

## **REPORT PERSPECTIVES IN LUNG CANCER 2010 AMSTERDAM**

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### **Introduction**

Perspectives in Lung Cancer (PILC) is an educational meeting in the field of Respiratory Oncology. The aim of this meeting is to provide a concise overview of the new data of the last year. The 11<sup>th</sup> edition was held in Amsterdam on March 5-6, 2010, and was attended by approximately 900 participants.

### **Session I: Epidemiology**

The relation between smoking and lung cancer is well established, with around 85% of all lung cancers attributable to smoking. Both increasing governmental efforts for smoking cessation, as well as continuing advice for smoking cessation – consisting of behaviour and drug therapy – by individual doctors remain the basic approach to reduce lung cancer incidence.

A new type of lung cancer is, however, emerging. A never smoking status is associated with a biologically distinct subtype of non-small cell lung cancer (NSCLC), especially adenocarcinoma in females, with other underlying genomic changes (EGFR mutation), than the one previously described in smokers with adenocarcinoma (K-ras mutation).

Evidence is also growing that gender in general should receive more attention, with aspects such as different DNA repair capacity, differences in metabolism of carcinogens, in proliferative stimuli and hormonal interactions.

In the epidemiology of lung cancer, integration of molecular and genetic markers is needed to identify biomarkers of exposure, risk and outcome in lung cancer. Ongoing research e.g. focuses on exposure markers and genetic susceptibility to tobacco, cancer risk based on genetic susceptibility, genetic alterations and DNA-repair and influence on drug metabolism.

### **Session II: Diagnosis and staging**

The evaluation of the solitary pulmonary nodule (SPN) remains a challenge. Clinical risk factors and findings on CT- and PET-scan provide a certain profile of the nodule that helps in differentiation of malignant from benign nodules. Ground-glass lesions deserve particular attention because of their high probability of malignancy despite slowly growth.

The large-scale NELSON study (Nederlands Leuvens Screening ONderzoek) reported on CT screening in a selected population of current or former smokers. It documented a new strategy to look at SPNs in this setting. The volume of a new nodule or nodule growth pattern and volume doubling

time allow a better distinction between malignant and benign nodules, resulting in better follow-up algorithms and less needless invasive tests.

Histological subtyping of NSCLC has become very important in the guidance of treatment, but small histological or cytological samples increase the difficulty to come to an accurate diagnosis. The detailed histologic subtyping in the WHO 2004 classification was based on resection specimens. For small cytology and biopsy samples, it should probably better be replaced by a more easy to handle classification splitting NSCLC in 3 main groups: adenocarcinoma, squamous cell carcinoma and NSCLC-NOS (not otherwise specified).

Another important factor in the classification of tumours is tumour heterogeneity, as well in one lesion as between different lesions in one patient. Molecular profiling becomes increasingly important, but several questions remain open such as the amount of tissue needed, the best techniques and correlation between histology and molecular findings.

### **Session III: Diagnosis and treatment of early stage NSCLC**

A new guideline for the functional assessment of patients with resectable NSCLC has recently been published. Cardiopulmonary exercise testing receives a central role and is to be performed when the preoperative FEV1 (forced expiratory volume in one second) and/or DLCO (diffusion lung capacity for carbon monoxide) values are less than 80% of normal. When this test results in a predicted post-operative VO<sub>2</sub>max (maximal oxygen consumption) of less than 10mL/kg/min, surgery is contraindicated. This guideline reinforces the central role of the pulmonologist or respiratory oncologist in potentially curative approaches of NSCLC.

In relation to adjuvant and neo-adjuvant chemotherapy in early stage NSCLC, the highest level of evidence is in favour of adjuvant cisplatin-based chemotherapy, with improvements of overall and disease-free survival recently confirmed in long-term observations. The benefit of adjuvant chemotherapy is most important in stages II-III A and for PS 0-1 patients, but benefit has also been demonstrated in some patients with stage IB (tumor  $\geq$  4cm). Current trials are investigating the role of pharmacogenomics driven adjuvant therapy. Some factors, such as population impact, compliance and time-to-chemotherapy, seem to be favourably influenced by a neo-adjuvant approach, but a large-scale direct comparison of the neo-adjuvant versus the adjuvant approach is not available.

### **Session IV: New agents**

Agents against type-1 insulin-like growth factor receptor (IGFR1) are under investigation. IGFR1 is an ubiquitously expressed transmembrane receptor tyrosine kinase with a key role in regulating cell proliferation and apoptosis. IGFR1 is particularly important squamous cell NSCLC. Consequently, this pathway seems to be attractive for the development of new drugs.

Mitochondria are implied in the regulation of apoptosis via death receptors and BAX/BCL2 proteins. Apoptotic agents acting on this mitochondrial pathway are an other clinical research strategy in NSCLC.

Histone deacetylases (HDACs) are implied in cancer by modulating histone proteins involved in oncogenesis. The HDAC inhibitor vorinostat induced disease stabilization NSCLC patients. Phase II studies combining vorinostat and chemotherapy are promising.

Poly ADP-ribose polymerase (PARP) is activated in response to DNA damage, facilitates DNA repair, and is therefore associated with resistance to DNA-damaging agents like cisplatin. As PARP-1 is overexpressed in NSCLC, PARP inhibitors are promising for further development.

Another attractive strategy to combat cancer is vaccination. With this approach, the immune system of the patient is primed to recognize tumor cells as noxious to the patient. Recent vaccination strategies are including well defined antigens with strong adjuvant agents, and are studied in well defined populations. These studies show better antigen recognition, better immune effector cell activation and better estimation of clinical potential, with low toxicity. Several agents are in phase III testing.

### **Session V: Radiotherapy**

Progress in radiotherapy for locally advanced NSCLC in recent years is based on an increase of total irradiation dose, more precise definition of radiation volume, and timing of chemotherapy and radiotherapy. For fit patients concurrent chemoradiotherapy is the preferred approach in case of curative intent. Better identification of the target volume beside more optimal radiation delivery taking in account tumour motion is still needed.

Radiotherapy also has an important role in the palliative setting. It can be considered for locally advanced disease or thoracic symptoms from the intrathoracic component of metastatic disease. It can also be administered for the prevention of symptoms (prophylactic palliation). If the intent of palliation is durable symptom relief, there is evidence that higher doses of palliative thoracic RT are significantly better than lower doses for improvement of Total Symptom Score and overall survival. In patients where short term palliation is needed – fast symptom relief with minimal toxicity and inconvenience – a short course of palliative thoracic radiotherapy is preferred.

Prophylactic cranial irradiation (PCI) in limited disease small cell lung cancer in response after chemotherapy reduces the incidence of brain metastasis and improves survival. A total dose of 25 Gy remains the standard as delivery of higher doses did not show a supplemental advantage. For patients with NSCLC treated with curative intent there is insufficient evidence to use prophylactic PCI.

### **Session VI: Advanced NSCLC**

Histologic subtyping in NSCLC has become an essential element in treatment decision. For instance, Scagliotti et al. showed that cisplatin-pemetrexed yields a better survival in first-line therapy of advanced non-squamous cell NSCLC, when compared to cisplatin-gemcitabine, while the opposite

was true for squamous cell NSCLC. Histological subtyping can increasingly be done on limited cytological samples and is not necessarily expensive. Pharmacogenomic markers have the potential of providing even more detailed criteria for treatment selection, since these markers may reveal resistance of tumours against specific cytotoxic agents.

In anti-angiogenic strategies for NSCLC, a distinction can be made between vascular endothelial growth factor (VEGF) antibodies, tyrosine kinase inhibitors blocking the VEGF receptor (VEGFR-TKIs), and vascular disrupting agents (VDAs). While several studies showed improved response rate with chemotherapy combined with the VEGF antibody bevacizumab in non-squamous NSCLC, the effect on patient outcome, in particular overall survival, was variable across studies. The role of VEGFR-TKI in 1<sup>st</sup>-line treatment is under investigation, but not particularly promising, with worrisome toxicity in patients with squamous cell tumours. Phase III data for the VDA ASA404 are pending.

Maintenance therapy is the use of further systemic therapy following 1<sup>st</sup> line treatment but before disease progression. While the historical experience with continuation of the same therapy beyond 4 to 6 cycles was disappointing, recent studies with consolidation with an other agent than the ones used in 1<sup>st</sup> line therapy are challenging. An overall survival benefit has been noted in two recent phase III studies: a 5 months overall median survival difference with pemetrexed in non-squamous histology patients and a 1 month difference with erlotinib in unselected patients. For erlotinib, most of the benefit was generated in patients with tumours harbouring EGFR activating mutations. It may well be that the benefit of consolidation therapy is a consequence of the clinical reality that approximately 30-40% of patients without maintenance strategies are unable to receive second-line therapy at the time of progressive disease.

### **Session VII: Biomarkers**

Since years, there is a growing interest in the use of biomarkers to select patients for targeted therapies. Gefitinib is a notorious example in this respect. Approval of gefitinib by the EMEA is for patients with NSCLC harbouring EGFR activating mutations in exons 19 and 21, because they strongly predict for response and progression-free survival benefits. In the lack of appropriate data, is unclear if the now wide-spread use of erlotinib should be restricted in the same perspective.

### **Session VIII: Mesothelioma**

During the last year, nothing has really changed the diagnosis, staging and treatment of malignant pleural mesothelioma (MPM).

Biomarkers (e.g. for diagnosis or response evaluation) are under investigation and not validated.

The current staging system, proposed by the International Mesothelioma Interest Group (IMIG), is outdated, and we are looking forward to a new one, hopefully as a result of the staging effort of the International Association for the Study of Lung Cancer (IASLC) by the year 2014.

For patients with MPM, adequate palliation of dyspnea and pain is a priority. Fit patients with advanced disease should receive a combination of cisplatin and pemetrexed, as this has an impact on outcome in MPM. This chemotherapy can also be considered in case of sensitive relapse. Palliative radiotherapy has its indication in pain relief in case of chest wall infiltration. Prophylactic track irradiation is often used but remains controversial for some. Selected early stage patients can be considered for radical multi-modality treatment in dedicated centres and/or in clinical trials.