

Lung Cancer: Recent Advances

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Lung cancer is the leading cause of cancer related mortality in the world. It accounts for almost a million deaths annually and resulted in more deaths than prostate, breast and colon cancers combined.¹ As majority of lung cancers are advanced or metastatic at presentation, current therapies that include surgical resection, platinum-based doublet chemotherapy and radiation therapy alone or in combination are rarely curative, and an overall 5-year survival remains dismal at 16%.¹

Eighty-five percent of lung cancers are caused by tobacco smoke, and there are 2 major histological subtypes: small cell lung cancer (SCLC) (15%) and non-small cell lung cancer (NSCLC) (85%) of which adenocarcinoma is the most common followed by squamous-cell and large cell carcinomas. Progress with tobacco control programmes in the developed world are offset by growing tobacco promotion and usage in the developing world, moreover benefits derived from improved cardiovascular outcomes due to smoking cessation are undercut by the long-term carcinogenic consequence of tobacco exposure. Nearly half of all lung cancers are now diagnosed in former smokers.² Thus, identifying former smokers at risk of lung cancers with biomarkers as well as detecting lung cancer at an early stage remain important priorities that are central to considerable research. Discovery of new drugs compatible with molecular phenotypes of lung cancer that allows targeted therapy with minimal side-effects and improved survival lends promise in the treatment of advanced lung cancer.^{3,4}

A computed tomography (CT) screening trial has demonstrated effectiveness in detecting peripheral lung cancers at early stage. When these were surgically treated led to a 10-year survival in excess of 90%.⁵ However, the question remains if CT is the tool that changes lung cancer mortality outcomes, and recently a large scale randomised controlled trial confirmed in its preliminary analysis that timely treatment of CT detected asymptomatic peripheral lung cancers resulted in 20% reduction in cancer mortality.⁶ In contrast to the peripheral airways and lung parenchyma where most adenocarcinomas arise, squamous cell carcinomas arise in the central airways which can be radiographically occult. However, changes in the

bronchial epithelium in the central airways are accessible to bronchoscopy and autofluorescence bronchoscopy that induces tissue fluorescence by means of blue light illumination is a sensitive tool for the identification of these pre-invasive lesions (dysplasia and carcinoma-in-situ). These early lesions are then amenable for lung sparing interventions such as photodynamic therapy, bronchoscopic electrocautery, cryotherapy and brachytherapy.⁷

Molecular genetic studies of lung cancer show that clinically overt lung cancers harbour multiple genetic and epigenetic alterations,⁸ that are shared with pre-invasive lesions and histologically normal bronchial epithelium therein suggesting that lung cancer develops through a multi-step process coincident with cigarette smoking. Differences in clinical outcomes and responses to treatment are attributed to tumor heterogeneity, and molecular signatures have been identified as independent predictors of outcome with greater accuracy than conventional tumour, node, metastases (TNM) staging.^{9,10} Research into molecular markers with the goal of personalising therapy in patients with advanced lung cancer have led to the discovery of vascular endothelial growth (VEGF) and epidermal growth factor receptors (EGFR), and drugs targeting these molecular changes are being developed and tested for clinical use.⁴ The advantage of targeted therapy is the drug specificity for altered molecules within the lung cancer cells, and spares the normal cells, monoclonal anti-VEGF antibody bevacizumab (Avastin) and EGFR tyrosine kinase inhibitor (Tarceva) are examples that have demonstrated significant impact on patient survival.^{11,12} In addition, gene expression signatures to predict response to cisplatin and pemetrexed have been developed in-vitro, which require validation in clinical studies.¹³ For molecular profiling, tumour tissue is required, and the last decade has witnessed major advances in bronchoscopic techniques for targeting primary lung cancer and mediastinal staging. Navigation bronchoscopy that maps out the route to the primary lung cancer akin to GPS,^{14,15} and the incorporation of endobronchial ultrasound that allows real-time biopsy of lymph nodes for more accurate mediastinal staging^{15,16} have proffered tissue specimens that further enhance our understanding of tumour heterogeneity and behaviour at the

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primary and metastatic sites.¹⁷ Novel techniques of capturing circulating tumour cells in the blood for molecular genetic profiling may usher a new era of non-invasive testing that potentially allows personalised cancer prescription, disease monitoring and prognostication.¹⁸

In lung cancer therapeutics, discovery of EGFR has led to personalised therapy where EGFR tyrosine kinase inhibitors (EGFR-TKI) are found to be effective against NSCLC that harbour EGFR mutations (24%). These mutations (deletions, insertions and missense point mutations) are limited to the first 4 exons of the TK domain, and deletions in exon 19 (44%) as well as missense mutations in exon 21 (41%) account for more than 80% of all EGFR mutations.^{3,4} Presence of these mutations not only correlates with tumour drug sensitivity, they also tend to occur in adenocarcinoma histology, never smoker, East Asian and female gender.¹⁹

Most patients who experience initial response to EGFR-TKI (erlotinib, gefitinib) will suffer relapse,^{20,21} and studies have identified EGFR T790M mutations (in exon 20) to be causative. Irreversible EGFR-TKIs that also suppress T790M mutant tumour cells in-vitro may represent a promising drug.²² Several trials have evaluated EGFR-TKIs as monotherapy or in combination with conventional chemotherapy. Monotherapy with erlotinib has prolonged the survival of previously treated NSCLC by 2 months¹² but gefitinib has not, and this contrast may be related to a lower dosage of gefitinib used.²³ EGFR-TKI combined with conventional chemotherapy has not resulted in survival benefit,^{24,25} and strategies to better integrate EGFR TKIs with chemotherapy as well as combining drugs targeting at different molecular pathways should be explored. The most common adverse effect of EGFR-TKIs (erlotinib and gefitinib) is rash and a correlation between rash and response/survival is observed thereby promoting the presence of rash as a surrogate marker for response and prognosis marker. Other side effects include diarrhoea which can be controlled by loperamide, and interstitial lung disease (ILD) that tends to occur more frequently in East Asians. The male gender, smoking history and presence of interstitial pneumonia prior to EGFR-TKI are postulated predictors for EGFR-TKI induced ILD.²⁶

VEGF is another molecular marker that deserves mention as it plays a critical role in angiogenesis pivotal for tumour growth and metastasis.²⁷ Bevacizumab is a monoclonal antibody that neutralises VEGF, and when added to chemotherapy regimens for advanced non-squamous NSCLC has led to significant survival advantage.²⁸ An adverse effect observed is fatal pulmonary haemorrhage when bevacizumab is used for squamous cell carcinoma affecting the central airway, thus careful patient selection and monitoring is crucial when this drug is used.

November is lung cancer awareness month, year 2010 and

beyond spells an exciting time for physicians and researchers interested in lung cancer. As our understanding of tumour biology and pathways continues to increase exponentially, advances in imaging and optical technologies to facilitate early detection and intervention, rapid development of targeted therapeutics and robust smoking cessation programmes, these interventions herald hope for cure and possibly eradication of lung cancer in the future. Let's make lung cancer history!

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