Lung cancer diagnosis and management

This special oncology section is devoted to lung cancer, which tends to have the poorest prognosis of all cancers. Steve Williamson describes the main types of lung cancer and outlines the treatment options.

Introduction

Lung cancer is a big disease, worldwide it is the most common cancer. In the UK it is the second most common cancer after breast cancer with 38,000 (22,000 men, 16,000 women) cases per year.[1] Lung cancer is rare under the age of 40 years with 85% of cases occurring in those aged more than 60 years. The incidence in women is changing, mirroring the increase in smoking among women, with the male: female ratio moving from 6:1 recorded in the 1950's to 1.4:1 now. This article will explore the diagnosis and management of lung cancer, highlighting some of the latest therapeutic advances in drug therapy.

Epidemiology of lung cancer

There are two main types of lung cancer — small cell lung cancer (SCLC) accounting for about 20% of cases, and non-small-cell lung cancer (NSCLC) accounting for 80% of cases. Non-small-cell lung cancer includes squamous cell (35%), adenocarcinomas (27%) and large cell (10%) carcinomas.[2] As well as the two main groups of lung cancer there are other thoracic cancers, malignant pleural mesotheliomas and tumours of the thymus. Until recently the various NSCLC pathological types were thought to have fairly homogeneous clinical behaviour and were treated the same, but trials with pemetrexed have highlighted differences in treatment depending on histology.

The overall incidence of lung cancer has fallen by more than 40% since a peak in 1970's, mainly because of a fall in smoking rates in men. But despite this drop in incidence, lung cancer is the most common cause of death from cancer for men and women in the UK. The death rate is close to the incidence with 24% of all male cancer deaths and 19% of all female cancer deaths caused by lung cancer. At present about only 25% of all lung cancer patients are alive at one year and 7% alive at 5 years.[3] This is partly because more than two-thirds of patients are diagnosed at a late stage when curative treatment is not possible. Most drug treatments are palliative and although there have been many new agents offering improvements in survival, none are curative. Surgery remains the best chance of cure.

Risk factors

Smoking is definitely the most significant risk factor for lung cancer. Although not all smokers get lung cancer the majority of patients with lung cancer have smoked. Cancer Research UK estimates 90% of lung cancers in men and 83% of lung cancers in women are caused by smoking.[4] The duration and number of cigarettes smoked are related to the risk of lung cancer. Smoking cessation has significant health benefits at all ages and is strongly recommended. Pharmacists are ideally placed to help counsel people to stop smoking and provide advice on nicotine replacement therapy. The NHS has invested heavily in stop smoking services to improve the overall public health and to reduce the incidence of lung cancers. Cancer Research UK figures show a lifelong male smoker has a risk of 15.9% for developing lung cancer by the age of 75 years, but stopping at 60, 50, 40 and 30 years reduces this risk to 9.9%, 6.0%, 3.0% and 1.7% respectively.[5] Other risk factors include exposure to naturally occurring radon gas, industrial carcinogens including arsenic, some hydrocarbons and asbestos.

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Presentation and diagnosis

Early diagnosis of lung cancer is critical and pharmacists have an important role in referring patients with symptoms suspicious of lung cancer. National guidance on *The diagnosis and treatment of lung cancer*[6] summarises symptoms that should prompt urgent referral for a chest X-ray. These are:

- ☐ a new cough that does not go away after two to three weeks
- ☐ worsening of a long-standing cough
- ☐ long-standing chest infection
- ☐ haemoptysis (coughing blood)
- ☐ persistent chest or shoulder pain
- ☐ unexplained persistent breathlessness and/or hoarseness
- ☐ weight loss and unexplained tiredness
- ☐ chest signs and finger clubbing on clinical examination.

On referral, patients with symptoms suggestive of lung cancer should be seen

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by a member of a multidisciplinary team (MDT) specialising in the management of lung cancer within two weeks. Pharmacists should ensure any patients who they see with these symptoms are advised to immediately visit their GP who will arrange a referral under the NHS two-week rule system. Chest x-ray is routinely undertaken, but it must be noted that chest x-rays can be 'clear' even the presence of cancer, so all patients with suspicious symptoms should have a CT scan of chest and upper abdomen to exclude liver metastases. A biopsy will need to be taken, usually via a bronchoscopy (for central lesions), or guided needle biopsy for peripheral lesions.

The diagnostic and investigations stage of the patient's journey is critical for lung cancer patients because there is potential for curative surgery for a small number of patients. The cancer must be accurately staged to determine its size, any involvement with lymph nodes and whether it has spread beyond the original site (metastasised) to plan the best treatment strategy. Unfortunately SCLC has nearly always metastasised by the time it is diagnosed and treatment is palliative with very little chance of surgical cure. SCLC is staged very simply as either limited stage disease, where the tumour is confined to one side of the chest and the involved lymph nodes can be treated with radiotherapy, or extensive disease beyond these bounds.[7]

Staging is more complex with NSCLC and is based on the TMN (tumour, node, metastases) system. Table 1 gives a summary of the main stages.

Access to PET (^{18}F-deoxyglucose positron emission tomography) scanning is required for patients who are staged as candidates for surgery or for radical radiotherapy to look for involved intrathoracic lymph nodes and distant metastases. Until recently NHS infrastructure to deliver PET scans has been limited. In 2005 there were only six PET scanners available to UK patients.[8]

Mesothelioma is a rare, but aggressive, tumour that is directly related to asbestos exposure. It presents with chest pain and shortness of breath plus constitutional symptoms such weight loss and fatigue. Thoracoscopy plus CT or MRI scans are used to confirm diagnosis.

Treatment of lung cancers

Small cell lung cancer

Although SCLC is very aggressive and has nearly always metastasised by the time of diagnosis, treatment with chemotherapy can initially produce quite good responses. Table 2 gives the commonly used chemotherapy regimens for lung cancers. Combination regimens such as CAV, EP, and CE can produce response rates of 80%.[9]

The cyclophosphamide-based regimens CAV and CAE were the traditional regimens of choice, but have now been superseded by etoposide and platinum combinations, which have the benefit of less myelosuppression. One of the biggest comparative trials showed that EP gave a superior median survival compared with CAV of 14.5 vs. 9.7 months respectively and a five year survival of 10% vs. 3% for limited stage disease.[10] Experience with the UK standard carboplatin-based regimen CE, which is essentially a modification of EP, suggests it is as effective. Carboplatin is less toxic and easier to administer, which is important when treatment is palliative, and the clinician needs to balance the benefits of treatment with the effects of the toxicities on the patient's quality of life. Until recently there had been very little progress in chemotherapy for SCLC, but interest now focuses on the camptothecin derivatives, topotecan and irinotecan, which show promising activity. Topotecan was recently granted a UK license as monotherapy for the treatment of adult patients with relapsed SCLC.

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When treating SCLC most patients experience a good initial response with stabilisation of disease and palliation of symptoms but unfortunately will relapse at some point. If the patient has had at least six months stable disease, they will often be retreated with the same chemotherapy regimen used as first line. If the relapse is sooner than six months a second line regimen may be tried or they will receive best supportive care (BSC). BSC is defined as treatment to support and control the symptoms, but not actually to treat the cause of the disease.

Radiotherapy is used in SCLC — particularly thoracic and cranial — because

Table 1. Staging of lung tumours

Stage I	Small tumour (IA = < 3cm and IB >3cm) with minimal invasion of surrounding pleural tissue.
Stage II	Small tumour spread to local lymph nodes or larger tumour with direct extension into chest wall.
Stage III	Larger tumour with direct extension into chest wall plus local lymph nodes (IIIA) or any size tumour with extensive lymph node spread (IIIB).
Stage IV	Any size tumour, lymph node spread, distant metastases.

NICE recommends first line therapy chemotherapy for advanced NSCLC should be a combination of a one of the third generation drugs docetaxel, gemcitabine, paclitaxel or vinorelbine plus a platinum — either carboplatin or cisplatin.

it has been shown to improve disease control and have a survival benefit when compared to chemotherapy alone. Patients with SCLC are also particularly prone to paraneoplastic syndromes, which are defined as hormonal, neurological, haematological, and other clinical and biochemical disturbances associated with the cancer, but not directly related to invasion by the primary tumour or its metastases.

Treatment of non-small-cell lung cancer

The best chance of cure is surgery for stage I and stage II disease. Surgery involves resection of the tumour by lobectomy, bi-lobectomy or pneumonectomy. The surgery is challenging and should only be undertaken in a unit with an appropriate level of expertise and experience. There is approximately a 5% postoperative mortality rate and patients can experience significant post surgical complications including haemorrhage, respiratory failure, infection and arrhythmias. There is an increasing role for adjuvant chemotherapy given after surgery to improve overall survival. The regimen NP, cisplatin and vinorelbine, is most commonly used. This combination has been shown in clinical trials to increase median survival to 65.7 months compared with 43.7 months in patients with no adjuvant chemotherapy, giving a 8.6% improval in overall survival at five years.[11]

Radical radiotherapy is the choice for early stage NSCLC patients who are not suitable for surgery. How the radiotherapy is administered can be significant — traditionally the total radiotherapy dose is calculated and the dose divided into smaller portions known as fractions. These fractions are then given daily over three to four weeks. However, because of the way NHS services were set up doses were not given at weekends. Recent research had focused on delivering the fractions more quickly in a schedule known as CHART (continuous, hyperfractionated, accelerated radiotherapy). CHART uses smaller doses of radiation than standard radiotherapy, but therapy is carried out three times per day over 12 consecutive days. This means that the total dose is the same or slightly less than what a patient would get with standard radiotherapy. CHART has a small but significant survival advantage over traditional radiotherapy, but it has proven difficult to adopt in the UK because of constraints on services — in particular having enough radiotherapy machines, linear accelerators, and the staff to operate them! However, it is recommended by NICE and shown to be cost-effective.[12]

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Chemotherapy for NSCLC

Platinum-based combinations have become the standard of care for treating advanced NSCLC. The 2005 NICE lung cancer guidance advises 'chemotherapy improves survival and although the increase is modest, it must be considered alongside the poor life expectancy in this group. The benefits must be carefully weighed against the risks of toxicity for the individual patient'.[7] In the past drugs used to treat NSCLC were not particularly effective and so chemotherapy was rarely offered. A 1995 meta-analysis showed chemotherapy was valuable with response rates of 15% as single agents for drugs such as ifosphamide, mitomycin c, cisplatin and vinblastine.[13] However, it was the arrival of newer, so called third generation drugs, vinorelbine, paclitaxel, docetaxel and gemcitabine that had the greatest impact. NICE recommends first line chemotherapy for advanced NSCLC should be a combination of a single third generation drug plus a platinum — either carboplatin or cisplatin. The choice of the combination will vary according to clinician or centre preference with gemcitabine and carboplatin being one of the most commonly used regimens. See Table 2 for regimen details. The regimens are usually given for four cycles unless there is evidence that the patient has progressive disease in which case they are stopped. Although palliation is effective, survival benefit is modest — these drugs offer a 30% to 40% response rate and median survival of around 10 months. For patients who are less fit and not thought able to tolerate combination chemotherapy single agent gemcitabine 1200–1250 mg/m^2 or oral vinorelbine 60–80mg/m^2 may be used.

There is an ongoing clinical debate, about the choice of platinum — either carboplatin or cisplatin — many clinicians use the two agents interchangeably, and in the UK carboplatin is often preferred because of its convenience and more manageable toxicity profile. However, there is a body of opinion that considers cisplatin to be superior and a large UK based trial, BTOG2 (Table 2), is underway comparing the two drugs in combination with gemcitabine.

Upon disease progression the patient is assessed for suitability for second-line chemotherapy, usually with docetaxel (Taxotere) as a single agent. The TAX317 trial of docetaxel versus BSC provided the first evidence from a randomised controlled trial that second-line chemotherapy could be beneficial.[14] At a dose of 75mg/m^2 a clear survival benefit could be seen relative to BSC, in which a 40% one-year survival rate was found with docetaxel versus a 16% with BSC. However, a large proportion of patients experienced moderate-to-severe

neutropenia. Neutropenia is an expected side-effect of chemotherapy but can cause significant problems if not managed, and can result in death from sepsis.

More recently pemetrexed (Alimta®) and erlotinib (Tarceva®) have been licensed as second-line treatments for NSCLC. However, both these drugs were initially turned down by NICE as not being cost-effective and banned from use in the NHS. Fortunately this appears to be changing, and Roche, the manufacturers of erlotinib, have proposed a scheme to allow the price of treating with erlotinib to be reduced to match that of treating with docetaxel. This will allow erlotinib to be offered as a cost-effective alternative to docetaxel. NICE appear to have accepted the scheme, but final guidance is awaited. It is perhaps worth mentioning that in the North East of England we have already adopted such a scheme and our patients have had access to erlotinib for more than one year.

Erlotinib is one of a new class of anti-cancer drugs; it is not a traditional cytotoxic agent, but a small molecule inhibitor of epidermal growth factor receptor (EGFR). EGFR is part of the control mechanism of cell growth that is fundamentally deranged in cancer. When EGFR is stimulated a chemical message is generated that reaches the nucleus via a variety of biochemical pathways. The common first step in these pathways is activation of a receptor-linked tyrosine kinase (TK) enzyme. EGFR over-production is common in NSCLC — ie lung cancer cells have too much EGFR and hence have more signals telling them to grow and proliferate. EGFR over-production is associated with aggressive tumour cell biology, chemotherapy resistance and reduced survival. Erlotinib is administered as a 150mg once-daily dose given until disease progression. The dose may be reduced if the patient experiences toxicity. Erlotinib toxicities profile is different from traditional chemotherapy with patients being prone to diarrhoea and severe skin reactions.

As second- or third-line treatment erlotinib was shown in the BR21 study[15] to have comparable survival benefit to docetaxel in the TAX317 study,[14] but without the neutropenia and myleotoxicity associated with chemotherapy. The BR21 study showed erlotinib increased the median overall survival from 4.7 months in the placebo arm to 6.7 months in the erlotinib arm. Only 22% of placebo patients were alive after 12 months compared with 31% of patients having erlotinib. On reflection this two-month increase in survival is modest, but it can be argued that if we are to make any advance against lung cancer we must embrace all the small advantages that are gained. The big issue is the cost of these new medicines. Cancer drugs are at the forefront of the debate over the access to high cost medicines with very small benefits, which are often turned down by NICE.

Another NICE-rejected drug for NSCLC is the antimetabolite cytotoxic agent, pemetrexed, which also has been shown to have similar efficacy to that of

Table 2. Combination chemotherapy regimens for thoracic cancers

Regimen name	Comments
Small cell lung cancer (SCLC)	
EP[21]	
Cisplatin 60–80 mg/m^2 IV day 1 Etoposide 115 mg/m^2 IV day 3 to 5	Cisplatin is very effective but highly toxic and requires prolonged administration with IV fluid support to avoid renal toxicity. Nausea is particularly bad with cisplatin. May be given with concurrent radiation.
CE[22]	
Carboplatin AUC5 IV day 1 Etoposide 120 mg/m^2 IV day1 Etoposide 240 mg/m^2 oral day 2 and 3	Carboplatin is substituted for cisplatin to produce a better tolerated regimen. A variety of slightly different etoposide dose schedules are used. Carboplatin is dosed using the Calvert formulae.[23]
CAE[24]	
Cyclophosphamide 600 mg/m^2 Day 1 Doxorubicin 40 mg/m^2 Day 1 Etoposide 120 mg/m^2 Day 1 Etoposide 240 mg/m^2 Days 2 and 3	Now most commonly used as second-line therapy.
CAV[25]	
Cyclophosphamide 750 mg/m^2 IV Day 1 Doxorubicin 50 mg/m^2 IV Day 1 Vincristine1.2 mg/m^2 IV Day 1	Now most commonly used as second-line therapy.
Non-small cell lung cancer (NSCLC)	
GemCarbo[26]	
Carboplatin AUC 5 IV day 1 Gemcitabine 1250 mg/m^2 IV day 1 and 8	See comments in text on choice of platinum. BTOG2 trial will be comparing this regimen with the cisplatin version. Carboplatin is dosed using the Calvert formulae.[23]
GemCis[27]	
Cisplatin 70 mg/m2 IV day 1 Gemcitabine 1200 mg/m2 IV day 1 amd 8	See comments in text on choice of platinum. BTOG2 trial will be comparing this regimen with the carboplatin version.
Paclitaxel/Carboplatin[28]	
Paclitaxel 175 mg/m^2 IV day 1 Carboplatin AUC 5 IV day 1	Carboplatin is dosed using the Calvert formulae.[23]
Paclitaxel/Cisplatin[29]	
Paclitaxel 175 mg/m^2 IV day 1 Cisplatin 70 mg/m^2 IV day 1	
NP[30]	
Cisplatin 60–80 mg/m^2 IV day 1 Vinorelbine 25–30 mg/m^2 (60mg max) days 1 and 8	Oral vinorelbine can be substituted for IV at a dose of 60–80 mg/m^2.
Docetaxel / Cisplatin [31]	
Docetaxel 75 mg/m^2 IV day 1 Cisplatin 75 mg/m^2 IV day 1	A fairly toxic regimen not often used first-line because clinicians prefer to have option of second-line single agent docetaxel.

second-line docetaxel.[16] Pemetrexed exhibits a more favourable toxicity profile than docetaxel, but is more expensive. Recently a large trial of a first-line combination of pemetrexed plus cisplatin was shown to offer a significantly longer survival than gemcitabine/cisplatin (median of 12.6 months compared with 10.9 months) in patients with adenocarcinoma.[17] This was the first time a difference has been shown in response to NSCLC chemotherapy depending on the histology. This has led to a change in the license of pemetrexed to reflect the increased activity in the non-squamous population and renewed interest in use of second-line pemetrexed. Pemetrexed is administered at dose of 500 mg/m^2 every three weeks.

One other drug worth mentioning is bevacizumab (Avastin®) 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[18] and AVAiL[19] both 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 to 10.3 months for chemotherapy alone. However, the AVAiL study using the gemcitabine and cisplatin regimen, showed was no overall survival benefit for bevacizumab in this trial, despite improvements in progression-free survival. These mixed trial results coupled with concerns over pulmonary haemorrhage caused by bevacizumab have led to modest demand from UK oncologists for its use.

Treatment of mesothelioma

For many years no standard chemotherapy regimen has existed for the treatment of malignant pleural mesothelioma, with BSC being seen as the most appropriate option. This changed when a trial of pemetrexed and cisplatin versus single agent cisplatin gave a median survival of 13.3 months vs 10 months respectively.[20] This established pemetrexed and cisplatin as the gold standard for this disease.

Conclusions

Lung cancer remains one of the cancers with the worst outcomes for patients, and with very poor survival rates. However, progress is being made with newer agents making modest improvements in the average survival times. Early diagnosis and speedy treatment are key and pharmacists need to be aware of the role they can play in encouraging patients with suspicious symptoms to seek immediate medical attention. ✣

Declarations of interest

The author has no interests to declare.

Steve Williamson, consultant pharmacist in cancer services, Northumbria Healthcare and North of England Cancer Network

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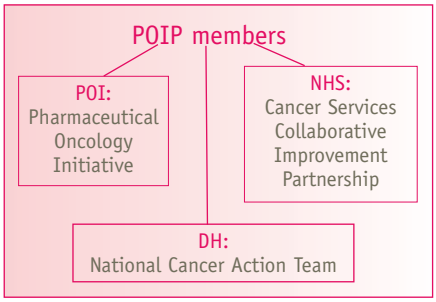
The Pharmaceutical Oncology Initiative Partnership aims to ensure access to cancer medicines and services for all who need them

The Pharmaceutical Oncology Initiative (POI) is a collaborative comprising 18 pharmaceutical companies who research, develop and supply innovative cancer medicines — all members of the Association of the British Pharmaceutical Industry (ABPI) — who are working with the NHS towards improving access to cancer medicines for patients across the UK.

The POI, set up in 2005, arose out of the recognition that there were significant variations in the usage of NICE-approved cancer medicines across cancer networks making access to treatment unequal across the UK, and that the uptake of new cancer medicines was slower than the average across Europe.[1] In December 2007, the Department of Health (DH) announced steps it was taking to address these challenges in its *Cancer reform strategy*.[2] A formal collaboration between the POI, the NHS — specifically the Cancer Services Collaborative Improvement Partnership[3] (now known as NHS Improvement) — and the National Cancer Action Team of the DH, led to the formation of a unique partnership — the Pharmaceutical Oncology Initiative Partnership (POIP). The main objective of the POIP is identifying and implementing projects that will benefit cancer patients by improving uptake and access to cancer drugs.[3]



The POIP have developed two major projects to assist the NHS in commissioning and delivering better cancer care. These are the chemotherapy planning oncology resource tool (C-PORT)[4] and the cancer commissioning toolkit (CCT).[4]

The chemotherapy planning oncology resource tool (C-PORT)[4]

C-PORT[4] is web-based chemotherapy planning simulator, which can help chemotherapy suites and pharmacy units identify how they may best deliver services with existing resources and what might be re-designed to cope effectively with demand and changing chemotherapy. Here, users can simulate potential re-design scenarios or assess the impact of a new chemotherapy agent, identify likely problems, define changes that need to be tested and plan a clinical implementation strategy, for example. The website has been successfully piloted and is now being used widely throughout cancer networks. The central housing of data permits sharing of knowledge and case studies are available to illustrate where several 'what if' scenarios, including the impact of planning the introduction of a new medicine, making comparisons between trusts and benchmarking trusts in the same network. It is likely that this tool will, therefore, prove useful in developing best practice for sharing across networks.

The cancer commissioning toolkit (CCT)[5]

This interactive web-based resource is intended to be used to support commissioners and cancer service providers across the NHS in implementing the *Cancer reform strategy*. It includes a range of key cancer commissioning information to inform decision-making, broadly following the chapters of the *Cancer reform strategy* and linking to these where appropriate. The key cancer metrics can be examined in detail with links to information relevant to all stages of a patient's journey — including prevention, screening, referral, treatment and living with cancer as well as end of life care. Reports can be generated, which can be customised to include selected networks, PCTs, trusts or SHAs and these can be exported. This can help clinicians plan patient pathways effectively, and PCTs and cancer networks benchmark various aspects of cancer delivery, make quality, safety and value-for-money assessments and forward plans. There is an on-going commitment to refine and update the CCT and improve it in response to user feedback. Also a link between a C-PORT financial module and CCT is being developed. Data such as the cost-to-treat by regimen and cancer type, and regimen volumes and tariffs will be obtainable through this integrated module, which will enable chemotherapy units to evaluate the cost of chemotherapy delivery and compare this to the revenue generated from a national tariff. (For readers wishing to know more, educational meetings are being held on the CCT — see p258).

Declaration of competing interests:
The author has no competing interest to declare.

Christine Knott, editor

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