Tailored therapy in lung cancer

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Historically, all non-small cell lung cancers were essentially grouped together and considered to be a single disease. However, it is now recognized that non-small cell lung cancer actually comprises a genetically diverse group of tumours. This, in turn, affords a new opportunity for the development of effective treatments tailored to individual tumours and patients. Advances in molecular biology have made possible the development of drugs against specific molecular targets on cancer cells, most notably the tyrosine kinase inhibitors. The relevant literature and current practice guidelines are discussed. In addition, other related areas of active investigation, including tumour vaccines and pharmacogenetics, are briefly reviewed.

Key Words: Biomarkers; Lung cancer; Targeted therapy

Historically, although several histological subtypes have been recognized, non-small cell lung cancers (NSCLC) were essentially grouped together and considered to be a single disease. Advances in molecular biology, however, have shown that NSCLC actually comprises a genetically diverse group of tumours. Furthermore, molecular analysis has enabled the characterization of individual tumours as well as identification of potential molecular targets for targeted drug therapy (1-3).

MOLECULAR TARGETS IN NSCLC

Epidermal growth factor receptor

The epidermal growth factor receptor (EGFR) is a tyrosine kinase transmembrane receptor that activates a crucial pathway regulating cell proliferation. The EGFR is frequently upregulated in NSCLC but may also be mutated. Most EGFR mutations involve two specific mutations in exons 19 and 21, and are more frequent in adenocarcinoma, Asians, and light or never-smokers (approximately 15% of lung cancers in Canada) (1-3).

The principle means of blocking the EGFR is using tyrosine kinase receptor inhibitors (TKIs; gefitinib, erlotinib, afatinib). Several trials have evaluated the efficacy of TKIs as first-line therapy in advanced NSCLC. Two of the first are the IRESSA Pan-Asia Study (IPASS) trial and the First-Line Single-Agent Iressa Versus Gemcitabine and Cisplatin (FIRST-SIGNAL) trial (4,5). Importantly, both trials selected patients based on clinical characteristics alone rather than molecular analysis of the EGFR, and tested gefitinib against platinum-based chemotherapy. Both trials showed a statistically significant improvement in progression-free survival (PFS), although the overall survival was unchanged (ranging from 18 to 22 months). Subsequent trials have selected patients based on molecular analysis showing an EGFR mutation and have been highly consistent in showing a statistically significant improvement in PFS, ranging from three to nine months when compared with standard platinum-based chemotherapy regimens (likelihood of tumour progression HR ranging from 0.16 to 0.49) (6-8). However, it is important to point out that most of these trials also failed to show an improvement in overall survival, a result that may be due, in part, to the high crossover rate between treatment modalities. Studies of TKIs as second-line therapy in metastatic disease reported similar outcomes (9-11). In contrast, TKIs used in combination, either with other TKIs or with chemotherapy, did not provide any added benefit (12-15).

Un traitement personnalisé du cancer du poumon

Par le passé, tous les cancers pulmonaires non à petites cellules étaient essentiellement regroupés et considérés comme une seule maladie. On sait désormais que ce type de cancer se compose d'un groupe de tumeurs diversifié sur le plan génétique. Cette découverte ouvre de nouvelles possibilités pour élaborer des traitements efficaces adaptés à chaque tumeur et à chaque patient. Les progrès en biologie moléculaire permettent d'élaborer des médicaments visant certaines cibles moléculaires situées sur les cellules cancéreuses, notamment les inhibiteurs des tyrosines kinases. Les publications pertinentes et les lignes de pratique à jour sont abordées. En outre, des domaines connexes de recherche active, y compris les vaccins contre les tumeurs et la pharmacogénétique, font l'objet d'un bref aperçu.

Importantly, an analysis of IPASS participants clearly demonstrated the importance of EGFR status on treatment response. Patients with a positive EGFR had a significantly reduced risk of tumour progression or death (HR 0.48; $P < 0.001$) whereas in EGFR-negative patients the risk was increased (HR 2.85; $P < 0.001$); overall, these findings had a major effect on practice, and have led the American Society of Clinical Oncology to recommend testing all patients with advanced disease for a mutant EGFR to offer TKIs as first-line therapy (16).

Encouraging results in advanced disease logically led to the evaluation of TKIs in the adjuvant and neoadjuvant settings. Two phase 3 studies did not find an advantage to TKIs as adjuvant therapy and, in fact, showed a trend toward decreased survival (3). The methodology of these initial studies has been questioned and several randomized controlled trials are currently attempting to resolve this issue.

Echinoderm microtubule-associated protein-like 4 and anaplastic lymphoma kinase fusion gene

A second important molecular target in NSCLC is the echinoderm microtubule-associated protein-like 4 (EML4) and anaplastic lymphoma kinase (ALK) fusion gene (EML4-ALK). The EML4-ALK gene rearrangement acts as an oncogene and is present in 5% to 7% of lung adenocarcinomas; rates are much higher in younger patients, and in light or never-smokers. Crizotinib is a potent and selective oral inhibitor of ALK. Published data from the three crizotinib trials to date show consistently impressive responses and PFS (seven to nine months) in patients with advanced ALK-positive NSCLC (17-19). Crizotinib was generally well tolerated, with patients mostly experiencing grade 1 or 2 adverse effects (visual disturbances, gastrointestinal disorders). Multiple guidelines state that EML4-ALK testing should be performed in all patients with NSCLC with an adenocarcinoma component, and crizotinib offered to those who test positive (20,21).

Vascular endothelial growth factor

Vascular endothelial growth factor is overexpressed in most human cancers and is generally associated with more aggressive tumour behaviour. Bevacuzimab is a monoclonal antibody that targets vascular endothelial growth factor and, when combined with chemotherapy, was associated with increases in overall survival and PFS in NSCLC in two large phase 3 trials (22,23), although the absolute increases were <2 months. This benefit is limited to nonsquamous

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NSCLC because bevacuzimab has been associated with pulmonary hemorrhage in squamous cell lung cancer.

For now, only drugs targeting the EGFR and *EML4-ALK* have found their way into clinical practice; however, other potential molecular targets are being investigated. In effect, most current research in advanced lung cancer therapy is focusing on such targets. In addition, the recognition of resistance mechanisms to available molecules is the focus of further study.

TUMOUR VACCINES

The principle of tumour vaccines is to stimulate the development of immunity to specific tumour components. Various techniques have been developed for the harvest and delivery of such component molecules to achieve optimal stimulation of the immune system (24). MAGE-3 and MUC-1 are examples of candidate molecules that have been singled out as being potentially significant. Several phase 3 studies evaluating the efficacy of tumour vaccines in NSCLC are currently underway, both in advanced disease and in the adjuvant setting (24,25).

PHARMACOGENETICS

Although not an analysis of molecular targets per se, pharmacogenetic profiling of tumours may enable customized conventional chemotherapy by choosing a regimen tailored to specific tumour characteristics to increase efficacy and maximize synergy between individual drugs. Several genetic markers have been identified as a way to predict responses to various chemotherapeutic agents including platinum compounds (ERCC1), gemcitabine (RRM1), pemetrexed (TYMS) and taxanes (25). Unfortunately, study results to date have been conflicting and such an approach has yet to be adopted into routine practice.

CONCLUSION

Following the present brief discussion, it is important to recognize that the development of targeted therapy in NSCLC is the direct result of an evolution of our understanding of lung cancer: we now recognize that NSCLC is not one uniform disease but rather comprises a genetically diverse group of tumours. This, in turn, affords a new opportunity to develop effective treatments tailored to individual tumours and patients. The development of molecular agents targeting mutant EGFR and ALK has significantly affected practice, and both of these are now routinely tested for in most specialized centres. Although the impact on survival remains small and often limited to subpopulations of patients, targeted therapy in lung cancer has clearly shown the potential to positively affect oncological outcomes and improve quality of life with minimal toxicity. Future research is key and will, no doubt, focus on the identification of new, broader targets and the development of novel therapeutic agents, conceivably incorporating them into multidrug combinations to increase their efficacy.

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