Non-small cell lung cancer (NSCLC) is the most common type of lung cancer. There have been a number of treatment developments for this condition in recent years so this article focuses mainly on the treatment of NSCLC. The treatment of small cell lung cancer is discussed in Box 1 (p110).

Surgery
Surgery provides the best chance of cure for patients with stage I or stage II NSCLC. It involves removal of the tumour through resecting one or more lobes of the lung (lobectomy or bi-lobectomy) or through removal of the whole lung (pneumonectomy). The surgery is challenging and should only be undertaken in a unit with an appropriate level of expertise. The postoperative mortality rate is about 5% and patients can experience significant complications after surgery, including haemorrhage, respiratory failure, infection and arrhythmias. It is of vital importance, therefore, that patients are carefully selected and are fit for surgery. Assessment of a patient’s “performance status” is mentioned in the accompanying article (p106). Pulmonary function tests are also routinely carried out before both surgery and radical radiotherapy.

Increasingly, adjuvant chemotherapy is being given after surgery to improve survival. Cisplatin plus vinorelbine is the most commonly used regimen and has been shown to increase median survival. In one study patients who were given the combination had a median survival of 19.4 months compared to 13.6 months for patients who received only surgery. 

SUMMARY
Surgery provides the best chance of cure for patients with stage I and II non-small cell lung cancer (NSCLC). However, many patients with early NSCLC are not suitable for surgery and, for such patients, radiotherapy is the treatment of choice.

First-line treatment of patients with advanced NSCLC is usually with a chemotherapy regimen that includes one platinum-based drug plus a third-generation medicine (eg, paclitaxel). In recent years the use of targeted treatments (eg, erlotinib or gefitinib) has improved outcomes for patients with advanced NSCLC.
Radiotherapy

Radiotherapy with curative intent is the choice for patients with stage I to III NSCLC who are not suitable for surgery. Traditionally the total radiotherapy dose is calculated and the dose is then divided into smaller portions known as fractions. These fractions are given once daily over three to four weeks.

Recent research has focused on delivering the fractions more quickly in a schedule known as CHART (continuous, hyperfractionated, accelerated radiotherapy), with smaller doses of radiation given three times a day over 12 consecutive days. CHART has a small but significant survival advantage over traditional radiotherapy but has proven difficult to adopt in some European countries due to constraints on services, such as the availability of the linear accelerators required and the staff who operate them.

Chemotherapy

Platinum-based chemotherapy combinations are the standard first-line treatment for advanced NSCLC. The National Institute for Health and Clinical Excellence recommends using a combination of a single third-generation medicine (e.g., vinorelbine, gemcitabine or
docetaxel) plus a platinum-based drug (carboplatin or cisplatin). The choice of the combination will vary according to the preferences of the clinician and the treating centre. Details of commonly used regimens are outlined in Box 2. The regimens are usually given for four cycles unless there is evidence that a patient’s disease has progressed, in which case the regimen will be stopped.

Recently a large trial of a first-line combination of pemetrexed plus cisplatin was shown to offer a significantly longer survival than gemcitabine plus cisplatin (median of 12.6 months compared with 10.9 months) in patients with adenocarcinoma of the lung. This was the first time a difference had been shown in response to NSCLC chemotherapy depending on the disease histology. This led to a change in the licence of pemetrexed to reflect the higher activity in patients with non-squamous NSCLC. Pemetrexed is administered at a dose of 500mg/m\(^2\) every three weeks.

Although chemotherapy can improve symptoms, survival benefit is modest. The response rate is around 30–40% and the median survival is around 10 months. For patients who are less fit and considered unable to tolerate combination chemotherapy, single agent gemcitabine (1,200–1,250mg/m\(^2\)) or oral vinorelbine (60–80mg/m\(^2\)) can be used. If a patient’s disease progresses despite first-line treatment, he or she is assessed for suitability of second-line treatment with docetaxel or pemetrexed monotherapy.

The TAX317 study of docetaxel versus best supportive care (BSC) showed a clear survival benefit with docetaxel (75mg/m\(^2\)) — the one-year survival rate was 37% for docetaxel versus 11% for BSC. However, the response rate was low (7%) and a large proportion of patients experienced moderate-to-severe neutropenia with docetaxel. Pemetrexed has been shown to have similar efficacy to that of second-line docetaxel. Pemetrexed exhibits a slightly more favourable toxicity profile than docetaxel, but is more expensive.

**Toxicity** Management of side effects of chemotherapy is important; clinicians treating lung cancer must ensure there is a balance between toxicity and benefit. In principle, toxic therapy is not acceptable if prolongation of survival and palliation of symptoms is unlikely.

Patients receiving chemotherapy must be monitored and counselled on the risks of bone marrow suppression and neutropenia. Patients must be warned that if they develop a febrile illness, or are feeling unwell with symptoms of infection, they immediately require their full blood count and neutrophil count to be checked by their GP, hospital emergency department or oncology ward. See Box 3 (p113) for an outline of some of the supportive therapies used.

**Targeted therapies**

**Erlotinib** Erlotinib was the first targeted therapy to have a significant impact in NSCLC. It is a small molecule inhibitor of epidermal growth factor receptor (EGFR) tyrosine kinase. EGFR is part of the control mechanism of cell growth that is fundamentally deranged in cancer. EGFR overproduction is common in NSCLC and is associated with aggressive tumour cell biology, chemotherapy resistance and reduced survival.

Second- or third-line erlotinib was shown in the BR21 study to have a survival benefit comparable to that of docetaxel in the TAX317 study, but without the neutropenia and myelotoxicity associated with chemotherapy. Erlotinib was administered as a 150mg once-daily dose given until disease progression. In the BR21 study median overall survival was 4.7 months in the placebo arm compared with 6.7 months in the erlotinib arm. The percentage of patients surviving at 12 months was 22% and 31%, respectively. This two-month increase

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**Box 2: Combination chemotherapy for NSCLC**

The following are options for first-line intravenous chemotherapy treatment of advanced non-small cell lung cancer:

- **Gemcitabine plus carboplatin (21-day cycle)**
  - Gemcitabine 1,250mg/m\(^2\) on day 1 and day 8
  - Carboplatin 5 × AUC on day 1

- **Paclitaxel plus carboplatin (21-day cycle)**
  - Paclitaxel 175mg/m\(^2\) on day 1
  - Carboplatin 5 × AUC on day 1

- **Paclitaxel plus cisplatin (21-day cycle)**
  - Paclitaxel 175mg/m\(^2\) on day 1
  - Cisplatin 70mg/m\(^2\) on day 1

- **Vinorelbine plus cisplatin (21-day cycle)**
  - Vinorelbine 25–30mg/m\(^2\) (maximum 60mg) on day 1 and day 8
  - Cisplatin 60–80mg/m\(^2\) on day 1

- **Docetaxel plus cisplatin (21-day cycle)**
  - Docetaxel 75mg/m\(^2\) on day 1
  - Cisplatin 75mg/m\(^2\) on day 1

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in survival could be considered modest, but there are many anecdotal examples of a small proportion of patients having a significant and prolonged response.

The advantage of a targeted therapy in these cases is that, unlike traditional chemotherapy with cumulative bone marrow toxicity, some patients can continue to take erlotinib for a long period. Erlotinib is not free from toxicity — the adverse effect profile of the EGFR inhibitors is different from traditional chemotherapy — with patients prone to diarrhoea and severe skin reactions.

Early results from a study on the use of erlotinib for patients with EGFR mutations are promising. The OPTIMAL study compared first-line erlotinib with combination chemotherapy using gemcitabine and carboplatin. Preliminary findings show a response rate of about 84% with erlotinib versus about 37% with chemotherapy. The progression-free survival with erlotinib was reported to be 13.1 months, compared with 4.6 months for chemotherapy. The full trial results are needed to confirm these findings.

Gefitinib Gefitinib is another EGFR inhibitor that has been under investigation for several years, but early trials yielded poor results, which slowed the development of the drug. More recently, when used in trials that specifically identified patients with EGFR-TK mutations, the benefit of gefitinib has become clear. The "Iressa pan-Asia study" (IPASS) investigated patients with lung adenocarcinoma who had never smoked or were very light smokers. The trial showed that, in the subgroup of patients with an EGFR-TK mutation, the median progression-free survival with gefitinib was 9.5 months versus 6.3 months for those treated with paclitaxel plus carboplatin. The objective
tumour response rate was higher for gefitinib (71.2% versus 47.3%). However, there was no statistically significant difference in the estimates of overall survival between groups and gefitinib was shown to be inferior, compared with carboplatin plus gemcitabine, for patients without the EGFR-TK mutation.

There has been some debate over the applicability of the IPASS trial to a western population since the evidence for clinical effectiveness was derived mainly from a trial of gefitinib in east-Asian women who were non-smokers and had tumours with adenocarcinoma histology. Nonetheless, it is likely that the efficacy of gefitinib depends on the EGFR-TK mutation status of the patient, and that EGFR-TK mutation-positive patients are likely to respond to gefitinib irrespective of their gender, ethnicity, smoking status or the histology of their tumour.

**Bevacizumab** Another targeted therapy is bevacizumab, which is licensed to be given in addition to platinum-based chemotherapy for the first-line treatment of patients with locally advanced metastatic or recurrent non-squamous NSCLC. Data from two large studies (ECOG 4599 and AVAiL)\(^{26,27}\) showed a small survival advantage when bevacizumab was added to standard combination chemotherapy. The ECOG study showed a median overall survival of 12.3 months in patients taking bevacizumab plus paclitaxel and carboplatin compared with 10.3 months for chemotherapy alone.\(^{26}\) However, the AVAiL study showed no overall survival benefit with the addition of bevacizumab to gemcitabine and cisplatin therapy, despite improvement in progression-free survival. The mixed trial results, high cost and concerns over pulmonary haemorrhage caused by bevacizumab are barriers to its use.\(^{27}\)

**Maintenance treatment**
The role of erlotinib in the management of NSCLC has expanded to include maintenance treatment after first-line chemotherapy. In the SATURN study, erlotinib was given to patients with locally advanced or metastatic NSCLC who did not progress immediately after four cycles of platinum-based double chemotherapy.\(^{28}\) Erlotinib demonstrated improved mean progression-free survival (22.4 weeks compared with 16.0 weeks for placebo) and median overall survival. Quality of life was no worse for patients treated with erlotinib than for those in the placebo group, although it could be argued that patients need to be continuously monitored for this is not required.

Erlotinib and gefitinib are oral medicines that are taken continuously until a patient’s disease progresses. They have the advantage of not causing myelosuppression and, therefore, regular monitoring for this is not required. However, other significant side effects need to be managed — 75% of patients taking erlotinib develop a rash and over 50% experience diarrhoea.\(^{30}\) The toxicities seen with these oral agents are often idiosyncratic and so it is vital that patients receive appropriate information and counselling on how to take their medicines, the likely side effects and whom to contact in the case of any problems. Most cancer centres operate a 24-hour helpline or triage service for patients.

Many specialist oncology pharmacists have expanded their role into chemotherapy counselling and toxicity management clinics. There is a current trend in oncology for chemotherapy to be delivered closer to patients’ homes and coping exercises are being undertaken to assess the feasibility of community pharmacies dispensing oral anticancer treatments (some already do so for private prescriptions). The responsibilities of pharmacists in ensuring safe and effective use of oral anticancer treatments are almost certainly going to develop further.

**The future**
There are many new treatment options for NSCLC in development. At the European Society of Medical Oncology conference, held in Milan, Italy, in October 2010, the first evidence of use of the next generation of TK inhibitors was presented. Afatinib irreversibly inhibits EGFR-TK and has activity against EGFR mutations not sensitive to erlotinib or gefitinib. The placebo-controlled LUX-Lung 1 study\(^{31}\) sought to establish the role of afatinib
for patients who had failed a first-line EGFR-TK inhibitor. The study reported a 7% response rate in the patients receiving afatinib and a progression-free survival of 3.3 months compared with 1.1 months for placebo. However, there was no difference in overall survival found, which may have been due to placebo patients in the trial crossing over to active treatment. More data are needed to establish the role of this potential therapy.

References

Steve Williamson is a consultant pharmacist for cancer services at Northumbria Healthcare NHS Trust and North of England Cancer Network and Simon Purcell is a specialist oncology pharmacist and teacher practitioner at Clatterbridge Centre for Oncology NHS Foundation Trust. E: steve.williamson@nhct.nhs.uk

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