## Screening

Regular chest X-rays and sputum cytology have been proposed for screening populations at high risk of lung cancer in the hope of detecting early stage disease curable by surgery. There was conflicting evidence for survival benefit from a number of large trials in the 1970s and 1980s; results from current screening programmes are awaited. As with other cancers the need is for a more sensitive and specific tumour marker for effective screening (Flehinger and Melamed, 1994).

## Lung cancer services in the UK

The UK has one of the highest rates of lung cancer in the world. The trend in UK males has decreased slightly but in females it continues to rise. The 5-year survival rate for all patients with lung cancer is 7% in the UK compared with 14% in the USA. The majority of these survivors have undergone surgery. The resection rate for lung cancer, barely 10% in the UK, is over 20% in the USA. There are dangers in comparing crude statistics from different countries, but it is difficult to avoid the conclusion that surgical stage lung cancer is undertreated in the UK, where a 7% improvement in survival would represent a saving of over 2000 lives per annum (Whitehouse, 1994).

The recent Calman report recommended a major reorganization of cancer services in the UK. With lung cancer, emphasis must be on a multidisciplinary team approach in which the surgeon's main role is to ensure that all patients with operable disease are identified and offered surgery.

**KEY POINTS**

- **Lung cancer is the most common fatal malignancy.**
- **Complete surgical excision offers the best chance of cure for non-small cell lung cancer.**
- **Selection of patients for surgery is based on accurate tumour staging and cardiopulmonary assessment.**
- **The main direction of current clinical trials is the evaluation of combining surgery with chemotherapy (neoadjuvant or induction therapy).**
- **Screening for early stage, surgically curable disease is the subject of current studies. The search continues for an effective screening tool.**
- **Surgical stage lung cancer is undertreated in the UK.**
- **Reorganization of lung cancer services based on multidisciplinary teams is necessary.**


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# New drugs for the management of lung cancer

Giuseppe Giaccone



In the last few years a number of new anticancer agents which have definite activity in lung cancer and other common malignant diseases have been developed. Interestingly, some of these new agents have activity not only in small cell lung cancer (SCLC), which is generally sensitive to chemotherapy, but also in non-small cell lung cancer (NSCLC), a far less sensitive tumour. Among the new active compounds are the taxanes, paclitaxel and docetaxel, and the topoisomerase I inhibitors, irinotecan and topotecan, which are drugs with novel mechanisms of action. The new antimetabolites, such as gemcitabine, and the new vinca alkaloid vinorelbine have also been shown to have substantial activity.

The mainstay treatment for SCLC is combination chemotherapy, which achieves approximately 80% or higher response rate; common regimens for the treatment of this disease include cyclophosphamide and doxorubicin in combination with vincristine or etoposide, or cisplatin and etoposide. Despite the high response rate, the vast majority of patients relapse within 2 years, and less than 5% can eventually be

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cured. Active drugs for SCLC are listed in *Table 1*.

Surgery is the mainstay treatment of NSCLC; however, surgery can only cure a minority of these patients. Chest irradiation and chemotherapy do not greatly influence the survival rate of locally advanced or metastatic NSCLC patients, although symptomatic improvement may be achieved in over 50% of the patients treated with both modalities. Only a small number of drugs, including cisplatin, ifosfamide, vinblastine, vindesine, mitomycin and etoposide, have activity in more than 15% of NSCLC patients. Current combination chemotherapies which are mainly cisplatin-based yield up to 50% response rates in advanced NSCLC, but the complete response rate is <10% and the gain in survival is marginal at the cost of substantial toxicity, as shown by a recent metaanalysis (Stewart et al, 1995).

The most interesting new drugs with activity in lung cancer will be discussed here. Remarkably, more experience has been rapidly gained in NSCLC than in SCLC, partly probably due to the more problematic ethical issue of testing new drugs in untreated SCLC than in NSCLC. Because a large number of small phase II studies have been reported, unpublished results or results not published in peer-review journals will be kept to a minimum in this review.

**Table 1. Active agents in small cell lung cancer**

| | |
|---|---|
| Anthracyclines | Doxorubicin |
| | Epirubicin |
| Epipodophyllotoxins | Etoposide |
| | Teniposide |
| Alkylating agents | Cyclophosphamide |
| | Ifosfamide |
| | Cisplatin |
| | Carboplatin |
| | Nitrogen mustard |
| | Hexamethylmelamine |
| | Lomustine |
| | Carmustine |
| | Nimustine |
| Antimetabolites | Methotrexate |
| Vinca alkaloids | Vincristine |
| | Vindesine |
| | Vinblastine |

## New antimetabolites

### Gemcitabine

Gemcitabine (2'-deoxy-2',2'-difluorodeoxycytidine) is a novel pyrimidine antimetabolite which inhibits DNA replication and repair. Its activity in NSCLC has been reported in a recent study on 76 evaluable untreated patients to whom gemcitabine was given at 1000–1250 mg/m$^2$/week for 3 weeks out of every 4 weeks; in this study a response rate of 20% was obtained (Abratt et al, 1994). Only very modest myelotoxicity is seen with the use of gemcitabine, causing mild emesis and alopecia. Another study of 79 assessable patients also reported a 20% response rate with lower doses of 800–1000 mg/m$^2$ given in an identical schedule (Anderson et al, 1994). Several other studies in NSCLC have reported similar preliminary results, and are reviewed elsewhere (Sorenson, 1995).

In 29 assessable patients with untreated extensive SCLC a response rate of 27% was obtained with gemcitabine (Cormier et al, 1994). The schedule and dose used was the same reported for NSCLC (Abratt et al, 1994).

Because of the relative mild toxicity profile it will be interesting to use gemcitabine in combination with other drugs, particularly those where myelotoxicity is the major side-effect. Reports of combinations of gemcitabine with cisplatin in advanced NSCLC are extremely promising with over 50% response rates (Crino et al, 1995).

### Edatrexate

Edatrexate (10-ethyl-10-deaza-aminopterin) is a derivative of methotrexate, with superior in-vitro potency compared with the parent compound. Its activity in NSCLC was first demonstrated in 1988 (Shum et al, 1988), with a 32% response rate in 19 assessable NSCLC patients previously untreated by chemotherapy. Major toxicity was mucositis and in this study, where edatrexate was given at 80 mg/m$^2$/week for 5 weeks, myelosuppression was negligible. However, two more recent studies failed to demonstrate an activity of >15% in a total of 75 advanced NSCLC previously untreated by chemotherapy (Lee et al, 1990; Souhami et al, 1992). Edatrexate has been recently investigated in combination chemotherapy with cisplatin and cyclophosphamide. The addition of leucovorin rescue allowed a dose of 80 mg/m$^2$ to be maintained on days 1 and 8 in this combination, without severe mucositis, and a response rate in excess of 40% was achieved (Lee et al, 1992).

## New microtubuline inhibiting agents

### Vinorelbine

Vinorelbine is a synthetic vinca alkaloid antitumour agent, with minimal neurotoxicity, and myelotoxicity as the limiting toxicity. It has been developed with changes brought into the catharanthine nucleus of the vinca alkaloid chemical structure, with the aim of reducing neurotoxicity while preserving antimitotic activity. This drug has shown definite activity in breast cancer and NSCLC. Extensive investigations have already been performed with vinorelbine as a single agent and in combination chemotherapy.

In a phase II study a 33% response rate was obtained in 70 evaluable untreated patients with NSCLC, at a weekly dose of 30 mg/m$^2$ given intravenously (Depierre et al, 1991). Neutropenia was severe in less than 20% of cycles and neurotoxicity was observed in 36% of patients but was of mild intensity.

However, in a large multicentre randomized trial of 612 patients comparing vinorelbine alone at 30 mg/m$^2$ *vs* cisplatin (120 mg/m$^2$) and vinorelbine *vs* cisplatin and vindesine, vinorelbine alone achieved only a 14% response rate, while the combination of vinorelbine with cisplatin achieved a 30% response rate (Le Chevalier et al, 1994). The control arm, cisplatin and vindesine, yielded a 19% response rate. The median survival time of the cisplatin and vinorelbine arm (40 weeks) was significantly better than those of the other two arms (31 and 32 weeks for the vinorelbine alone and the control arm respectively). This study confirms the necessity of reassessing the results obtained in single institution studies, and raises concern about the level of activity of this drug in NSCLC as a single agent. Similar results were obtained in another large randomized study (231 eligible patients) comparing vinorelbine *vs* vinorelbine with cisplatin 80 mg/m$^2$ (Depierre et al, 1991). In this study there was also a superior response rate (43% *vs* 16%) and longer progression-free interval in the combined arm than in the single agent arm, although survival was similar.

Interestingly, vinorelbine is also absorbed by the oral route, and a large phase II study in 162 stage IV NSCLC patients achieved a response rate of

14.5%, following administration of 40 mg of the drug every week. Given the palliative intent of chemotherapy in stage IV NSCLC, further investigation of this route is warranted, although the bioavailability is only around 20% and nausea and vomiting are more frequent than with the intravenous administration (Vokes et al, 1995).

In a study of pretreated patients with SCLC, vinorelbine obtained only a 16% response rate (Jassem et al, 1993) in 25 assessable 'sensitive' patients (see definition below).

### Taxanes

Paclitaxel and docetaxel have both been shown to have significant activity in lung cancer. The taxanes are a new class of anticancer agents which stimulate the polymerization of microtubules and inhibit their depolymerization. The latter action distinguishes the taxanes from vinca alkaloids, which are pure spindle poisons. Both taxanes show significant activity in ovarian cancer patients and breast cancer patients.

**Paclitaxel:** Several studies have demonstrated significant activity of paclitaxel in advanced untreated NSCLC (*Table 2*). The first two studies employed paclitaxel with 24-hour infusion. In these initial studies a response rate of 21–24% was reported with relatively high doses given every 3 weeks (Chang et al, 1993; Murphy et al, 1993). Interestingly, in both reports, the 1-year survival was somewhat longer than expected in this patient population (42% and 30% respectively). The major toxicity was granulocytopenia, which was life-threatening in 16 patients in the study performed with the higher dose, and one patients died of sepsis. The prophylactic use of colony-stimulating factor at this dose level is indicated. As both studies employed premedication with dexamethasone, diphenhydramine and cimetidine, allergic reactions were only a minor problem, in contrast to initial findings in paclitaxel studies.

Shorter infusion times and lower doses have also been investigated in NSCLC, based on the finding that shorter infusion times produce less haematological toxicity than longer infusions, without substantially reducing the activity (Eisenhauer et al, 1994). On the other hand, dose might influence response rate and progression-free survival. Interestingly, in a study of 53 patients with assessable metastatic NSCLC, 1-hour infusion was given in 1 day or over 3 days at 135 or 200 mg/m$^2$. The overall response rate was 25%, but it was only 12% in the lower dose *vs* 31% in the higher dose (Hainsworth et al, 1995). Toxicity was mild in this study, with only 12% of the courses given at the higher dose producing grade 3–4 leukopenia. There was no difference in response rate between the 1-day or the 3-day fractionated doses. However, in one study, a 3-hour infusion of 175 mg/m$^2$ paclitaxel produced only a 10% response rate (Millward et al, 1996), which contraindicates the use of shorter infusion times outside appropriate clinical trials.

Several combinations of paclitaxel with other drugs have been tested; very promising results of combinations with cisplatin or carboplatin have been reported. In a combination of paclitaxel 135 mg/m$^2$ in a 24-hour infusion, together with carboplatin given at 7.5 AUC (area under the concentration x titre curve; using the Calvert formula), followed by granulocyte-colony stimulating factor (G-CSF), a response rate of 62% with 9% complete responses were obtained in 54 treated patients with advanced NSCLC (Langer et al, 1995). Interestingly, the 1-year survival was 54%. Similar results were obtained in other reported studies, also employing shorter infusion times (3-hour) of paclitaxel.

Paclitaxel has radiosensitizing properties, and has been investigated in combination with chest radiotherapy in patients with locally advanced NSCLC. Oesophagitis was the dose-limiting toxicity in a weekly administration of 3-hour infusion of paclitaxel, at the maximum tolerated dose of 60mg/m$^2$/week (Choy et al, 1994).

Activity of paclitaxel has been demonstrated in 34% of 32 assessable SCLC patients who had extensive disease which had not been pretreated by chemotherapy (Ettinger et al, 1995).

**Docetaxel:** Docetaxel is a semisynthetic taxane extracted from a quickly renewable source, the needles of the European plant *Taxus baccata*, an easier drug supply than the bark of the pacific yew *Taxus brevifolia*, from which taxol is extracted. The mechanism of action of docetaxel is identical to that of paclitaxel. The toxicity profile of docetaxel is similar to that of paclitaxel, although the development of peripheral oedema and effusions have been reported only in patients treated with docetaxel for prolonged periods of time. Docetaxel is active in ovarian cancer, breast cancer and lung cancer (*Table 3*).

The response rate in untreated NSCLC varied between 23% and 38% (Cerny et al, 1994; Fossella et al, 1994; Francis et al, 1994). A study tried to reduce infusional reactions and rash by giving a lower dose of docetaxel (75 mg/m$^2$ every 3 weeks instead of 100 mg/m$^2$) in combination with premedication with prednisone, to 20 previously untreated NSCLC patients (Miller et al, 1995). The response rate was 25%, with a reduction of allergic episodes and skin toxicity, but a similar level of neutropenia. The authors suggested that premedication be used with the higher dose of 100 mg/m$^2$. In another study, of 42 patients with advanced (stage IIIb or IV) NSCLC who were refractory to prior cisplatin-based chemotherapy, a 21% response rate was obtained (Fossella et al, 1995).

Activity of docetaxel in several malignancies has recently been reviewed (Cortes and Pazdur, 1995): in a total of 262 NSCLC patients reported in 9 studies, cumulative response rates of 31.3% in chemotherapy-naive patients and of 19.4% in platinum-pretreated patients were observed.

So far only one study of SCLC has been published (Smyth et al, 1994), in which a partial response rate of 25% was obtained in 28 previously treated patients.

**Table 2. Results of phase II studies of paclitaxel in lung cancer**

| | No. of evaluable patients | Dose (mg/m$^2$) | Infusion time (hours) | Response rate (%) | Reference |
|---|---|---|---|---|---|
| Non-small cell lung cancer | 25 | 200 | 24 | 24 | Murphy et al (1993) |
| | 24 | 250 | 24 | 21 | Chang et al (1993) |
| | 53 | 135 or 200 | 1 (in 1 or 3 days) | 25 | Hainsworth et al (1995) |
| | 51 | 175 | 3 | 10 | Millward et al (1996) |
| | 37 | 225 | 3 | 22 | Gatzemeier et al (1995) |
| Small cell lung cancer | 32 | 250 | 24 | 34 | Ettinger et al (1995) |

This table only includes published studies. No patients had been pretreated by chemotherapy.

## Topoisomerase I inhibitors

Three topoisomerase I inhibitors, camptothecin derivatives, are undergoing major clinical evaluation: irinotecan (CPT-11) and topotecan (which have already shown evidence of activity in lung cancer; *Table 4*), and 9-amino-camptothecin.

### Irinotecan

CPT-11, or 7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyoxy-camptothecin, was developed in Japan in the early 1980s, where it first entered clinical trials. The drug is now being studied in Europe and the USA. Reports of activity of CPT-11 have been published for lung cancer, colorectal cancer, leukaemias and lymphomas, and other malignancies. Granulocytopenia and diarrhoea are the limiting toxicities reported. In a large phase II trial with 100 mg/m$^2$ weekly administration, a partial response rate of 32% was obtained in 72 untreated NSCLC patients (Fukuoka et al, 1992). Based on this, combinations of CPT-11 with other active drugs have been studied. A dose-finding study in which CPT-11 was administered weekly, in combination with cisplatin, to 27 untreated NSCLC patients achieved a 54% partial response rate (Masuda et al, 1992a). The recommended doses for phase II trials of this combination are CPT-11 60 mg/m$^2$ on days 1, 8 and 15, and cisplatin 80 mg/m$^2$ on day 1, every 4 weeks. In a further attempt to increase the doses of the drugs, 20 previously untreated NSCLC patients were given prophylactic G-CSF as well; but diarrhoea became the dose-limiting toxicity and prevented significant dose escalation. Safe doses of 80 mg/m$^2$ for both drugs were recommended for further studies in combination with G-CSF, representing a dose increase of 33% over the original regimen (Masuda et al, 1994a). There were 10 partial responses (50%) in this study, a comparable rate to the previous study (Masuda et al, 1992a).

A dose-finding study of combination irinotecan with etoposide has been undertaken in 25 advanced lung cancer patients. CPT-11 was given at escalating doses on days 1, 8 and 15, in combination with etoposide given at a fixed dose (80 mg/m$^2$) for 3 days (Masuda et al, 1994b). The dose-limiting toxicities were leukopenia and diarrhoea, the maximum tolerated dose being irinotecan 90 mg/m$^2$. The recommended doses for previously untreated and pretreated patients were 80 and 70 mg/m$^2$, respectively, with G-CSF support from days 4 to 21 at 2 µg/kg/day. Response rates of 58% and 22% were observed in 12 SCLC and 9 NSCLC patients respectively. Most SCLC patients were pretreated by chemotherapy.

A three-drug combination (irinotecan, cisplatin and vindesine) has been investigated in a dose-finding study, undertaken in patients with advanced NSCLC (Shinkai et al, 1994). In two cohorts of patients CPT-11 was given on days 1 and 8, together with a fixed dose of 3 mg/m$^2$ vindesine and either high- (100 mg/m$^2$) or low- (60 mg/m$^2$) dose cisplatin on day 1. Colony-stimulating factor support was not allowed in this study. Grade 4 granulocytopenia associated with grade 3 diarrhoea was dose-limiting at 50 and 100 mg/m$^2$ CPT-11 in the two groups of patients respectively. The recommended doses of CPT-11 were 37.5 and 80 mg/m$^2$ respectively. The response rate was in the range of that reported for CPT-11 combinations with cisplatin.

A small study in 15 evaluable SCLC patients treated with the weekly schedule of irinotecan obtained a 47% response rate. All patients received prior chemotherapy, but all patients except one could be classified as 'sensitive' (see below) (Masuda et al, 1992b).

### Topotecan

Topotecan is another water-soluble camptothecin analogue synthesized in Europe. Two studies have been published in untreated advanced NSCLC with modest results: the first obtained no responses in 20 previously untreated patients (Lynch et al, 1994), and the second obtained a 15% response rate in 40 assessable patients, with 30% 1-year survival (Perez-Soler et al, 1996). The main toxicity of topotecan is myelosuppression, with neutropenia more pronounced than thrombocytopenia.

Topotecan has definite activity in untreated SCLC patients and in patients who are still relatively 'sensitive' to chemotherapy despite prior treatment (i.e. patients who responded to prior chemotherapy and had an off-chemotherapy time >3 months, after only one regimen). The response rate was 39% and 7% in the 44 'sensitive' and 43 'refractory' patients respectively, indicating clearly that topotecan is largely cross-resistant to previously administered chemotherapy agents, which mostly included topoisomerase II inhibitors (Ardizzoni et al, 1994; and personal communication). The response rate in untreated patients was 37% in a preliminary analysis of another study (Schiller et al, 1994). Both studies used 30 minutes infusion for 5 days, the former at a daily 1.5 mg/m$^2$ dose and the latter at 2 mg/m$^2$.

## Other drugs of interest

Etoposide is a topoisomerase II inhibitor for which a clear schedule dependency has

**Table 3. Results of phase II studies of docetaxel in lung cancer**

| | No. of evaluable patients | Dose (mg/m$^2$) | Response rate (%) | Reference |
|---|---|---|---|---|
| Non-small cell lung cancer | 35 | 100 | 23 | Cerny et al (1994) |
| | 29 | 100 | 38 | Francis et al (1994) |
| | 39 | 100 | 33 | Fossella et al (1994) |
| | 20 | 75 | 25 | Miller et al (1995) |
| | 72 | 60 | 25 | Kudo et al (1994) |
| | 42* | 100 | 21 | Fossella et al (1995) |
| Small cell lung cancer | 28 | 100 | 25 | Smyth et al (1994) |

This table only includes published studies. *Cisplatin-refractory patients; all other non-small cell lung cancer patients had not been pretreated by chemotherapy.

**Table 4. Results of phase II studies of camptothecins in lung cancer**

| | Drug | No. of evaluable patients | Response rate % | Reference |
|---|---|---|---|---|
| Non-small cell lung cancer | CPT-11 | 72 | 32 | Fukuoka et al (1992) |
| | Topotecan | 20 | 0 | Lynch et al (1994) |
| | Topotecan | 40 | 15 | Perez-Soler et al (1996) |
| Small cell lung cancer | CPT-11 | 15 | 47 | Masuda et al (1992) |
| | Topotecan | 18 | 39 | Schiller et al (1994) |
| | Topotecan | 87 | 23 | Ardizzoni et al (1994) |

been demonstrated in SCLC patients (Slevin et al, 1989). Repeated administrations over several days are clearly advantageous over a single administration. Recently, chronic administration of oral etoposide has produced interesting results in both SCLC patients (Einhorn et al, 1990) and in those with other malignancies. Chronic oral etoposide administration has also shown activity in NSCLC patients, although contradictory results have been published (Waits et al, 1992). Epirubicin, another topoisomerase II inhibitor and a derivative of doxorubicin, has shown activity in NSCLC, but only when given at high doses.

## New strategies for drug development and conclusions

A better understanding of the biology of lung cancer will offer new possibilities for drug development in the future. The challenge for new drug discovery would be to develop novel and selective therapies based on the molecular alterations responsible for the malignant phenotype.

The new drugs described here clearly represent progress over older drugs, both in terms of increased efficacy and, at least for some of them, better tolerance (e.g. gemcitabine). The overall response rate in NSCLC is superior to that of older drugs and survival may be prolonged, although the complete response rate remains <10% in advanced disease, and results of phase III trials are still awaited. Investigation of new combinations regimens is certainly warranted.


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### KEY POINTS

- **In the last few years, several new chemotherapeutic agents with substantial activity in advanced lung cancer have become available.**
- **New drugs active in small cell lung cancer also have a significant activity in non-small cell lung cancer.**
- **For the first time after at least a decade of poor results, new drugs are being introduced into the treatment of non-small cell lung cancer which may offer advantages over older drugs.**
- **Some of the new active drugs for lung cancer are also relatively less toxic than the older drugs.**