Report on the 2nd European Lung Cancer Conference (ELCC)
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The 2nd European Lung Cancer Conference was held from 28 April to 1 May 2010, in Geneva, Switzerland. This article is a brief overview of the most relevant aspects for clinical practice in the management of lung cancer that emerged from plenary, keynote lectures and oral presentations. The report does not cover the poster, educational and Meet the Professor Sessions. References in brackets refer to the Supplement to the Journal of Thoracic Oncology.

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Introduction

After a very successful inaugural Conference in 2008 The European Society for Medical Oncology (ESMO) and the International Association for the Study of Lung Cancer (IASCL) agreed that a regular scientific and educational meeting in this field is important for providing a comprehensive overview of the most significant advances in lung cancer research and treatment. Over the past few years, molecular biology has revolutionized the knowledge regarding the natural history of this illness. Treatment must be approached by multiple specialists and the strategy must be tailored for every patient. Thus the Conference discussed current trends in surgical, radiotherapy and chemotherapeutic approaches to lung cancer with individualization of therapy based on clinical, histological and molecular characteristics. Also it presented the application of established targeted agents as well as the introduction of emerging ones, emphasizing the mechanism of action and preclinical and clinical results. It also covered issues like prevention, early detection, epidemiology and tobacco control. The Conference format comprised keynote lectures, workshops, educational meet-the-expert and controversy sessions. It also included state-of-the-art presentations in early stage I-II non-small cell lung cancer (NSCLC), stage III and metastatic NSCLC on which this report will focus.

Early NSCLC stage I-II: State-of-the-art

Surgery is considered to be the cornerstone in treating patients with stage I NSCLC. A lobectomy or an anatomical segmentectomy in selected cases with a lymph node dissection is considered to be the standard. A wedge resection is less optimal with higher rate of local relapse. Today several alternatives to surgery have emerged for occult lung cancer such as: cryosurgery, endoluminal brachytherapy or phototherapy. For larger tumors stereotactic body radiotherapy (SBRT) and radiofrequency are two modalities challenging surgery for high-risk patients (1). Radiofrequency is an invasive procedure with the risk of pneumothorax. SBRT has the advantage to be a non-invasive approach. The drawback is the absence of histological diagnosis and nodal sampling. But in the PET-CT era, the rate of positive nodes in the absence of mediastinal uptake and the number of isolated nodal relapse are relatively low in the different published series. In the absence of tissue confirmation, there is a risk treating benign disease, but using strict criteria, positive PET-CT, history of tobacco smoking, successive CT enlargement, this probability is very low and the outcome of patients with or without tissue diagnosis is very similar in the different published series. The current data for different modalities yields very similar results, but we must be aware of the limitations of many reported series: short follow-ups, wide varieties of cases.

Intra-operative lymph node (LN) evaluation in stage I-II disease is critical since it provides staging and prognostic information and guides the choice of treatment (2). In 2006 the European Society of Tho-
ractic Surgeons established guidelines on intraoperative LN staging for NSCLC (Lardinois, 2006). For complete resection, a systematic nodal dissection (SND) is recommended in all cases. The mediastinal, hilar and in the cases of lobectomy or segmentectomy, interlobar LNs are dissected and put in different vials with separate labeling. The highest removed mediastinal LN should be identified. Despite the systematic use of PET-CT and invasive techniques as indicated by recent guidelines (De Leyn, 2008) SND will detect positive N1 and N2 nodes in 19% patients with clinical stage I NSCLC (Cerfolio, 2009). In a meta-analysis, mediastinal LN dissection was associated with improved survival (S), pooled HR= 0.78, CI: 0.65 to 0.93, compared to nodal sampling in patients undergoing resection for early stage I-III NSCLC. A recent meta-analysis on the use of adjuvant chemotherapy after complete resection of NSCLC showed clear benefit in patients with N1 and N2 disease. So by performing SND, more patients will be accurately staged and treated.

Charloux A. (3) tried to develop up-to-date clinical guidelines on fitness for surgery and chemoradiotherapy. The first step is a cardiologic assessment based on validated index estimates. Patients at low cardiologic risk or with an optimized cardiologic treatment could proceed with pulmonary evaluation. Patients with FEV1 or DLCO or both below 80% of predicted values should undergo a formal cardiopulmonary exercise test with peak oxygen consumption (VO2) measurement. Lower values of VO2 than 35% and predicted post-operative FEV1 or DLCO than 35%, are regarded as a prohibitive risk for major lung resection (lobectomy or pneumonectomy). There are no recommended cut-off values or algorithms before radiochemotherapy due to lack of data.

The role of neoadjuvant chemotherapy remains unclear in early-stage disease. The NATCH trial (4) is the first one which compares surgery alone to 3 cycles of neoadjuvant Carboplatin/ Paclitaxel followed by surgery, or surgery followed by the same chemotheraphy regimen in pts with IA, IB, II or T3N1 NSCLC considered resectable by the attending thoracic surgeon. More patients were able to receive neoadjuvant than adjuvant chemotherapy (97% compared to 66%) and there was a trend for improved five-year disease-free survival (DFS) when compared to surgery alone (38.3% vs 34.1%, HR=0.92, p=0.74). Five-year DFS rates were 36.6% in the adjuvant arm vs 34.1% in the surgery arm (HR= 0.96, p=0.74), but the trial was not powered to address the benefit of adjuvant chemotherapy in resected patients. Median overall survival was 55.2, 50.3 and 48.8 months for the neoadjuvant, adjuvant and surgery arm.

How close are we to customizing chemotherapy in early NSCLC? This was a question formulated by Souglakos J, who emphasized for example that three-gene signature (CSF1, EGFR, and CA IX) was associated with prognosis in early-stage squamous cell carcinoma, while a four-gene model based on the expression of WNT3a, ERBB3, LCK, and RND3 could discriminate patients with poor prognosis lung adenocarcinoma (5). Although there have been remarkable advances in the understanding of NSCLC, biology has not yet been translated into real benefit for patients with operable NSCLC.

**Stage III NSCLC: State-of-the-art**

Multimodality treatment concepts have become a therapeutic option for patients with stage IIIA and in selected cases stage IIIB NSCLC. An important question remains whether a better local control (LC) and S are obtained by induction treatment and surgery compared to standard chemoradiotherapy and how to restage a patient after a preoperative treatment. It is considered that at the present time neither CT, PET nor PET/CT scan are accurate enough to make final further therapeutic decisions for mediastinal nodal involvement (6). An invasive technique providing cytopathological information is still recommended at the present time by the European Society of thoracic Surgeons (ESTS). Endoscopic (EBUS-FNA or and EUS-FNA) or surgical (mediastinoscopy, VATS) invasive procedures may be utilized.

Concerning the morbidity of surgery after induction treatment, a decrease in the percent diffusion capacity of the lung for diffusion of carbon monoxide after chemotherapy and chemoradiotherapy has been reported (7). On the contrary other reports suggest that preoperative doses of 60 Gy are safe (Sonett 2004, Cerfolio 2009, Milman 2009), obtaining important therapeutic benefits without higher rates of postoperative complications as broncho-pleural fistula.

In spite of the refined staging system, the heterogeneity of stage III disease, and the difference in treatment related mortality and morbidity of surgically treated patients makes it difficult to recommend briefly who is the candidate for surgery in stage III disease. Two categories are here to be discussed, T3/T4 and N2 disease. There are a few basic rules for surgical treatment of lung cancer. In general, patients profit from surgery only, when resection is complete with free resection margins. Complete resection of metastatic lymph nodes is defined when the highest mediastinal lymph nodes are free (8).
Recent randomized controlled trials have failed to show an improvement in survival for patients undergoing surgical resection following either chemoradiotherapy or chemotherapy vs. radiotherapy following induction chemotherapy for stage IIIA, N2 positive disease (9). However, patients who underwent lobectomy appeared to have an improved outcome. On the other hand a recent metaanalysis of 5 studies presented at the British Theoretic Oncology Group demonstrated that radiotherapy provided no advantage over surgery with a better outcome for surgery. Therefore in certain N2 patients populations surgery followed by adjuvant chemotherapy +/- postoperative radiotherapy may result in the optimal long term survival. For the patient with unresectable N2 or N3 disease the optimal treatment based on current evidence is sequential or concurrent chemoradiation. The concurrent chemoradiotherapy can be given in fit patients, meaning good performance status (PS =0-1), good pulmonary function tests, no co-morbidities (10). Whether induction or consolidation chemotherapy is better to add to the concurrent setting remains to be evaluated in further studies. To further optimize multimodal approach, targeted therapies are evaluated in different treatment designs.

Improving the therapeutic ratio of chemoradiation is an important task. Better understanding of the biological determinants and advanced radiation technology led to improved outcome after chemoradiation in patients with lung cancer. The milestones were the optimization of time-dose-fractionation and schedules of combined therapies, introduction of functional imaging for treatment planning and monitoring of response, novel radiation techniques as well as implementation of image-guidance allowing high-precision delivery and control for respiratory motion. Advances in imaging and radiation technology allowed the increase of the radiation dose and the sparing of the normal tissues (11).

Metastatic NSCLC: state-of-the-art

Until recently NSCLC was considered as a single disease entity, whereby the treatment decisions were mainly based on the stage of tumor, performance status and co-morbidities of the patient. Currently we are at the dawn of customized treatment for advanced NSCLC based on the prognostic and predictive characteristics of both the patient and the tumor. However most of these predictive biomarkers still require validation in phase III trials of customized treatment. Histology, namely non-squamous, has recently emerged as a potential predictive factor for treatment with EGFR-TKIs or pemetrexed. However beyond histology, it is clear that underlying molecular factors are responsible for these findings. The IPASS trial proved that EGFR mutation status predicts the benefit from EGFR-TKIs. The sensitivity to pemetrexed seems to be correlated to the thymidilate synthase expression: high in squamous cell carcinoma, low in adenocarcinoma and variable in large cell carcinoma. Although the relationship between DNA repair system and survival in NSCLC patients treated with platinum-based chemotherapy has been extensively studied it needs prospective validation. Currently such a trial using BRCA1 and RAP 80 as genetic markers is ongoing. Patient-related factors correlate with treatment related toxicities. For example, a deficiency of serum cytidine deaminase activity is associated with the occurrence of early severe toxicities with Gemcitabine (12).

Molecularly targeted therapies have recently emerged and it is questionable whether they can be extended in first-line treatment in advanced NSCLC (13). Bevacizumab is the first monoclonal antibody against VEGF which in combination with chemotherapy compared to chemotherapy alone, as first line treatment has shown to increase by two months the median survival of advanced non-squamous NSCLC patients. Other antiangiogenic agents, including Sorafenib, VEGF-trap and ASA404 are being tested in ongoing clinical trials. Cetuximab when added to first-line chemotherapy significantly prolongs survival compared to chemotherapy alone in a FLEX trial.

Trials incorporating TKIs with chemotherapy failed to produce a survival improvement, therefore identification of patients that are likely to benefit from EGFR TKIs became a priority, for patients with advanced NSCLC. Recently in the IPASS phase III trial in chemotherapy-naive Asian patients with adenocarcinoma who were never or former light smokers, Gefitinib was more effective than Carboplatin plus paclitaxel in prolonging progression-free survival. In a subgroup analysis, EGFR-mutation-positive status predicted a better outcome with Gefitinib. The EURTAC trial assessing the role of Erlotinib in EGFR mutated tumors is ongoing. Thus incorporating novel targeted agents should consider selection of patients on clinical and molecular factors.

Maintenance therapy (first-line treatment continued or switched to another agent beyond 4-6 cycles of chemotherapy is gaining recognition as a possible approach, as clinical trials have demonstrated a survival benefit (14). For example, Pemetrexed was tested in a phase III study as a maintenance therapy, versus placebo, in patients with advanced NSCLC who did not progress after 4 cycles of platinum-based doublet chemotherapy. Progression free survival (PFS)
was significantly longer (4.3 vs 2.6 mo, HR=0.50) and also overall survival (OS) significantly improved (13.4 vs 10.6 mo, HR=0.79). A subset analysis showed in non-squamous histology a survival benefit of 5 months (HR=0.70). Pemetrexed was generally well tolerated during long-term exposure. Erlotinib was also explored in the maintenance setting. In one phase III study, 889 patients who did not progress after 4 cycles of platinum based chemotherapy, were randomized to maintenance with Erlotinib vs. placebo. A statistically significant improvement in PFS (12.3 vs. 11.1 weeks, HR=0.71) and OS (12 vs. 11 mo, HR=0.81). The available evidence supports the maintenance approach for patients with response or stable disease, without relevant toxicities and asking to continue therapy. For those with clinical relevant toxicity with first-line therapy or preferring a treatment holiday and good monitoring, starting timely second-line therapy remains an appropriate alternative.

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