Recent Advances in the Management of Non-Small Cell Lung Cancer

Dr. James CM Ho
MBBS MRCP FHKCP FHKAM (Medicine)
Division of Respiratory Medicine, University Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong SAR, China

Prof. Wah-kit Lam
MD FRCP FRACP FHKCP FHKAM (Medicine)
Division of Respiratory Medicine, University Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong SAR, China

Introduction

Lung cancer has become the leading cause of cancer mortality in both men and women over the past few decades, with high incidence of 1.2 million new cases yearly and a staggering annual mortality of 1.1 million deaths worldwide in 2001.1 In Hong Kong, lung cancer has remained the commonest malignancy in men and second commonest in women, (and the commonest cancer killer in both sexes), accounting for a total of 3,972 new cases and 3,403 deaths in 2003.2 The majority (>80%) of lung cancer is non-small cell carcinoma (NSCLC), which is predominantly in advanced or metastatic stages upon presentation. The high mortality is mainly ascribed to disease recurrence after curative lung resection and the lack of effective treatment for advanced disease. In the past decade, there has been encouraging progress in various aspects of lung cancer treatment (e.g., chemotherapy, molecularly-targeted therapy, radiotherapy, surgery) and staging procedures. This review serves as an update for general physicians and practitioners on the latest advances and will mainly focus on the drug treatment for NSCLC both in the early and late stages of disease, together with highlights on other treatment modalities and diagnostic procedures.

Beyond Lung Resection for Resectable NSCLC: Adjuvant Chemotherapy

The staging system of NSCLC is based on the extent of involvement of primary tumour (T), regional lymph nodes (N) and distant metastases (M).3 Early resectable stages often refer to stage I or II and selected stage IIIA with either ipsilateral microscopic mediastinal lymph node involvement or chest wall invasion. The current standard treatment for early disease is still complete surgical resection, unless medically contraindicated. However, the 5-year survival rate of resected early-stage disease is still suboptimal, mainly due to presence of micrometastases leading to subsequent recurrence in distant sites.4 Therefore the use of adjuvant chemotherapy after lung resection appears to be the logical step to improve outcome. As early as in 1995, a meta-analysis from the Non-small Cell Lung Cancer Collaborative Group already suggested a slight survival benefit, though statistically insignificant, with the use of post-operative cisplatin-based chemotherapy.5 More recently, there have been several large-scale randomized controlled trials reporting on adjuvant chemotherapy in over 3,400 patients with early-stage NSCLC.6-8 In the largest randomised controlled trial reported so far, the International Adjuvant Lung Cancer Trial (IALT),7 there were 1,867 patients with stages I to III NSCLC recruited into either postoperative chemotherapy (cisplatin combined with etoposide, vinorelbine, vinblastine, or vindesine) or no adjuvant chemotherapy. After a median follow-up of 56 months, the overall survival was significantly prolonged in the chemotherapy arm, with a 4.1% absolute survival benefit at 5 years and 14% relative reduction in risk of death (HR 0.86, 95% CI 0.76-0.98, p<0.03). This was also accompanied by an improved disease-free survival with postoperative chemotherapy (HR 0.83, 95% CI 0.74-0.94, p=0.003). A more recent study also consistently demonstrated survival benefit of adjuvant chemotherapy in patients after resection for stage IB and II NSCLC, with improved overall survival by 15%.9 The reported toxicity schedule.

Novel Agents for Treatment of Advanced or Metastatic NSCLC

Although surgery can offer the best chance of cure for lung cancer, it is unfortunately only feasible for a minority of patients, in which there is no regional involvement of mediastinal lymph nodes, pleural or pericardial malignant effusion, or distant metastases. In the presence of extensive mediastinal lymphadenopathy and locally advanced diseases, the current standard treatment is combined systemic chemotherapy and radiotherapy, either given in concurrent or sequential manner.10,11 Over the years, systemic chemotherapy has become the standard first-line treatment for those with malignant effusion or distant metastases.12 In such patients with good performance status, a combination of...
platinum (cisplatin or carboplatin) and a newer generation chemotherapeutic agent (e.g. paclitaxel, docetaxel or gemcitabine) has been demonstrated to improve overall survival, disease-free survival and quality of life compared to best supportive care alone or older generation chemotherapy combinations in the first-line setting.13 An Asian multicentre phase II study of the efficacy and safety of docetaxel plus cisplatin in patients with metastatic or locally advanced NSCLC has been performed in 12 centres in seven Asian countries/regions, and showed an overall response rate of 46.9% and 14 months median survival.14 The overall international experience, however, showed that the improvement in survival is modest (around 2 months prolongation of median survival compared to best supportive care alone) and the time to disease progression is usually within a few months since commencement of chemotherapy.15 Upon disease progression after first-line treatment, docetaxel as second-line monotherapy has been shown to have survival advantage over best supportive care alone or alternative chemotherapy,16,17 although the improvement is fairly modest at the expense of significant toxicity. Therefore there have been continued efforts looking for novel agents in treatment of advanced or metastatic NSCLC.

Anti-angiogenesis agent in combination with chemotherapy as first-line

It has long been recognised that angiogenesis, regulated by proangiogenic and antiangiogenic factors, plays a crucial role in tumour growth and development of distant metastases. One of the most important proangiogenic factors involved in tumour angiogenesis is vascular endothelial growth factor (VEGF), which serves as the main target for antiangiogenic therapy in NSCLC. Bevacizumab (Avastin®) is an anti-VEGF recombinant humanised monoclonal antibody, which blocks the binding of VEGF to its receptors and subsequent downstream biologic activities. A randomized 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, but with increased risk of life-threatening haemoptysis in squamous cell carcinoma (a sub-type of NSCLC).18

As a result, 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 naïve non-squamous NSCLC.19 Although the final analysis is still awaited, the planned interim analysis has demonstrated a statistically significant survival benefit favouring the bevacizumab combination arm (median survival 12.5 months vs 10.2 months in bevacizumab vs chemotherapy alone arms, p=0.0075). The major toxicity appeared to be related to bleeding complications, in which the 5 deaths due to haemoptysis were exclusively from bevacizumab arm.

Pemetrexed as second-line chemotherapy

With the current standard first-line chemotherapy treatment for advanced NSCLC, tumour response is expected to be transient with disease progression mostly occurring within a few months after cessation of chemotherapy.

Pemetrexed (Alimta®) is a novel multitargeted antifolate chemotherapy that has been shown to be active against NSCLC, which acts by inhibiting the three key enzymes in pyrimidine and purine synthesis. A recent randomised phase III trial comparing pemetrexed (with vitamin B12 and folate supplementation) versus docetaxel as monotherapy second-line treatment in advanced NSCLC has demonstrated similar median progression-free survival (2.9 months for each arm) and median survival (8.3 vs 7.9 months for pemetrexed vs docetaxel).20 Importantly, pemetrexed treatment was associated with significantly less severe neutropenia, febrile neutropenia, neutropenia with infections, and hospitalisations for neutropenic fever compared with docetaxel. Based on this study, pemetrexed has been widely approved as second-line treatment for advanced NSCLC, equally effective as docetaxel but with more favourable toxicity profile.

Epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI)

In recent years, the concept of molecularly targeted therapy has evolved rapidly in the management of advanced NSCLC, which is best exemplified by the inhibition of EGFR pathway. Unlike conventional cytotoxic agents leading to non-specific cell damage or death, this class of novel agent targets specifically at the critical and unique pathway involved in tumourigenesis. The EGFR forms part of the signaling 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 (Iressa®) was the first EGFR TKI used in the treatment of advanced NSCLC. Large-scale phase III trials (INTACT 1 and 2) failed to show clinical benefit by combining gefitinib with modern platinum-based first-line chemotherapy in 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, with objective response rate up to 18% and median survival of 7-8 months, that it was approved as second-line treatment.21,22 The common toxicities included skin rash and diarrhoea, with rare occurrence of interstitial pneumonitis. However, a more recently reported randomised, placebo-controlled phase III study (ISEL) of gefitinib in patients with advanced NSCLC refractory or intolerant to chemotherapy failed to demonstrate significant survival benefit compared to placebo, despite some benefit among never smokers and patients of Asian descent.23 Similarly, a later developed EGFR TKI, erlotinib (Tarceva®), has been studied in a randomised, placebo-controlled phase III trial in advanced NSCLC after failure to previous chemotherapy.24 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, which led to subsequent regulatory approval as secondary- or third-line treatment of advanced NSCLC.

Based on the recent studies of gefitinib and erlotinib in treatment of advanced NSCLC, there were several clinical and molecular predicting factors for response to treatment being identified (Table 1). 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. The exact clinical application of the mutation study is currently still under investigation.

Modern Treatment Algorithm

With the aforementioned new armamentaria in the treatment of NSCLC, a suggested treatment algorithm is shown in Table 2.

Highlights Of Other Advances

As in other solid malignancies, the prognosis of lung cancer depends heavily on staging, which is crucial in the decision of treatment modalities. Among other imaging modalities, positron emission tomography (PET) has been extremely useful in the evaluation of solitary pulmonary nodule, clinical staging of lung cancer, and perhaps subsequent monitoring of treatment response. With the evaluation of metabolic activity based on Standardised Uptake Value (SUV), preferably with the incorporation of computed tomography for accurate anatomical delineation, PET-CT allows a whole-body search of potentially occult distant metastases which can affect the overall plan of management of lung cancer.26 Endobronchial ultrasound (EBUS) is a recently emerging technique to permit access to mediastinal lymph nodes with real-time ultrasonound-guided needle aspiration via bronchoscopy, which can potentially spare some of the invasive staging procedures by mediastinoscopy.27 Video-assisted thoracoscopic surgery (VATS) is now performed in both staging and major pulmonary resections (either lobectomy or pneumonectomy) for lung cancer, which entails early postoperative recovery.28 New modes of radiotherapy, including Intensity Modulated Radiotherapy (IMRT) and tomotherapy, have also been introduced in Hong Kong, aiming at delivery of high radiation dose to the planning treatment volume (maximise efficacy) while preserving the adjacent normal tissues (minimise toxicity).29

Conclusion

Over the past few years, there has been encouraging progress in both clinical and basic research on non-small cell lung cancer, which still remains the most devastating malignancy worldwide. The future directions in treatment will undoubtedly be the development of various types of novel molecularly-targeted therapy and their combination with existing chemotherapy (concurrent or maintenance treatment) at different stages of disease. With all the advances in diagnosis, staging and treatment modalities, the overall prognosis of lung cancer may hopefully be improved in the near future.

### Table 1. Predictors for response to EGFR TKI in patients with advanced NSCLC*

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Molecular</th>
</tr>
</thead>
<tbody>
<tr>
<td>East Asian descent</td>
<td>EGFR TKI domain-sensitising mutations</td>
</tr>
<tr>
<td>Female gender</td>
<td>EGFR polymorphisms</td>
</tr>
<tr>
<td>Non-smokers</td>
<td>EGFR amplification</td>
</tr>
<tr>
<td>Adenocarcinoma histology</td>
<td>Erbb3 expression</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage</th>
<th>First-line treatment</th>
<th>Second-line treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIA-IIIA</td>
<td>Surgery + adjuvant (cisplatin-based chemotherapy (especially in younger patients with good performance status)</td>
<td>Surgery for selected metastatic stage IIA + adjuvant chemotherapy/RT Combination of cisplatin-based chemotherapy and thoracic RT for non-resectable stages (concurrent more effective than sequential)</td>
</tr>
<tr>
<td>IIB (non-effusion)</td>
<td>Options: Cisplatin-based chemotherapy (doublets) Bevacizumab combined with cisplatin-based doublet chemotherapy (non-squamous NSCLC)</td>
<td>Options: Bevacizumab, Docetaxel, Pemetrexed EGFR TKI</td>
</tr>
</tbody>
</table>

RT, radiotherapy; EGFR TKI, epidermal growth factor receptor tyrosine kinase inhibitor

### References

MCHK CME Programme Self-assessment Questions

Please read the article entitled “Recent Advances in the Management of Non-Small Cell Lung Cancer” by Dr. James CM Ho and Prof. Wah-kit Lam, and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded 1 CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or by mail to the Federation Secretariat on or before 31 January 2007. Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

Questions 1-10: Please choose the best answer.

1. Which of the following about lung cancer in Hong Kong over the past few years is/are true?
   a. >80% due to non-small cell carcinoma
   b. Around 4,000 new cases per year
   c. Top cancer killer in both men and women
   d. Majority presented with advanced or metastatic diseases
   e. All of the above

2. Based on recent randomised controlled studies on adjuvant chemotherapy post-resection for early stage non-small cell lung cancer, adjuvant cisplatin-based chemotherapy can improve 5-year survival up to:
   a. 15%
   b. 25%
   c. 35%
   d. 45%
   e. 55%

3. The current optimal treatment for medically fit patients with locally advanced (extensive mediastinal lymphadenopathy) non-small cell lung cancer is:
   a. Surgery
   b. Radiotherapy alone
   c. Chemotherapy alone
   d. Combined chemotherapy and radiotherapy
   e. Epidermal growth factor receptor tyrosine kinase inhibitor

4. The following are current standard first-line chemotherapy options for young and medically fit patients with metastatic non-small cell lung cancer except:
   a. Docetaxel and cisplatin
   b. Paclitaxel and carboplatin
   c. Pemetrexed monotherapy
   d. Gemcitabine and cisplatin
   e. Gemcitabine and carboplatin


5. The following are true about bevacizumab (Avastin™) except:
   a. A recombinant humanised monoclonal antibody
   b. An anti-angiogenesis agent
   c. Combination with platinum-based chemotherapy has shown promising improvement in survival for stage IIIB or IV non-small cell lung cancer
   d. Can be used in treatment of squamous cell lung cancer
   e. Severe life-threatening haemoptysis can occur in treatment of lung cancer

6. The following are true about pemetrexed (Alimta™) except:
   a. A multi-targeted tyrosine kinase inhibitor
   b. Currently approved in Hong Kong as second-line treatment for advanced non-small cell lung cancer
   c. Needs vitamin B12 and folate supplementation to reduce myelosuppression
   d. Similar efficacy as docetaxel in second-line treatment for advanced non-small cell lung cancer
   e. More favourable toxicity profile compared to docetaxel

7. Which of the following is/are regulated by the epidermal growth factor receptor signaling pathway in non-small cell lung cancer?
   a. Tumour cell proliferation
   b. Invasion
   c. Angiogenesis
   d. Metastasis
   e. All of the above

8. The following are true about erlotinib (Tarceva™) except:
   a. An epidermal growth factor receptor tyrosine kinase inhibitor
   b. Combination with platinum-based chemotherapy can improve survival compared to chemotherapy alone in advanced non-small cell lung cancer
   c. Approved as second-line treatment for advanced non-small cell lung cancer
   d. Common side effects include skin rash and diarrhoea
   e. Available as oral preparation

9. Which of the following are favourable factors for good response to gefitinib (Iressa™) or erlotinib (Tarceva™) in treatment of advanced non-small cell lung cancer?
   a. Asian descent
   b. Female gender
   c. Never smoker
   d. Adenocarcinoma
   e. All of the above

10. Which of the following staging investigations is based on increased “metabolic activity” of tumour cells?
    a. Computed tomography scan
    b. Positron emission tomography
    c. Endobronchial ultrasound
    d. Video-assisted thoracoscopic surgery
    e. Magnetic resonance Imaging

Recent Advances in the Management of Non-Small Cell Lung Cancer

Dr. James CM Ho  MBBS MRCP FHKCP FHKAM (Medicine)  
Prof. Wah-kit Lam  MD FRCP FRACP FHKCP FHKAM (Medicine)

Division of Respiratory Medicine, University Department of Medicine, 
The University of Hong Kong, Queen Mary Hospital, Hong Kong SAR, China

Name: __________________________ HKMA No.: __________________________
HKID No.: ________-________-________ X X (x)  Others Membership No. (please indicate): __________________________
Contact Tel No.: __________________________

Answers to December 2006 issue