach of tumors that invade the chest wall. The diversity of histological types and presentations of these tumors was addressed.

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