Targeted Therapy for Non-small Cell Lung Cancer

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Introduction

Lung cancer, predominantly non-small cell carcinoma (NSCLC), has remained the top cancer killer in Hong Kong, with more than 4,000 new cases every year and the 5-year survival around 15% only. The poor prognosis is mainly due to rather late presentation with metastatic diseases in the majority and the propensity of occult distant metastases even for early resectable stages. Systemic platinum-based chemotherapy has been the cornerstone treatment for advanced diseases over the past two decades. Because of the non-specific killing of rapidly proliferating cells, systemic chemotherapy is notoriously associated with a wide spectrum of adverse effects, often limiting the use in elderly subjects with multiple co-morbidities and poor performance status. At the turn of the century, with better understanding of lung cancer biology, the concept of targeted therapy has emerged from bench to bedside, with more specific killing of cancer cells. The most promising targeted approaches include anti-angiogenesis, anti-epidermal growth factor receptor (EGFR), and more recently the inhibition of anaplastic lymphoma kinase (ALK). This review serves to highlight the important advances in targeted therapy for NSCLC.

Anti-angiogenesis

In general, malignant tumours cannot grow beyond 2mm in size without developing a vascular supply. Angiogenesis, whether physiological or pathological, is controlled by the balance between proangiogenic and antiangiogenic factors. The most important proangiogenic factor involved in tumour angiogenesis is the vascular endothelial growth factor (VEGF), which has become the target for antiangiogenic therapy in NSCLC. The VEGF pathway can be inhibited by agents that target VEGF or VEGF receptors. In particular, bevacizumab is an anti-VEGF recombinant humanised monoclonal antibody, which contains the human immunoglobulin G1 framework (93%) and murine VEGF-binding complementarity-determining regions (7%) blocking the binding of VEGF to its receptors and subsequent downstream biologic activities. A randomised phase II study of bevacizumab in combination with carboplatin and paclitaxel or same chemotherapy alone as first-line treatment in patients with stage IIIB or IV NSCLC has demonstrated superior response rate, time to progression and survival in the bevacizumab combination arm, with increased risk of life-threatening haemoptysis in squamous cell carcinoma.

In view of these promising results, a recent randomised phase III study (E4599) was conducted comparing the combination of bevacizumab with chemotherapy (carboplatin and paclitaxel) versus chemotherapy alone in the treatment of advanced chemo naive non-squamous NSCLC. There was a statistically significant survival advantage that favoured the bevacizumab combination arm (median survival 12.3 months vs 10.3 months in bevacizumab vs chemotherapy alone arms, hazard ratio for death 0.79, p=0.003). The major reported toxicities in bevacizumab versus chemotherapy alone arms were grade 3/4 neutropenia (25.5% vs 16.8%), grade 3/4 hypertension (7% vs 0.7%), grade 3/4 proteinuria (3.1% vs 0%) and grade 3/4 haemorrhage (4.4% vs 0.7%). Out of the 17 treatment-related deaths, 15 were in bevacizumab arm and 2 in chemotherapy alone arm, in which the 5 deaths related to haemoptysis were exclusively from the bevacizumab arm. This is the first landmark study to demonstrate superiority in combination of targeted therapy and chemotherapy compared to chemotherapy alone (standard-of-care) in the first-line treatment of patients with advanced NSCLC. In addition, another similar study has been conducted with the combination of bevacizumab and gemcitabine and cisplatin in advanced NSCLC (AVAil study), with favourable progression-free survival in the bevacizumab arm compared to chemotherapy alone arm.

Anti-epidermal Growth Factor Receptor (EGFR)

With advancement in molecular research, it becomes logical to target specific and crucial pathways involved in carcinogenesis to achieve better control of tumour growth while minimising the detrimental effects on normal body tissues. This concept of molecularly targeted therapy has been best exemplified by the inhibition of EGFR pathway in the treatment of NSCLC. The EGFR forms part of the signalling pathway that regulates tumour cell proliferation, invasion, angiogenesis, metastasis, and apoptosis. Since overexpression of EGFR is commonly found in NSCLC, various novel agents that inhibit EGFR pathway have been developed for treatment of this neoplasm. Apart from the use of monoclonal antibody that targets the EGFR extracellular binding site, small molecules that
target the intracellular adenosine triphosphate (ATP) binding site of EGFR tyrosine kinase have been studied extensively.

Gefitinib (or Iressa) was the first EGFR tyrosine kinase inhibitor (TKI) used in the treatment of advanced NSCLC. Previous large-scale phase III trials (INTACT 1 and 2) failed to show clinical benefit by combining gefitinib with platinum-based chemotherapy in first-line treatment of advanced NSCLC. It was based on two large phase II trials (IDEAL 1 and 2) of gefitinib monotherapy in previously treated patients with advanced NSCLC that it was approved as second-line treatment. From these trials, the objective response rate was up to 18% with encouraging median survival of 7-8 months, without the inclusion of a placebo arm. The most common toxicities were skin rash and diarrhoea, with rare occurrence of interstitial pneumonitis. Later a randomised, placebo-controlled, phase III study (ISEL) was reported on gefitinib versus placebo in treatment of advanced NSCLC who were refractory or intolerant to chemotherapy. It was shown that gefitinib (250mg daily) was not associated with significant improvement in survival compared to placebo (median survival 5.6 vs 5.1 months in gefitinib vs placebo), despite some benefits among never smokers and patients of Asian descent. The commonest toxicities were skin rash (37%) and diarrhoea (27%). On the other hand, a subsequent phase III study of gefitinib versus docetaxel as second-line treatment for advanced NSCLC (INTEREST trial) suggested similar clinical efficacy between gefitinib and docetaxel.

Erlotinib (or Tarceva) is a later developed EGFR TKI that has also been extensively studied in treatment of NSCLC. Similar to gefitinib, large-scale phase III trials (TALENT and TRIBUTE) showed no clinical benefit in adding erlotinib to standard platinum-based chemotherapy as first-line treatment of advanced NSCLC. A randomised, placebo-controlled, phase III trial of erlotinib versus placebo in treatment of advanced NSCLC after failure to previous chemotherapy was reported. The erlotinib treatment arm was found to be superior in response rate (8.9% vs 1%), progression-free survival (2.2 vs 1.8 months) and overall survival (6.7 vs 4.7 months) compared to placebo arm. The more frequent adverse effects associated with erlotinib treatment were skin rash (76% vs 17%), anorexia (69% vs 56%), stomatitis (19% vs 3%), diarrhoea (55% vs 19%), ocular toxic effect (28% vs 9%) and infection (34% vs 21%) compared to placebo.

From earlier studies of gefitinib and erlotinib in treatment of advanced NSCLC, several clinical and molecular predicting factors for response to treatment were identified. Specific mutations in the EGFR tyrosine kinase domain (exons 18-21) have been shown to be associated with treatment response, while other mutations might predict drug resistance. Interestingly, activating EGFR mutations that predict sensitivity to EGFR TKI are more prevalent among females, Asians, never smokers, and adenocarcinoma, in which these predictive clinico-epidemiological factors have previously served as the selection criteria for treatment. Undoubtedly, the more exciting development derives from the recent reports of several first-line clinical trials of EGFR TKI in NSCLC carrying activating EGFR mutations. The first of such landmark phase III clinical trial (IPASS study) was conducted to investigate the clinical efficacy of first-line gefitinib compared with standard chemotherapy (paclitaxel and carboplatin) in an epidemiologically enriched population of advanced NSCLC (adenocarcinoma, never-smokers or former light smokers, Asians). It was found that only around 60% of tumours carried EGFR mutations, despite selection based on favourable clinico-epidemiological factors predicting response to EGFR TKI. Among the subgroup of tumours with activating EGFR mutations, gefitinib demonstrated superior objective response rate (71.2% vs 47.3%) and progression-free survival (hazard ratio 0.48, 95% CI 0.36-0.64) compared with standard chemotherapy. On the contrary, among tumours without EGFR mutations, gefitinib fared worse in terms of objective response rate (1.1% vs 23.5%) and progression-free survival (hazard ratio 2.85, 95% CI 2.05-3.98) compared with standard chemotherapy. The findings were subsequently confirmed with a Japanese study comparing first-line gefitinib versus paclitaxel/carboplatin in advanced adenocarcinomas of lung carrying EGFR mutations. Recently, the preliminary findings of a first-line study comparing erlotinib with standard chemotherapy (gemcitabine and carboplatin) in NSCLC with EGFR mutations (OPTIMA study) were also reported with very promising improvement in progression-free survival in the erlotinib arm. Based on these recent confirmatory data, the need for sufficient tumour tissues at diagnosis for EGFR mutation testing has been widely recognised and the first-line treatment with EGFR TKI in advanced NSCLC carrying activating EGFR mutations is now the standard-of-care.

Emerging Approaches of Targeted Therapy

Very similar to the evolution of EGFR targeting approach, it has been recently found that a novel oncogene (anaplastic lymphoma kinase (ALK) rearrangements, commonly EML4-ALK fusion) could account for lung carcinogenesis in around 5%. Interestingly, the occurrence of ALK rearrangements is particularly more prevalent among those with high chances of EGFR mutations (i.e. never-smokers, adenocarcinoma) and yet confirmed to be EGFR wild-type (i.e. lack of mutations). A recent phase I study has provided very promising evidence that a specific ALK inhibitor (Crizotinib) could result in significant tumour response among those NSCLC carrying the ALK rearrangements. Ongoing phase II and III clinical trials on Crizotinib are underway to establish its role in management of this subgroup of NSCLC.

As the majority of advanced NSCLC would progress shortly after completion of first-line systemic chemotherapy, the role of EGFR TKI as a maintenance treatment has recently been investigated and shown to offer survival benefits than the conventional approach (i.e. observation after completion of first-line chemotherapy). Since EGFR TKI is mostly well-tolerated even for years, this approach of maintenance therapy has recently been investigated and shown to offer survival benefits compared to standard chemotherapy.
Conclusions

The era of targeted approach in the management of advanced NSCLC has certainly begun over the past few years and the field is expected to be evolving rapidly in the near future. Lung cancer is no longer considered a homogeneous disease. Despite the traditional classification based on histology, there is increasing clinical demand of tumour molecular profiling to allow logical choice of specific targeted treatment. Second-generation targeted agents and multi-targeted agents are currently tested in clinical trials, which will help to expand the existing armamentaria in the battle against lung cancers.

References