Reflections on the 14th World Conference on Lung Cancer: A European Perspective

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Lung cancer remains the leading cause of cancer death worldwide. More than 7,000 delegates attended the 14th World Conference on Lung Cancer (WCLC) that was held in Amsterdam July 3–7, 2011. The focus of this meeting was on emerging research ushering in the era of more personalized lung cancer treatment. Besides advances in therapy, the conference program also addressed early detection, imaging, the new International Association for the Study of Lung Cancer (IASLC) staging system, palliative care, and patient advocacy. The increasingly multidisciplinary nature of lung cancer care was reflected in well-attended sessions addressing topics of a multidisciplinary character such as molecular pathology, treatment options for high-risk and elderly patients, epidemiology, cancer in never-smokers, and salvage therapy.

As expected, advances in genetic subclassifications of advanced non-small cell lung cancer (NSCLC) were a major focus at the meeting because ~50% of lung adenocarcinomas have been shown to have an identifiable driving oncogene [1] (Fig. 1). A key study presented was the phase III European Tarceva® (erlotinib) versus Chemotherapy (EORTC) study of 174 western patients with NSCLC who had an epidermal growth factor receptor (*EGFR*) mutation [2]. First-line treatment of such patients with the drug erlotinib nearly led to a progression-free survival interval that was nearly double that observed with chemotherapy, 9.4 months versus 5.2 months, respectively. Nearly 55% of patients responded to erlotinib, in contrast to 15.5% who responded to chemotherapy. The lack of a significant difference in the overall survival times (22.9 months versus 18.8 months, respectively) was likely a result of

the high crossover rates observed in such trials. Taken together with recent studies of this class of agent in Asian mutation-positive patients, this finding establishes that patients with *EGFR* mutation benefit from receiving initial treatment with the less toxic and more efficacious targeted agents. Emerging data on the newer generation *EGFR* inhibitors currently in early clinical trials raise the prospect of further therapeutic improvements in the near future.

However, it must be kept in mind that 1,227 patients had to be screened in order to identify the enriched population of 174 mutation-positive patients treated in the EORTC study. Because clinical characteristics alone do not identify suitable patient subgroups, the need to obtain sufficient tissue to perform molecular analyses of tumors is evident. A more aggressive attitude on the part of both physicians and patients is required to achieve this goal, a point that was repeatedly stressed at well-attended workshops, educational sessions, and a hands-on session. A small proof-of-concept study demonstrated that in vivo detection of mutated tumors was possible using labeled erlotinib as a tracer for positron emission tomography scanning [3]. Such an approach may be promising in cases for which obtaining tissue for mutation analysis is impossible or very risky. Besides the issue of *EGFR* mutations, the degree of expression of *EGFR* by tumor cells was also reported to be an important predictor of benefit from treatment with an anti-*EGFR* antibody in combination with conventional chemotherapy [4]. This is especially interesting for squamous cell lung carcinoma because limited clinical progress has been achieved for this histological subtype.

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Figure 1. Overview of genetic alterations in non-small cell lung cancer, with targeted agents directed towards these driver mutations, based on a treatment approach proposed by the Spanish Lung Cancer Group.

Abbreviations: ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; EML, echinoderm microtubule-associated protein-like; HER-2, human epidermal growth factor receptor 2; MEK, mitogen-activated protein kinase/extracellular signal-related kinase kinase; PIK3CA, phosphoinositide-3-kinase, catalytic, α polypeptide; TKI, tyrosine kinase inhibitor; wt, wild-type.

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Another driving oncogene that has successfully been targeted in clinical trials has been the echinoderm microtubule-associated protein-like 4–anaplastic lymphoma kinase (*EML4-ALK*) mutation, which is estimated to be present in 3%–5% of all lung carcinomas. Overall survival data from 82 *ALK*⁺ patients who received the novel drug crizotinib versus matched historical controls revealed 1- and 2-year overall survival rates of 77% and 64%, versus corresponding survival rates of 73% and 33%, respectively, in controls [5]. In contrast to many molecular targeted therapies available for lung adenocarcinoma, none has yet been reported for squamous cell lung carcinoma until recently. Following the identification of possible therapeutic targets in up to 63% of squamous cell lung carcinomas [6], these targets will need to be validated in pre-clinical models, and early clinical trials using fibroblast growth factor receptor (FGFR)-1, FGFR-2, phosphoinositide-3-kinase, catalytic, α polypeptide, and discoidin domain receptor tyrosine kinase 2 inhibitors are either planned or ongoing.

The topic of screening for lung cancer also received much attention at the meeting. The publication just prior to the WCLC meeting of results from the National Lung Screening Trial (NLST) in the U.S. revealed that there were 20% fewer lung cancer deaths and a 7% lower all-cause mortality rate when smokers, defined as current or former smokers with ≥ 30 pack-years of smoking, were regularly screened using low-dose spiral computed tomography (CT), compared with standard chest x-ray [7]. The study followed $>53,000$ current and former smokers aged 55–74 years and was closed prematurely as a result of the observed lower number of cancer deaths. A key remaining concern was the high rate of positive findings (24.15%) after CT screening, of which, 96.4% proved to be

false. Consequently, 26,722 individuals had to be screened in order to obtain 87 fewer lung cancer deaths in healthy (former) smokers.

The costs related to the entire NLST screening process, including follow-up examinations to evaluate findings suspicious for lung cancer and other illnesses, surgery for abnormal lesions, treatment initiated, etc., remain to be published. The IASLC issued a statement addressing, among other things, the need for measures to ensure the quality of screening management and participation of multidisciplinary groups of trained specialists [8]. The IASLC statement specifically referred to the need to await maturing data from European trials, the largest of which is the Netherlands Leuven Longkanker Screenings Onderzoek (NELSON) trial of $>20,000$ smokers [9]. Mortality data from the NELSON trial will become available in 2015, and that trial will also provide important additional information on mortality gains, cost-effectiveness, and clinical management outcomes of lung cancer screening. Because it is unrealistic to screen the large number of current and ex-smokers worldwide, the IASLC emphasized the need for effective tobacco control programs. Because only 10%–15% of smokers die as a result of lung cancer, new approaches that may identify patient populations with a strong predisposition to developing lung cancer may in turn allow for more targeted CT screening.

Some critics of screening hold the view that a complex and aggressive disease like NSCLC cannot be detected sufficiently early to affect outcomes, particularly because the potential benefits of detecting early-stage disease can be offset by the complications of therapy. Varying access to curative care has also been considered to be a factor accounting for differences in the cure rate for lung cancer among western European coun-

tries. In this context, a British study reporting a correlation between appointments of more thoracic surgeons and a 46% increase in the resection rate for early-stage lung cancer was encouraging [10]. However, the elderly represent the fastest growing group of patients with lung cancer, and the risks of surgery outside specialized centers for such patients are great. A population-based time trends analysis in The Netherlands population of 16 million Dutch identified a total of 4,605 patients aged ≥ 75 years who were diagnosed with stage I NSCLC in 2001–2009 [11]. In a country where many patients undergo surgery at low-volumes centers [12], the 30- and 90-day postsurgical mortality rates were 5.4% and 9.3%, respectively [11]. The Dutch population analysis revealed that, following the introduction of stereotactic radiotherapy in 2003, a 6.5% absolute increase in radiotherapy use was seen in elderly patients, as was a decline in untreated patients and an improvement in the median survival time of irradiated patients from 16.8 months in the early period to 26.1 months in the last period. These data indicate that issues surrounding centralization of surgical care as well as a need to provide more information on alternative therapies to surgical candidates at high risk for toxicity should be addressed urgently.

The advances presented at the Amsterdam meeting add to a growing conviction that only treatment by expert multidisciplinary teams can ensure optimal patient care and survival for lung cancer patients. Facilities for rapid diagnostic procedures, obtaining adequate histology specimens, expertise in molecular diagnostic protocols, access to guideline-compliant surgery

and stereotactic radiotherapy, and managing complications of combined-modality therapies are all essential. This was illustrated in a study analyzing 400 patients seen for a second opinion at a tertiary academic center [13]. In a majority of cases, the second opinion process was initiated by a treating pulmonologist (65%), but this was at the sole initiative of the patient in 31% of cases. The second opinion consultation resulted in changes in diagnosis, disease stage, or therapy with possible consequences for therapy outcomes in 44% of all patients, and a change in policy of a potentially major character in 25% of patients. Referrals of this nature can be expected to increase in Europe in coming years, given the growing awareness by both specialists and patient groups of crucial expertise available from expert multidisciplinary teams. With health care budgets in Europe and elsewhere facing growing financial constraints, strategies that focus on redeploying existing health care resources within such expert centers or networks may be a more realistic approach in the short term than is the expectation for additional resources. Arguably, such developments may be more feasible within the less-fragmented health care structures existing in some European countries. Nevertheless, hurdles involved in implementing more personalized lung cancer treatment approaches in Europe should not be underestimated.

AUTHOR CONTRIBUTIONS

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REFERENCES

1. Bover I, Rolfo C, Jantus-Lewintre E et al. Fifth Educational Symposium of the Spanish Lung Cancer Group: Report on the Molecular Biology Workshop. *Lung Cancer* 2011;74:535–543.
2. Gervais R, Rosell R, Vergnenegre A et al. O10.01: The EURTAC (European Tarceva® vs Chemotherapy) study: Interim results of a phase III randomized trial of erlotinib vs chemotherapy (CT) in advanced non-small-cell lung cancer (NSCLC) patients (p) with epidermal growth factor receptor (EGFR) activating mutations. *J Thorac Oncol* 2011;6(suppl 2):S314.
3. Bahce I, Lubberink M, Hendrikse NH et al. PRS. 5: In vivo selection of non-small cell lung cancer patients with activating mutations in the tumor epidermal growth factor receptor using [11C] erlotinib and positron emission tomography. *J Thorac Oncol* 2011;6(suppl 2):S40.
4. Pirker R, Pas Ares L, Eberhardt W et al. O01.06: Epidermal growth factor receptor (EGFR) expression as a predictor of survival for first-line chemotherapy plus cetuximab in flex study patients with advanced non-small cell lung cancer. *J Thorac Oncol* 2011;6(suppl 2):S276.
5. Shaw AT, Yeap B, Solomon B et al. O31.06: Crizotinib improves overall survival of ALK-positive patients with advanced NSCLC compared with historical controls. *J Thorac Oncol* 2011;6(suppl 2):S412–S413.
6. Hammerman P, Sivachenko A, Pho N, et al. PRS. 1: Genomic characterization and targeted therapeutics in squamous cell lung cancer. *J Thorac Oncol* 2011;6(suppl 2):S39.
7. Aberle DR, Adams AM, Berg CD, et al. National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* 2011;365:395–409.
8. International Association for the Study of Lung Cancer (IASLC). IASLC's 2011 Statement on CT Screening for Lung Cancer. Available at <http://iaslc.org/policies/statement-on-ct-screening/>, accessed October 18, 2011.
9. van Klaveren RJ, Oudkerk M, Prokop M et al. Management of lung nodules detected by volume CT scanning. *N Engl J Med* 2009;361:2221–2229.
10. Lau KKW, Waller D, Rathinam S. PRS. 7: The effects of investing in thoracic surgery on lung cancer resection rates. *J Thorac Oncol* 2011;6(suppl 2):S40.
11. Haasbeek CJ, Visser O, Palma D et al. PRS. 3: Improvements in survival of elderly patients with stage I NSCLC in the Netherlands between 2003–2009. *J Thorac Oncol* 2011;6(suppl 2):S40.
12. Wouters MW, Siesling S, Jansen-Landheer ML et al. Variation in treatment and outcome in patients with non-small cell lung cancer by region, hospital type and volume in the Netherlands. *Eur J Surg Oncol* 2010;36(suppl 1):S83–S92.
13. Schook RM, Ter MJA, Setten CH et al. O44.03 Second opinions in an expert center for lung cancer patients affect diagnosis and therapy. *J Thorac Oncol* 2011;6(suppl 2):S472.