

Lung cancer

— the role of chemotherapy

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Many patients with lung cancer will receive chemotherapy, either as the primary mode of treatment or in conjunction with surgery. This article details the drugs used, setting out their place in treatment regimens, which depends on factors such as the type and stage of disease and a patient's prognosis



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Chemotherapy, a key form of treatment for lung cancer, is administered to a patient

Chemotherapy plays an important role in treating many patients with both non-small-cell and small-cell lung cancer (respectively NSCLC and SCLC). For patients with early-stage NSCLC, drugs can be used either following surgery (ie, adjuvant chemotherapy) or before surgery is carried out (ie, neoadjuvant chemotherapy). The goal of chemotherapy here is to help “cure” the patient and improve long-term survival rates. Patients with SCLC and advanced NSCLC can also benefit from chemotherapy, with the aim of drug treatment being to prolong life (although most patients will ultimately die from their cancer), improve or maintain quality of life and control symptoms without causing unacceptable toxicity.

This article sets out information about the approaches taken to chemotherapy in NSCLC, providing details about some of the agents that are currently used. It also includes a summary of relevant National Institute for Clinical Excellence (NICE) guidance and highlights potential targets for drug development in the future. The treatment of SCLC is also set out.

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— Adjuvant chemotherapy

Adjuvant chemotherapy is given after surgery in patients with early-stage NSCLC (ie, stage I, II and some IIIa disease). The aim is to eradicate any cancer cells that are not removed during the operation — local and distant recurrences are common within the first two years after surgery and only approximately 50 per cent of patients survive five years post-surgery.

Randomised trials investigating the efficacy of adjuvant chemotherapy date back to the 1960s. Early studies used alkylating agents, either alone or in combination, and suggested that adjuvant chemotherapy did not improve long-term survival rates.¹ The use of what are now believed to be less effective chemotherapy agents, poor compliance and trials with insufficient statistical power to detect small benefits are believed to account for these unfavourable results. Much later, the NSCLC collaborative group performed a meta-analysis, published in 1995, examining the benefits of adjuvant chemotherapy. Only when the analysis was limited to eight trials using platinum-based adjuvant chemotherapy was there a trend towards improved survival in the chemotherapy group, which translated into a non-significant absolute survival benefit of 5 per cent at five

years.¹ The International Adjuvant Lung Cancer Trial (IALT) was designed to have the statistical power to confirm this potential benefit for cisplatin-based adjuvant chemotherapy. IALT compared cisplatin, plus a vinca alkaloid or etoposide, with no adjuvant chemotherapy in patients with completely resected stage I-IIIa NSCLC. The trial was large and showed that adjuvant chemotherapy was associated with a small, but statistically significant, absolute five year benefit in overall survival of 4.1 per cent.² However, two other recent studies investigating adjuvant chemotherapy in NSCLC, the Adjuvant Lung Project Italy and the Big Lung Trial, failed to show a significant difference in overall survival.^{3,4} It has been suggested that these studies were not large enough and therefore lacked the statistical power to detect any small benefits.

There therefore remains some debate as to whether adjuvant chemotherapy for resected NSCLC should become the standard of care. For other malignancies, oncologists do not generally use treatments that have as small a survival benefit as 4.1 per cent — 25 patients have to be treated to convert one person who otherwise would have died from the disease into a five-year survivor, with the other 24 patients being exposed to the toxicities of chemotherapy with no

benefit. However, it is important to note that patients with lung cancer are not the same as those with breast or colon cancer, because they frequently have significant additional comorbidities that can complicate chemotherapy. Detailed examination of the IALT study showed that patients older than 64 years of age and those with a World Health Organization (WHO) performance status of 2 did not benefit from adjuvant chemotherapy. Furthermore, patients with stage I disease had the least benefit from adjuvant chemotherapy and patients with stage III disease had the greatest benefit. These results suggest that patients with resectable NSCLC need to be carefully selected for adjuvant chemotherapy.

— Neoadjuvant chemotherapy

Neoadjuvant chemotherapy is administered before surgery and can be used in NSCLC. The clinical rationale for this approach is two-fold and is set out in Panel 1.

Most pre-operative chemotherapy studies have been carried out in patients with stage III disease. Response rates have ranged from 50–75 per cent, which suggests that the majority of patients appear to have chemosensitive disease before surgery. These studies have shown that neoadjuvant chemotherapy for NSCLC can be given safely and can achieve tumour shrinkage with beneficial results.

Two small randomised trials have compared surgery with or without pre-operative chemotherapy in patients with stage IIIa disease. Each produced results in favour of pre-operative chemotherapy. One trial, which used cyclophosphamide, etoposide and cisplatin combination chemotherapy, demonstrated that a larger proportion of patients who received chemotherapy underwent complete resection (35 per cent compared with 31 per cent in the surgery alone group).⁵ Median survival for patients who received chemotherapy was vastly improved (64 months compared with 11 months for the surgery alone group) and the trial was stopped early.

Both adjuvant and neoadjuvant chemotherapy with platinum-based compounds hold promise for extending survival in early stage NSCLC, but it is not yet clear whether pre-operative or post-operative chemotherapy is superior.

— Advanced disease

Lung cancer is defined as advanced if, at the time of presentation or recurrence, it has either metastasised to distant organs or is so locally invasive as to make curative surgical resection impossible. Advanced lung cancer includes non-resectable stage IIIa, stage IIIb and stage IV disease. Disease recurrence occurs commonly in the liver, brain and bone. Approximately 75 per cent of newly

Panel 1: The two-fold rationale for using neoadjuvant chemotherapy in NSCLC

- Regression of the primary tumour may be achieved, which can mean that less extensive surgery needs to be carried out and makes surgery more effective
- Micro-metastases are dealt with at the start of treatment

“NSCLC” means non-small-cell lung cancer

diagnosed patients have advanced NSCLC, of whom two thirds have advanced metastatic disease. The median survival of patients with untreated metastatic NSCLC is only four to five months, with a 10 per cent survival rate at one year.⁶

The role of chemotherapy in the treatment of NSCLC has increased over the past 10 years. A meta-analysis in advanced NSCLC demonstrated a significant, although small, survival benefit of 10 per cent at one year in patients treated with cisplatin-based chemotherapy regimens compared to BSC (“best supportive care”, that is, managing symptoms but not treating the condition) alone.¹ In addition, randomised studies comparing chemotherapy with BSC have shown chemotherapy reduces symptoms and improves a patient’s quality of life.⁷ Cisplatin-based combination chemotherapy has been the mainstay of treatment since the early 1980s. In the UK, chemotherapy treatment schedules for advanced NSCLC normally involve four cycles. Over the past five years, a number of newer agents have become available. Gemcitabine, docetaxel, vinorelbine and paclitaxel have shown significant activity in NSCLC.

— Cisplatin

Cisplatin is a cell-cycle non-specific agent that interferes with cell division by binding to DNA. It is administered by intravenous infusion. The treatment schedule must include pre- and post-treatment hydration with intravenous fluids and often involves an overnight stay in hospital. Hydration is necessary to dilute cisplatin in order to minimise renal toxicity. Nephrotoxicity caused by cisplatin is a major dose-limiting adverse effect. The aim of hydration is to maintain a urine output of 100ml/h during cisplatin administration and for 6–8 hours afterwards. Mannitol is often given to ensure adequate fluid output. Electrolytes such as potassium and magnesium are often administered in the infusion fluids to compensate for cisplatin-induced electrolyte wasting. Renal function must be estimated before

treatment with cisplatin. This is commonly achieved with a 24 hour urine collection to measure EDTA (ethylenediaminetetraacetic acid) clearance.

The side effect profile of cisplatin also includes bone marrow suppression (ie, myelotoxicity), severe nausea, vomiting and peripheral neurotoxicity (ie, sensory motor and occasionally autonomic neuropathy), which can be irreversible.⁸ Ototoxicity, manifested initially by high frequency hearing loss, can also occur.⁸

The NSCLC Collaborative Group reviewed 11 trials that compared chemotherapy with BSC for patients with advanced NSCLC. Eight of these trials used cisplatin,¹ which increased the overall median survival by 1.5 months. Furthermore, cisplatin-based combination regimens were the most successful of those reviewed and produced responses in 20–50 per cent of patients. The American Society of Clinical Oncologists (ASCO) recommends the use of a cisplatin-based regimen, plus radiation therapy, for patients with unresectable stage III NSCLC and the use of cisplatin-based combination chemotherapy for patients with stage IV NSCLC.⁹

As in other types of cancer, performance status is a clear indicator of prognosis in advanced NSCLC. Performance status is a measure of the patient’s functional status and takes into account the impact of tumour symptoms and any other pre-existing medical problems and co-morbidities, on a patient’s ability to function on a day-to-day basis and to care for themselves. Several performance status scales are available for clinical use, including the WHO scale (see SCLC section below), the Karnofsky scale and the Eastern Co-operative Oncology Group (ECOG) scale. Performance status gives an important indicator of how well cisplatin-based combination chemotherapy will be tolerated. Having a poor performance status has been shown to increase the incidence of toxic side effects, which can sometimes be fatal.¹⁰ It is usual practice only to offer combination chemotherapy with cisplatin to patients with a good performance status (ie, “0” or “1” on the WHO scale).

In the UK, cisplatin has been used in a number of older combination regimens including MVP (mitomycin, vinblastine and cisplatin) and MIC (mitomycin, ifosfamide and cisplatin). However, cisplatin-based combination regimens normally require admission to hospital, which can become a rate-limiting step on the number of patients treated per day. There has been a recent shift towards regimens that can be given in the outpatient setting.

Guidelines from NICE about the diagnosis and treatment of lung cancer were issued in February.¹¹ A summary of the guidance (including the role of cisplatin) in NSCLC is set out in Panel 2 (p140).

— Carboplatin

Carboplatin has a similar mode of action to cisplatin. It was introduced with the view of being less toxic than cisplatin — it causes less nephrotoxicity, neurotoxicity and ototoxicity. However, its dose-limiting side effect is myelosuppression, which is not a major problem with cisplatin. Carboplatin is administered by short intravenous infusion and does not require the patient to be hydrated. It is often given in an outpatient clinic.

There has been concern that carboplatin-based combination regimens may not be as effective as cisplatin-based ones in treating NSCLC. However, a randomised study comparing gemcitabine and carboplatin with either MIC or MVP chemotherapy showed that there was no significant difference in response or survival between the regimens and that the gemcitabine and carboplatin chemotherapy was easier to administer.¹² Gemcitabine and carboplatin chemotherapy is now a standard treatment for advanced NSCLC in the UK.

— Gemcitabine

Gemcitabine is a nucleoside analogue. It is a cell cycle specific cytotoxic agent that kills cells in the “S” phase (ie, undergoing DNA synthesis). Gemcitabine is administered by short intravenous infusion over 30 minutes, and is often given to patients in an outpatient clinic. Side effects of gemcitabine include mild alopecia, mild to moderate nausea, vomiting, mucositis and bone marrow suppression that manifests as anaemia, leucopenia and thrombocytopenia.¹³ A cutaneous rash occurs in 25 per cent of patients. This is often pruritic, but can be managed conservatively. Influenza symptoms are also common (occurring in 20 per cent of patients) but are normally self-limiting.

Gemcitabine is licensed for administration at a dose of 1,000mg/m² on a weekly basis

for three doses, with one week off per four-week cycle, or at a dose of 1,250mg/m² on a weekly basis for two doses, with one week off per three-week cycle.¹³ It can be given as a single agent or in combination with a platinum-based agent. A study comparing gemcitabine chemotherapy plus BSC with BSC alone in patients with locally advanced or metastatic lung cancer showed that quality of life and symptom control improved significantly in patients receiving gem-citabine, but that survival rates did not change.¹⁴ In other studies, the four-week schedule produced responses in 7–27 per cent of patients, with median survival times of 5.7 to 11 months.¹⁵

Gemcitabine has been widely studied in combination with both cisplatin and carboplatin. Results show improved response rates and one year survival rates, compared with gemcitabine alone.¹⁴ Studies also suggest that using the two-dose, three-week schedule is associated with less thrombocytopenia than the three-dose, four-week schedule. For example, 7 per cent of patients receiving gemcitabine and carboplatin on a three-week schedule had “grade 4” thrombocytopenia compared with 56 per cent of patients on a four-week schedule (with thrombocytopenia often leading to the omission of the third gemcitabine dose on the four-week schedule).¹⁶ Response rates and median survival times did not differ between the two schedules and so the two-dose, three-week schedule has replaced the three dose, four-week schedule in clinical practice.

Gemcitabine is licensed for use in combination with cisplatin as a first-line treatment in patients with locally advanced or metastatic NSCLC and for palliative treatment of patients with locally advanced or metastatic NSCLC.¹³ NICE recommends gemcitabine, paclitaxel or vinorelbine as an option for first-line chemotherapy for advanced (ie, stage III and IV) NSCLC patients, in combination with a platinum-based agent.¹¹

— Docetaxel

Docetaxel is a taxane and acts by disrupting the microtubular network, which stops the cells from dividing. Docetaxel is administered by short intravenous infusion in an outpatient clinic. Side effects of docetaxel include dose-limiting neutropenia, total alopecia, nausea, vomiting and sensory neuropathy.¹⁷ Patients must be pre-medicated with an oral corticosteroid, such as dexamethasone 8mg twice a day for three days, starting the day before docetaxel administration. This reduces the incidence and severity of fluid overload and hypersensitivity reactions.

Docetaxel has been shown in randomised studies to improve survival, compared with BSC, when used as a second-line treatment in patients with advanced NSCLC who have already received cisplatin-based chemotherapy.¹⁸ Docetaxel administered at a dose of 75mg/m² on a three-week cycle had a lower incidence of haematological toxicity, compared with docetaxel at a dose of 100mg/m² (67 per cent of patients having grade 3 or 4 neutropenia, as compared with 86 per cent of patients). There was no difference in survival rates between the two regimens. NICE recommends docetaxel monotherapy as an option where second-line treatment is appropriate for patients with locally advanced or metastatic NSCLC, where relapse has occurred after previous chemotherapy.¹⁶ Docetaxel has also been investigated in clinical trials as first-line treatment of advanced NSCLC in combination with cisplatin.

— Pemetrexed

Pemetrexed is a novel antifolate chemotherapy agent. Its primary mechanism of action is to inhibit the enzyme thymidylate synthase, resulting in decreased thymidine necessary for pyrimidine synthesis. Pemetrexed also inhibits dihydrofolate reductase. Side effects include myelotoxicity, nausea and vomiting, fatigue and hypersensitivity reactions.¹⁹ In order to reduce the incidence and severity of skin reactions, a corticosteroid should be given the day before, the day of, and the day after pemetrexed administration. The incidence of both haematological and non-haematological toxicity is reduced by supplementation with folic acid (400microgram daily) and vitamin B¹² (1,000microgram, given intramuscularly every nine weeks).

A randomised phase III trial of pemetrexed compared with docetaxel in patients with NSCLC who have previously been treated with chemotherapy, showed that treatment with pemetrexed resulted in clinically equivalent efficacy outcome, but had a significantly lower incidence of grade 3 and 4 neutropenia (5.3 per cent compared with 40.2 per cent) and febrile neutropenia

Panel 2: Summary of the National Institute for Clinical Excellence guidelines on the use of chemotherapy in NSCLC

- Chemotherapy should be offered to patients with stage III or IV NSCLC and good performance status (World Health Organization score of 0 or 1 [see sections about cisplatin and SCLC and Panel 3] or a Karnofsky score of 80–100), to improve survival, disease control and quality of life
- Chemotherapy for advanced NSCLC should be a combination of a third generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug. Either carboplatin or cisplatin may be administered, taking account of their toxicities, efficacy and convenience. Patients who are unable to tolerate a platinum combination may be offered single agent chemotherapy with a third generation drug
- Adjuvant chemotherapy should be offered to NSCLC patients who have had a complete resection (with the risks and benefits discussed with patients)
- Neoadjuvant treatment should not be offered to patients with stage I, II or IIIa NSCLC who are suitable for resection unless the procedure is part of a clinical trial

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(1.9 per cent compared with 12.7 per cent).²⁰

Pemetrexed has recently been licensed as monotherapy for the treatment of patients with locally advanced or metastatic NSCLC who have already had chemotherapy with another agent.¹⁹ It is also licensed for use in combination with cisplatin for the treatment of chemotherapy-naïve patients with unresectable malignant pleural mesothelioma (ie, a tumour of the membrane that surrounds the lung and lines the wall of the chest cavity, which is linked to asbestos exposure). The use of pemetrexed in combination chemotherapy regimens as first-line treatment of advanced NSCLC is under investigation.

— Biological agents

Epidermal growth factor receptor-2 is over-expressed in tumour cells in most cases of NSCLC.²¹ Many strategies have therefore been developed to target this receptor. The two most extensively evaluated are monoclonal antibodies against the extracellular domain of this receptor (ie, trastuzumab and herceptin) and inhibitors of the tyrosine kinase region of the receptor.

Two tyrosine kinase inhibitors (gefitinib and erlotinib) have antitumour activity in advanced NSCLC, even in patients in whom previous chemotherapy has failed.^{22,23} For example, a phase II, randomised, double-blind study evaluated tumour response, disease-related symptom response and the safety profile of gefitinib monotherapy in patients who had locally advanced or metastatic NSCLC and had already received at least two chemotherapy regimens, including platinum-based chemotherapy and docetaxel.²⁴ Tumour regression occurred in 11.8 per cent of patients receiving gefitinib (250mg) and symptom improvement occurred in 43 per cent. Gefitinib 500mg per day was found to have similar efficacy to 250mg per day but was less well tolerated. The most commonly reported adverse events included reversible diarrhoea in 48 per cent of patients and an acne-like skin rash in 43 per cent of patients. A phase III trial of gefitinib compared with placebo in patients with NSCLC who had previously received chemotherapy that had failed demonstrated a statistically significant improvement in tumour shrinkage in patients receiving gefitinib, but there was no statistically significant survival benefit.

Biological agents potentially offer a novel therapy for NSCLC that is more specific, more selective and less toxic than current chemotherapy agents and combination regimens. The place of tyrosine kinase inhibitors in the treatment of NSCLC is currently undetermined, but they may offer a third line treatment option for patients with advanced disease. These agents are not licensed in the UK.

— Small cell lung cancer

SCLC is a particularly aggressive disease. In contrast to NSCLC, surgery plays little role, if any, in the management of SCLC. Although SCLC is much more likely to respond to chemotherapy than NSCLC, even when the disease is extensive, responses to chemotherapy are often short lived.

At diagnosis, about 40 per cent of patients have “limited disease”, defined as tumour confined to the thorax (and see reference 25). With chemotherapy plus radiotherapy together with the selective use of prophylactic cranial irradiation, the median survival of these patients is 18–24 months, and up to 20 per cent of them survive for more than two years.²⁶ Without treatment, the median survival is only six to 12 weeks. Regimens for SCLC usually contain between two and four agents, including cyclophosphamide, doxorubicin, vincristine, etoposide, cisplatin or carboplatin, and ifosfamide. The response rate for patients with limited stage disease is 80–95 per cent, with up to 60 per cent achieving complete remission.¹⁵

The remaining 60 per cent of patients with newly diagnosed SCLC have “extensive disease”. At the time of diagnosis, many of these patients have metastases involving one or more sites such as the brain, liver or bone (and see reference 25). With combination chemotherapy, the median survival of these patients is seven to nine months.²⁶ The current standard chemotherapy regimen is etoposide plus cisplatin. This regimen produces a median survival of eight to 10 months and a two year survival rate of 10 per cent. Response rates of 60–80 per cent have been noted in patients with extensive disease, with remission occurring in 15–20 per cent of patients.

There is no firm evidence that one particular combination chemotherapy regimen is superior to any other.²⁷ A survey of clinicians treating lung cancer in 1998 established that many different chemotherapy regimens were in routine use with no firm consensus on standard chemotherapy for SCLC.²⁸

Patients with SCLC are often treated primarily according to their prognosis, not necessarily according to the extent of their disease. The “WHO performance status” and the “Manchester score” are the two most commonly used indicators of prognosis in SCLC. These are set out in Panel 3 (p143).

Patients with a good prognosis (ie, patients with a Manchester score of 0 or 1) are commonly treated with six cycles of either cisplatin and etoposide (PE), doxorubicin, cyclophosphamide and etoposide (ACE), or cyclophosphamide, doxorubicin and vincristine/PE (CAV/PE). Patients with poor prognosis (ie patients with a Manchester score of 2 or more) are commonly treated with four to six cycles of cyclophosphamide, doxorubicin, and vincristine (CAV).

NICE guidelines recommend all patients with SCLC should be offered platinum-

based chemotherapy and a multidrug regimen.¹¹ Four to six cycles of chemotherapy should be offered to patients whose disease responds. Patients with limited-stage SCLC should be offered thoracic irradiation concurrently with the first or second cycle of chemotherapy or following completion of chemotherapy if there has been at least a good partial response within the thorax. For patients with extensive disease, thoracic irradiation should be considered following chemotherapy if there has been a complete response at distant sites and at least a good partial response within the thorax. Second-line chemotherapy should be offered to patients at relapse only if their disease responded to first-line chemotherapy. The benefits are less than those of first-line chemotherapy.

— Conclusion

Drug treatment plays an important part in the treatment of many patients with lung cancer and can help cure the disease. Where cancer is of the type or stage such that remission is unlikely to be achieved, chemotherapy can still prolong life, improve or maintain a patient's quality of life and control symptoms. The development of biological agents targeting tumour cells might potentially result in these aims being achieved with less toxicity to patients.

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Other NICE cancer guidelines

Lung cancer guidelines were published by the National Institute for Clinical Excellence in February. Other forthcoming NICE guidelines include referral for suspected cancer (expected May), children and young people with cancer (expected July) and skin cancer (expected January 2006)

Panel 3: "World Health Organization Performance Status" and "the Manchester Score" systems used to determine the type of treatment given to patients with SCLC

WHO performance status

- 0=able to carry out all normal activity without restriction
- 1=restricted in physically strenuous activity, but ambulatory and able to carry out light work
- 2=ambulatory and capable of all self-care, but unable to carry out any work; up and about more than 50 per cent of waking hours
- 3=capable of only limited self-care; confined to bed or chair more than 50 per cent of waking hours
- 4=completely disabled; cannot carry out any self-care; totally confined to bed or chair

Manchester score

- 0=starting score
- Add 1 if lactate dehydrogenase >450U/L (upper normal limit)
- Add 1 if cancer is "extensive stage disease"
- Add 1 if serum sodium is <132mmol/L
- Add 1 if Karnofsky score is <60
- Add 1 if alkaline phosphatase >165 U/L (1.5 times the upper limit)
- Add 1 if serum bicarbonate <24 mmol/L

The range of possible scores is therefore 0–6

"SCLC" means small-cell lung cancer