3rd European Lung Cancer Conference (ELCC)

18-21 April, 2012
Geneva, Switzerland

INTRODUCTION

The 3rd European Lung Cancer Conference (ELCC), held in partnership between the European Society for Medical Oncology (ESMO) and the International Association for the Study of Lung Cancer (IASLC), was a resounding success. This year the Conference was attended by 1,500 participants from 75 countries. The comprehensive Conference program addressed real clinical situations and demonstrated the underlying need for multidisciplinary collaboration in the treatment of lung cancer.

Educational sessions on important topics presented by the world's leading authorities were complemented by debates on controversial topics, specialty-specific workshops and in-depth "Meet the Professor" sessions with a focus on clinically relevant issues that oncologists, radiotherapists, pathologists, surgical oncologists, thoracic surgeons, respiratory physicians and other specialists face in their daily practice. In order to keep abreast of the latest developments in basic, clinical and translational research, oncologists recognized that the 3rd ELCC was the thoracic continuing medical education (CME) conference to attend.

ADVANCED NSCLC

Two teams of researchers reported outcomes on the role of biomarkers (163O and 164O). Tsao and colleagues presented results of exploratory analyses for epidermal growth factor receptor (EGFR) activating mutations, KRAS mutations and EGFR gene copy num-ber, conducted following study completion on 319 (42%) tumor samples available in the TORCH trial. TORCH was a randomized phase 3 trial that compared first-line erlotinib followed at progression by cisplatin/gemcitabine vs. the standard reverse sequence in unselected patients (pts) with advanced non-small cell lung cancer (NSCLC). The team terminated the study after the first interim analysis showed inferiority of the experimental arm. Patients with known marker status were distributed similarly between arms. EGFR

and KRAS mutation and EGFR gene copy number status were identified in 275 (36%), 276 (36%) and 196 (26%) patients respectively. Mutations were found in 39/275 (14%) for EGFR and 73/276 (26%) for KRAS; 102/196 (52%) patients had tumors with high EGFR gene copy number. There was no interaction between any biomarker and treatment efficacy for overall survival (OS) and total progression-free survival (PFS) after both lines of therapy. For first PFS, EGFR mutants but neither KRAS mutants nor EGFR gene copy number showed significant interaction with treatment. Patients with EGFR mutation had improved first PFS with erlotinib (HR 0.60, 95% CI 0.30-1.20), compared to EGFR wild-type patients (HR 2.07, 95% CI 1.58-2.71 interaction p=0.006). Among EGFR wild-type patients, there was no interaction between EGFR gene copy number and treatment efficacy. The second report was presented by Garassino and colleagues on the role of KRAS in patients treated with first-line chemotherapy. KRAS mutations in NSCLC are supposed to indicate a poor prognosis and poor response to anticancer treatment. However, such evidence was only drawn from retrospective series giving controversial results. Moreover, it is possible that the various KRAS mutations affect prognosis, carcinogenesis and drug response differently, as demonstrated in preclinical setting. Out of 565 patients registered, 341 (60.5%) were evaluable for KRAS and 85(25%) were mutated. At a median follow-up of 17 months, KRAS-mutated patients showed a statistically-significant worse PFS (HR 1.42 95% CI 1.06-1.94; p=0.02). No differences among doublets were observed in KRAS-mutated patients. The conclusion was that patients mutated for KRAS seemed to have a higher risk of progression.

Two studies focused on the role of dacomitinib (165O and 166O). Blackhall and colleagues presented results on the activity of dacomitinib, an irreversible inhibitor of human epidermal growth factor receptors (HER)-1/EGFR, -2, and -4 tyrosine kinases (TKs) in refractory non-adenocarcinoma and compared with erlotinib in second-third-line setting. The primary endpoint was response rate. Of the sixteen refractory patients, one had a partial response (PR). For second-third-line there was a non-significant trend in favor of dacomitinib [HR 0.65, (95% CI: 0.36, 1.18), 2-sided p=0.152; with a median PFS of 8.7 weeks for dacomitinib compared with 8.0 weeks for erlotinib]. For OS, the HR was 0.74 (95% CI: 0.41, 1.34), 2-sided p=0.323; clinical benefit rate (CBR) was 21.9% (7/32; 1 PR, 1 complete response (CR)) for dacomitinib and 9.1% (3/33) for erlotinib. After initial results demonstrated drug activity, phase 3 trials in this population were performed. In the second trial O'Connell and colleagues evaluated the impact of dacomitinib on symptom control. In a global multicenter, open-label randomized phase 2 study (NCT00769067) of second-third-line treatment for NSCLC, dacomitinib showed improved PFS, which was a primary objective of the study with HR 0.66 (95% CI, 0.47, 0.91), two-sided p=0.012, and manageable toxicity vs. erlotinib. Patients progressing after one or two prior chemotherapies were randomized 1:1 to dacomitinib (45 mg) vs. erlotinib (150 mg) orally once daily. A secondary objective was to explore health-related quality of life. Disease/treatment-related symptoms were recorded using the EORTC QLQ-C30 and QLQ-LC13. Dacomitinib demonstrated favorable clinical benefit vs. erlotinib and improvements in common NSCLC symptoms.

Juan and colleagues (167O) illustrated results on the randomized, phase 2 study designed to address the clinical benefits of sequential administration of intermittent erlotinib and docetaxel. Seventy patients with advanced NSCLC and disease progression following previous chemotherapy were randomized. The primary endpoint was rate of progression free at six months, and secondary endpoints were PFS, OS, disease-control rate and safety. Although the primary objective was not met, the investigators noted an encouraging benefit on survival in the exploratory analysis, with a median overall survival of 11 months for patients treated with the sequential regimen.

Scagliotti and colleagues (168O) presented results on denosumab in a subgroup analysis of patients with lung cancer. Denosumab is a fully human RANKL antibody approved to prevent skeletal-related events in patients with solid tumors and bone metastasis. Patients were equally randomized to receive either a monthly subcutaneous denosumab injection (120 mg) or intravenous zoledronic acid (4 mg). An exploratory analysis was conducted to assess OS among patients with lung cancer within the phase 3 trial of denosumab versus zoledronic acid for preventing skeletal events in patients with bone metastasis from solid tumors (except breast and prostate) or with multiple myeloma, including both NSCLC and small-cell lung cancer (SCLC). A total of 811 patients with lung cancer (702 NSCLC; 109 SCLC) were enrolled. Within the limits of the subgroup analysis, treatment with denosumab was associated with significantly-improved overall survival in comparison to zoledronic acid in patients with lung cancer.

PREVENTION, EARLY DETECTION, PROGNOSIS, EPIDEMIOLOGY, TOBACCO CONTROL

Terzi and colleagues (63O) presented the one-year results of an observational study using digital chest tomosynthesis as a fast, new and inexpensive imaging technique for early detection of lung cancer. Digital tomosynthesis is limited angle tomography that is less expensive than computed tomography (CT), allows reconstruction of multiple image planes and provides high-resolution images in coronal planes at radiation doses. A total of 1703 subjects were evaluable, and at least one pul-monary abnormality was detected in 154 subjects. Lung cancer detection rate was 1.1%, similar to that obtained with the CT scan.

Roy and colleagues (64O) described a novel screening technique analyzing the cells inside the mouth to detect possible indications of lung cancer. Researchers performed a case-control study on 63 cases and determined that buccal mucosal interrogation with low coherence enhanced backscattering spectroscopy (LEBS) probe appears to accurately identify lung cancer patients. Despite using a modest sample size, the study showed that the buccal LEBS procedure represented a promising, minimally intrusive pre-screening technique for lung cancer.

Mascaux and colleagues (65O) analyzed the expression of selected microRNAs (miRNAs), circulating nucleic acids that are detectable in serum or plasma and potentially represent a new class of biomark-ers, as potential surrogate biomarkers in the prostacyclin analog iloprost lung cancer chemoprevention trial. This trial was the first study to meet a pre-determined pri-mary endpoint of bronchial histology improvement. In analyzing 14 different miRNAs, the study demonstrated that the change in miR-34c expression between baseline (BL) and follow-up (FU) biopsies was also inversely correlated with histology changes ($r=0.23$, $p=0.0003$, FDR<0.1), independent of treatment arm or smoking status. In addition, a lower miR-34c expres-sion at BL, and consequently its increase at FU, was significantly associ-ated with histological response in the iloprost study ($p=0.0022$, FDR<0.1) and placebo arms ($p=0.0025$, FDR<0.1). The changes in miR-34c (a transcrip-tional target of p53) expression were inversely correlated with histological changes at FU. In responders, miR-34c expression is significantly lower at BL and increased at FU, related with a worse histology at BL and downgrading at FU. Researchers concluded that the change in miR-34c expression in FU biopsies is correlated with histological response and may be a quantitative biomarker of response in lung chemoprevention studies.

Hernando and colleagues (250O) presented a new gene signature defining two prognostic groups among patients with completely resected early NSCLC. RNA was extracted from frozen samples with more than 70% tumor cells. Tumors were analyzed using microarray expression 4x44 K (Agilent), and two molecular subgroups of NSCLC were identified based on 50 genes. Most encoded proteins directly or indirectly related to B-lymphocytes (as immunoglobulin molecules, CD79a, CD19, POU2AF1 or pERp1). Other proteins such as TNFRSF17, SLAM7F, CD139; CXCL13, IRF4, CD27, Pim-2 or CD38, although not restricted to B-cells, were strongly associated with B-cell homeostasis, proliferation and survival. Disease-free survival was significantly better in the group with good prognosis [HR 3.4 (CI 95%: 1.6-7.3; $p=0.001$)]. The expression of these 50 genes could define subgroups of patients with different prognosis among those with completely resected early NSCLC.

As lung cancer risk is associated with airflow obstruction and increases with decreased FEV1, Nordin and colleagues (66O) investigated the feasi-bility of detecting high-risk individuals by identifying airflow obstruction and monitoring respiratory symptoms. A total of 2700 subjects were invited to participate, and 260 completed spirom-etry. The study reaffirmed that smokers with respi-ratory symptoms are at higher risk of having airflow obstruction, a powerful marker of lung cancer risk. Respiratory symptoms in smokers, with or with-out spirometry, may assist in targeting a high-risk population for lung cancer screening.

TRANSLATIONAL RESEARCH, BIOLOGY AND PATHOLOGY

Savic and colleagues (760) reported that the Vysis ALK Break Apart FISH Probe, a qualitative test to detect rearrangements involving the anaplastic lymphoma kinase (ALK) gene via fluorescence in situ hybridization (FISH), is approved by FDA and is applicable to diagnostic NSCLC specimens with a highly-improved hybridization success rate.

Brambilla and colleagues (77O) presented results of the bio-LACE trial. Out of 804 patients, 763 were evaluable. Intense lymphocytic infiltration was observed in 6% of the patients in the validation set, ranging between 4 and 7% according to the trial as compared to 11% in the IALT study. Intense lymphocytic infiltration was correlated with longer overall and disease-free survival (HR=0.45 [0.24-0.85], p=0.01 and HR=0.44 [0.24-0.78], p=0005) without heterogeneity among trials. However, the intense lymphocytic infiltration was found only in a small number of tumors.

Gautschi and colleagues (80O) presented results on phase 2 trials involving VeriStrat, a serum test proteomic classifier. They retrospectively explored VeriStrat's abil-ity to separate patients with advanced non-squamous NSCLC treated in first-line with bevacizumab and erlotinib (BE) into better and worse PFS and OS groups. The results suggest that VeriStrat may be useful for clinical decision-making as it represents a prognostic and potentially predictive biomarker for treatment with EGFR TKIs.

Planchard and colleagues (81O) presented results from studies in 2010-2011 in which 82 tumors from patients with lung cancer and melanoma were analyzed for AKT, ALK, BR AF, EGFR, ERBB 2, FGFR, GNAQ, HRAS, KIT, KRAS, MAP2K, MET, NOTC H1, PDGFRA, PI3KCA, PTEN, RET, ST K11, TP53, and VHL mutations. The study showed that mutational profiling of NSCLC could be used to distinguish rel-evant molecular subsets of lung cancer, and was used in targeted treat-ment based on tumor biology.

EARLY STAGE AND LOCALLY ADVANCED NSCLC

Hattori and colleagues (132O) performed pulmonary resection for lung cancer in 680 patients between 2008 and 2010. Findings of preoperative CT were reviewed for all patients and categorized into three parts: pure ground-glass opacity (GGO), mixed GGO, and pure solid. Patients were evalu-ated with positron emission tomography (PET), and maximum standard-ized uptake value (SUVmax) was recorded. A total of 227 patients with lung cancer showed solid or mixed GGO appearance on thin-section CT scan; among them, nodal involve-ment was found at pathological review in 42 (26%) patients with pure solid tumors, in contrast to four patients (6%) with mixed GGO tumors (p=0.0002). The frequency for lymph node metastasis was approximately 27% for patients having lung cancer with pure "solid" characteristics and high SUVmax even for T1a tumors. The researchers concluded that lymph node metastasis is frequently observed for pure "solid" lung

cancer, especially when tumors show high SUVmax.

Matsunaga and colleagues (133O) conducted a retrospective study on 572 patients with resected lung cancer of clinical stage IA between 2004 and 2011. All patients underwent preoperative chemotherapy, and the authors reviewed radiological findings for all cohorts. Lung cancers with dif-ficulties in measuring GGO were selected, and their clinico-pathological features were investigated. The consolidation was not eas-ily measurable due to its scattered distribution, so it was defined as lung cancer with scattered consolidation (LCSC). LCSC was observed in 71 cases (12%). The authors concluded that LCSC is a new category of lung cancer that is less invasive pathologically, has a more favorable prognostic factor and could be useful for preoperative evaluation of lung cancer.

Navarria and colleagues (135O) reported results of their institutional experience with stereotactic body radiotherapy (SBRT) using volumetric modulated arc therapy (VMAT) with flattening filter free (FFF) modality for medically inoperable early-stage NSCLC. Although the small series involved only 36 patients, the SBRT resulted in excellent local control and minimal toxicity in early-stage NSCLC. VMAT technique improved target coverage while mini-mizing higher dose to normal tissue with respect to coplanar beam arrange-ments.

Vano and colleagues (136O) evaluated the impact of early response after 40 Gy of radiochemotherapy on unresectable stage III NSCLC outcome. Early responders had a significant better time to progression and OS than non-responders.

MESOTHELIOMA

Van Meerbeeck and colleagues (227O) updated their analysis of EORTC 08983, a randomized trial of raltitrexed and cisplatin versus cisplatin in malignant pleural mesothelioma. The results of this updated analysis confirmed the superior effi-cacy of the raltitrexed/cisplatin combination over cisplatin alone in the first-line palliative treatment of patients with malignant pleural mesothelioma.

Feigen and colleagues (228O) presented results in 44 patients who underwent high-dose radiotherapy to an intact lung and received doses of 45-60 Gy to part or all of the hemithorax over six weeks, using 3D-conformal or, in 27 cases, intensity-modulated radiotherapy (IMRT). The authors provided clear evidence that radiation is arguably the most effec-tive single targeting agent for mesothelioma and that new technologies including IMRT allow high doses to be delivered safely to large volumes without compromising survival.

Cerciello and colleagues (229O) used mass-spectrometry (MS)-based tech-nologies for the identification and clinical verification of glycopeptide malignant pleural mesothelioma (MPM)

candidate biomarkers in serum. Glycopeptide MPM candidate biomarkers were selected from a pool of glycopeptides discovered through comparison of the surfaceome of MPM with control cells. The relative quantitative investigation of the MPM surfaceome revealed serum-accessible potential MPM candidate biomarkers. Selected reaction monitoring (SRM) technol-ogy enabled parallel verification of glycopeptide candidate biomarkers in serum samples of selected patient cohorts.

Kirschner and colleagues (230O) investigated the ability of certain miRNAs found in plasma and serum to serve as a diagnostic marker for MPM. MiR-625-3p was found to be present at significantly-higher levels (two-fold higher, p=0.006) in tumor specimens from 18 MPM patients who underwent extrapleural pneumonectomy than were present in normal mesothelium (pericardial tissue). The data indicated that miR-625-3p has the potential to serve as a novel blood-based biomarker for MPM.

Hagedorn and colleagues (231O) generated functional anti-FAP redirected T-cells and iden-tified fibroblast activation protein (FAP) as a target molecule in MPM. Experiments are underway to dem-onstrate antigen-specific functionality in FAP-positive tumors in vivo. The authors plan to start a pilot phase 1 trial in 2012 to investigate the safety of anti-FAP re-directed T-cells in patients with MPM who are not eligible for multi-modal therapy and who do not need immediate palliative chemotherapy.

RELATED INFORMATION

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Abstracts from the 3rd European Lung Cancer Conference are available at: http://journals.lww.com/jto/toc/2012/06001

Save the date: European Multidisciplinary Conference in Thoracic Oncology - EMCTO, Lugano, Switzerland, 9-11 May 2013

AFFILIATIONS AND DISCLOSURE

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The author has declared that she has received funding from Eli Lilly and Boehringer.