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Molecular diagnostics and targeted therapy in non-small-cell lung cancer

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In Ireland, lung cancer is responsible for approximately 11 per cent of all cancers, excluding non-melanoma skin cancer, and represents the fourth most common cause of malignancy after prostate, breast and colorectal cancers. Lung cancer remains the leading cause of cancer-related mortality worldwide, responsible for approximately 1.6 million deaths annually. The most recent data from Ireland states lung cancer is responsible for 18 per cent of cancer deaths in women and 22 per cent of cancer deaths in men. The poor prognosis observed in these patients is largely due to the aggressive nature of the disease, but other factors such as advanced age and stage at diagnosis contribute.

These malignancies may be broadly classified into two groups: small-cell lung cancer (SCLC), which represents approximately 10-15 per cent of all lung cancers, and non-small-cell lung cancer (NSCLC), which accounts for approximately 85 per cent of cases. NSCLC can be further divided into several distinct histological subtypes, and differentiation is important as it has prognostic and therapeutic implications. Adenocarcinomas comprise approximately 40 per cent of NSCLCs, most commonly observed in light or non-smokers and tend to arise on the periphery of the lung. Other subtypes include squamous cell lung cancer, which displays a strong correlation with smoking and large-cell carcinoma.

While efforts to advance treatment strategies in SCLC have until very recently largely been frustrating, there have been enormous breakthroughs in NSCLC therapeutics in recent years. Advances in translational research have increased our understanding of the molecular pathogenesis of these malignancies and have had a major impact on the diagnosis and management of these tumours. It is now widely accepted that the aforementioned subtypes of NSCLC may possess unique molecular signatures, or genetic alterations, that provide a target for personalised treatment. International guidelines now recommend screening for these predictive and prognostic biomarkers at diagnosis.

Genetic or driver mutations in the epidermal growth factor receptor (EGFR) are the most explored oncogenic events associated with NSCLC. EGFR is a transmembrane protein involved in cell growth and proliferation. Mutations and overexpression of this protein play a pivotal role in the pathogenesis of NSCLC. Approximately 15 per cent of patients diagnosed with primary lung adenocarcinoma harbour EGFR mutations. It is more commonly observed in non-smokers and it has been postulated that the presence of these mutations may also be race-dependent, with one study estimating that while 10 per cent of Caucasians may have the mutation, it can be found in up to 50 per cent of Asians. Oral tyrosine kinase inhibitors (TKIs) of EGFR, such as erlotinib and gefitinib, target the EGFR receptor and interfere with its activation. Multiple randomised controlled trials comparing first-line EGFR agents against standard chemotherapy regimens have reported a superior objective response rate, progression-free survival and quality-of-life in favour of these novel agents. Thus, upfront analysis of tumour specimens for predictive biomarkers is now recommended and if an activating EGFR mutation is detected, then EGFR TKIs are advocated as first-line therapy.

A subsequently identified and well-recognised oncogenic driver mutation in NSCLC involves the anaplastic lymphoma kinase (ALK) gene, found in approximately three to seven per cent of patients. As with EGFR, ALK gene rearrangements may be observed in specific populations: younger patients and non-smokers. The presence of EML4-ALK fusion is associated with resistance to EGFR TKIs; however, crizotinib, an ALK Inhibitor, gained FDA approval for use in these patients in 2011 based on Phase I/II studies demonstrating impressive response rates.

Possibly the most famous therapeutic advance in lung cancer that has garnered tremendous interest and excitement in recent years has been the development of immunotherapy as a viable and effective cancer treatment strategy. The concept of restoring the host's natural defence mechanisms and activating the immune system to specifically target cancer cells has been met with great enthusiasm and it has produced impressive results across multiple tumour sites (including NSCLC) in the clinical arena. By harnessing the exquisite specificity, potency and memory of our immune system to seek out and destroy cancer cells, immunomodulatory agents have demonstrated efficacy not only in lung cancer but also in an increasingly wide range of malignancies and their development continues at a breathtaking pace. The clinical validation of monoclonal antibody blocking of cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) has been particularly impressive and are now outperforming conventional chemotherapy regimens.

These agents first gained acceptance in the clinical domain after their success in advanced non-BRAF-mutated malignant melanoma, a disease historically associated with a grim prognosis largely due to a lack of efficacious treatment options. The introduction of immunotherapeutic agents as a novel treatment modality for these patients has resulted in unprecedented survival rates and has revolutionised how we now approach and manage these malignancies. This success led to the exploration of their use in other cancer types, and they now dominate clinical investigation in NSCLC.

In 2015 nivolumab was approved by the US Food and Drug Administration (FDA) for treatment in patients with advanced NSCLC progressing after platinum-based chemotherapy treatment. By binding to and blocking the PD-1 receptor, nivolumab prevents any interaction with its ligand PD-L1, thus reversing tumour-induced suppression of tumour-specific T-cells. In the
CHECKMATE 057 trial, a randomised Phase III trial involving 582 patients, nivolumab was compared to the standard of care at that time, docetaxel. The study favoured nivolumab in response rate (40 per cent vs 12 per cent) as well as median overall survival (12.2 months vs 9.4 months). Nivolumab was also associated with a more favourable toxicity profile.

Similarly, pembrolizumab is a fully human IgG4 programmed cell death 1 (PD-1) immune checkpoint inhibitor antibody that disrupts PD-1-mediated signalling by binding to the PD-1 receptor. Pembrolizumab has recently been approved as a first-line agent in patients with advanced NSCLC and PD-L1 expression on at least 50 per cent of tumour cells. PD-L1 is another molecular marker that should be tested for at diagnosis, as it identifies the patients with an enhanced likelihood of a response. The field of immunotherapy in lung cancer remains an active area of research.

Current immunotherapy lung cancer trials in Ireland are listed below and more information can be found at Cancer Trials Ireland’s website, which lists cancer trials open in Ireland www.cancertrials.ie.

- BMS CA209-172: A single arm, open-label, multicentre clinical trial with nivolumab monotherapy in subjects with advanced or metastatic squamous NSCLC who have received at least one prior systemic regimen for the treatment of stage IIIb/IV SqNSCLC. Open at St James’s Hospital and University Hospital Galway

- BMS 209-451: A randomised, multicentre, double-blind, Phase 3 study of nivolumab, nivolumab in combination with ipilimumab, or placebo as maintenance therapy in subjects with extensive-stage disease small-cell lung cancer (ED-SCLC) after completion of platinum-based first-line chemotherapy. Open at Tallaght Hospital, Cork University Hospital, St Vincent’s Private Hospital and University Hospital Galway

- HORT 2416 (PEARS): A randomised, Phase III trial with anti-PD-1 monoclonal antibody pembrolizumab versus placebo for patients with early stage NSCLC after resection and completion of standard adjuvant therapy. Open at Mater Misericordiae University Hospital, University Hospital Limerick, St Vincent’s University Hospital, University Hospital Waterford, St James’s Hospital and Cork University Hospital

Thus when approaching a patient with newly-diagnosed NSCLC, key factors that influence treatment decisions include not only the extent of disease, histological diagnosis and performance status, but also the presence or absence of a driver mutation, such as EGFR or ALK, and the presence of a high level of PD-L1 expression.

Traditionally tissue biopsy is the gold standard diagnostic procedure for any tumour. Obtaining adequate tissue material not only for histological diagnosis, but also for genotyping as demonstrated by the examples above in NSCLC remains paramount to identify these targeted mutations and allow for individualised treatment decisions. This approach, however, has several limitations. It has been previously reported that EGFR genetic testing was not being conducted in 19 per cent of advanced NSCLC cases, largely due to insufficient sampling and long turnaround time. In addition mutation test results were not available before the treatment decision was taken in 23 per cent of tested patients.

A liquid biopsy, or blood sample, is a novel approach that has become an increasingly appealing diagnostic tool in translational cancer research. Blood sampling is minimally invasive, less time consuming and can be easily repeated, and the first liquid biopsy test was approved by the FDA last year. By isolating circulating tumour cells (CTCs) and their DNA (circulating-free tumour DNA (cfDNA)), which are released by the primary tumour mass, this sample can provide information relating to the complete genetic landscape of a tumour, which may not always be possible with single-site tissue biopsies due to intratumour heterogeneity. It also represents an alternative method to detect mutations in patients where a tissue biopsy is not feasible. Furthermore, it offers the opportunity to monitor treatment response in real time as the amount of circulating tumour DNA (ctDNA) has been shown to correlate with tumour burden, and can thus offer early insights into the development of resistance.

With respect to current therapeutic relevance for liquid biopsy in NSCLC, recent advances pertaining to EGFR liquid biopsy are currently transitioning through clinical investigation to standard-of-care clinical practice. Despite good initial responses, all NSCLC patients harboring the aforementioned EGFR mutations eventually acquire resistance to EGFR-TKIs. In 40-60 per cent of these cases, this resistance is due to an amino acid substitution where methionine substitutes for threonine at position 790, referred to as T790M mutation. Tumour relapse is often witnessed in these patients as detection of this mutation has further therapeutic implications. Third-generation EGFR inhibitors, such as osimertinib, are capable of overcoming this T790M-associated resistance, are clinically effective and well-tolerated and have been recommended for use in these patients. Recent research, however, has shown that these mutations can be detected by analysis of cfDNA, negating the need for another invasive biopsy. Furthermore, current clinical trials, such as the TACEX trial in the UK, aim to record the evolution of the tumour using liquid biopsies, correlating tumour clonal heterogeneity with clinical outcomes (ClinicalTrials.gov Identifier: NCT02838601).

The role of liquid biopsies has also been studied with regards to the early detection and screening of lung cancer in high risk patients. Irie et al (2014) examined the presence of CTCs in combination with CT imaging in chronic obstructive pulmonary disease (COPD) patients without clinically detectable lung cancer. CTCs were able to be detected in patients with COPD and monitoring CTC-positive COPD patients allowed for earlier diagnosis of lung cancer.

It is evident molecular profiling in NSCLC has dramatically altered the treatment paradigm of the disease and enabled a more personalised approach due to the identification of unique molecular biomarkers. The welcome introduction of a less invasive and more readily accessible diagnostic test, such as the liquid biopsy, into the arena of cancer diagnostics and therapeutics has the potential to provide a valuable tool for screening and early detection of cancer, real-time monitoring of therapy and identification of resistance mechanisms.

This molecularly-based approach, along with ongoing developments in our understanding and manipulation of cancer immunotherapy heralds a new era in cancer research and will aid oncologists in developing tailored treatment strategies with the ultimate aim of optimising patient outcomes.

References available on request