Drug therapy of lung cancer

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SYNOPSIS

Lung cancer is the commonest cause of death from cancer in Australia. Almost all patients with small cell lung cancer are given chemotherapy either alone or in combination with radiotherapy. The use of chemotherapy in the management of metastatic non-small cell lung cancer has increased over the past decade. It can prolong survival and improve quality of life, when compared to best supportive care. Chemotherapy has an expanding role in the management of earlier stage disease and is now frequently included in combined modality treatment programs.

Index words: antineoplastics, chemotherapy.

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Introduction

Each year almost 7000 Australians die as a result of lung cancer, making this the commonest cause of death from cancer. Although efforts to reduce the proportion of the population who smoke have been successful in reducing the incidence of the disease in men, the number of new cases in women continues to rise. Up to 25% of patients present with early stage, localised disease that is amenable to surgical treatment. However, for the remainder, treatment often involves the use of chemotherapy, either as part of a potentially curative combination of therapies or as part of palliative therapy.

There are two major types of lung cancer. These are small cell lung cancer and non-small cell lung cancer. Small cell lung cancer accounts for approximately 20% of all lung cancer and is a discrete histologic and clinical entity. Non-small cell lung cancer, which accounts for the remaining 80% of cases, is a term that encompasses several histologic types of tumour. These include adenocarcinoma (also including bronchoalveolar carcinoma), squamous cell carcinoma and large cell carcinoma. As these tumours all behave in a similar way, their management is identical.

Chemotherapy for non-small cell lung cancer

Over the past decade there has been a marked increase in the use of chemotherapy. This has occurred as a consequence of two meta-analyses which showed that chemotherapy prolonged survival in metastatic disease[1,2], the availability of several new anticancer drugs[3] and a recognition that combined modality treatment which includes chemotherapy produces better outcomes in patients with locally advanced disease.

The newer drugs, which are associated with higher response rates and less toxicity than older drugs, include docetaxel, gemcitabine, paclitaxel and vinorelbine. However, none of these drugs was included in the meta-analyses. The newer drugs are usually used in combination with a platinum drug (either cisplatin or carboplatin) or, rarely, with one another. They may be used alone in less fit patients. Most people can be treated as outpatients. The usual administration schedules of these drugs, as well as common adverse effects, are summarised in Table 1. Febrile neutropenia is the most serious potential complication of chemotherapy for non-small cell lung cancer. This requires prompt assessment and management with broad-spectrum intravenous antibiotics.

All of the newer drugs produce responses (reduction of more than 50% in the cross-sectional area of tumours) in 15–25% of patients when they are used alone. Combinations which include cisplatin or carboplatin produce slightly higher response rates. Response rates are not good indicators of patient benefit. Therapeutic decisions should therefore not be based solely on response rates, but should take into account survival, control of symptoms, and quality of life.

Metastatic non-small cell lung cancer

Metastatic (stage IV) disease is incurable so the goals of treatment are to prolong life and palliate symptoms. Although early randomised trials failed to show a significant effect of chemotherapy on survival compared to best supportive care,

Table 1

Drugs used in the treatment of small cell and non-small cell lung cancer

Drug	*Usual duration and schedule for intravenous infusion*	*Commonest adverse effects*
Carboplatin	1 hour every 21 days	Thrombocytopenia, neutropenia, anaemia
Cisplatin	1–2 hours every 21 days	Nausea, vomiting, renal impairment, anaemia, neuropathy, tinnitus, hearing loss
Docetaxel	1 hour every 21 days	Neutropenia, fluid retention, neuropathy, alopecia
Etoposide	1 hour daily for 3 days every 21 days	Neutropenia, alopecia
Gemcitabine	30 minutes every 7 days	Thrombocytopenia, lethargy
Paclitaxel	3 hours every 21 days	Neutropenia, neuropathy, allergic reactions, alopecia
Vinorelbine	5–10 minutes every 7 days	Neutropenia, neuropathy, pain during infusion, erythema at infusion site

more recent studies, and two meta-analyses, have found that chemotherapy produces a modest prolongation of life. Just as important has been the demonstration of improvements in symptoms and quality of life in patients receiving treatment.[4,5] This is particularly the case for the symptoms patients with lung cancer commonly experience such as haemoptysis, shortness of breath, cough and chest pain.

One of the principal arguments against the use of chemotherapy has been the toxicity associated with many of the older drugs, such as cisplatin, vindesine and mitomycin. More modern drugs such as paclitaxel, docetaxel, gemcitabine and vinorelbine all provide increased efficacy with reduced toxicity. The use of carboplatin in place of cisplatin, and the availability of more effective antiemetics such as the serotonin ($5HT_3$) antagonists, have also reduced the nausea and vomiting that previously had a negative impact on the quality of life of patients undergoing chemotherapy.

Most chemotherapy involves a combination of two drugs (Table 2). Randomised trials have shown that these combination regimens have better outcomes than single drugs do. Single drug regimens may be appropriate for older patients, or those with poorer performance status (for example those who are confined to bed for more than 50% of the day or those with severe comorbidity). There is no advantage in using more than two drugs. In addition, there is no single 'best' regimen; any of the combinations shown in Table 2 is an acceptable first-line treatment for metastatic disease.[6]

Newer oral drugs such as the epidermal growth factor receptor tyrosine kinase inhibitors are expected to come into routine use in the near future. Their efficacy and lower toxicity mean that they may have a future role in treating frail patients. However, randomised trials have failed to show a survival benefit when one of these drugs, gefitinib, is added to standard chemotherapy.

There has been a gradual improvement in the survival of patients with advanced non-small cell lung cancer following chemotherapy. The median survival and one-year survival rate improved from four months and 15% with supportive care alone, to six months and 25% with early chemotherapy regimens. Modern chemotherapy usually results in a median survival of 10 months and a one-year survival rate of 35–40%, with the two-year survival rate up to 25% in several recent clinical trials.[7] While these are only modest improvements in outcome, patients regard them to be of value. Patients whose performance status is poor derive little benefit from chemotherapy.

Table 2

Commonly used combinations for treating non-small cell lung cancer

Cisplatin + gemcitabine
Cisplatin + vinorelbine
Cisplatin + docetaxel
Carboplatin + paclitaxel
Carboplatin + gemcitabine

Table 3

Treatment outcomes for small cell and non-small cell lung cancer

Stage	*Treatment*	*Median survival (months)*	*Long-term survival* (%)*
Non-small cell lung cancer			
IIIA†	chemotherapy/surgery	24	30
IIIB‡	chemotherapy/radiotherapy	12–18	10
IV	chemotherapy	10	< 5
Small cell lung cancer			
Limited	chemotherapy/radiotherapy	18–24	20–25
Extensive	chemotherapy	10–12	5

* percentage of patients still alive 3 to 5 years after diagnosis
† involved ipsilateral mediastinal lymph nodes
‡ involved contralateral mediastinal lymph nodes

In recent years there has been an increased interest in second-line chemotherapy (treatment given when the disease has progressed during or after initial chemotherapy). In a randomised trial, docetaxel has improved survival when compared to best supportive care in previously treated patients with good performance status. Non-randomised data also exist for gefitinib, showing symptom improvement in up to 40% of such patients.

Locally advanced non-small cell lung cancer

The cancer in patients with locally advanced (stages IIIA and B) disease is confined to the thorax, but has spread to involve the mediastinal lymph nodes. Traditional management approaches have used surgery or radiotherapy for these patients, but the results were poor with only 5–20% of patients surviving for 3–5 years. Recently, combined modality treatment has become more common.

Giving chemotherapy either before surgery and radiotherapy, or concurrently with radiotherapy, has resulted in modest improvements in survival (Table 3). One of the combination chemotherapy regimens is usually used and no specific combination has superiority. Three to four cycles of chemotherapy are usually given over 9–12 weeks before surgery, or concurrently with radiation therapy.

The addition of chemotherapy to the management plan for these patients also adds to the toxicity of treatment. In addition to the toxicities of chemotherapy itself, there are adverse effects that result from its combination with surgery and radiotherapy. Surgical morbidity is increased following chemotherapy and this may lead to small increases in mortality, however this is usually not excessive in the hands of experienced thoracic surgeons. Patients receiving chemotherapy and radiotherapy concurrently are at an increased risk of complications such as radiation pneumonitis and oesophagitis. These complications are usually self-limiting, but can be the cause of significant morbidity.

Some patients with stage IIIB disease present with substantial weight loss or a pleural effusion. Their outlook is poor, with

the disease behaving more like metastatic than locally advanced disease. Consequently, treatment for these patients should be identical to that given to patients with stage IV disease.

Small cell lung cancer

Two features of small cell lung cancer result in it being treated quite differently to non-small cell lung cancer. Firstly, the disease has a propensity for early and widespread metastases; even patients with disease that is clinically localised to the thorax are likely to be harbouring occult metastases. Secondly, small cell lung cancer is extremely chemo- and radiosensitive. The staging of patients is different from that of patients with non-small cell lung cancer. Patients with a small cell cancer confined to one hemithorax (including the ipsilateral supraclavicular fossa) are said to have limited disease while those with tumour beyond this have extensive disease.

Chemotherapy

For patients with limited disease, a combination of intravenous chemotherapy and thoracic radiotherapy is the mainstay of treatment. Ideally, these modalities should be given simultaneously.[8] Usually patients are treated as outpatients with the combination of intravenous cisplatin and etoposide, given each day for three days. Four cycles of treatment are given, with a 21-day gap between each cycle. Radiation is given daily for approximately 4–5 weeks. Concurrent chemotherapy and radiotherapy results in increased toxicity, particularly in the elderly and those with comorbidities (e.g. coronary artery disease). In these patients, it is common to use a sequential approach, with the radiation treatment not given until the conclusion of all chemotherapy.

The rationale for the use of thoracic radiotherapy is that relapse usually occurs at the site of bulk disease (usually in the lung or mediastinum). Hence radiation is directed toward this site. By contrast, patients who present with extensive disease are at risk of relapse at any of the tumour sites, and so there is no reason to target any one location using radiotherapy. The usual management of these patients is with intravenous chemotherapy alone, using carboplatin and etoposide, given daily for three days. Up to six cycles of treatment are given, with each cycle planned to be 21–28 days apart, depending on the extent of treatment-induced myelosuppression. Treatment results in an improvement in symptoms and a prolongation in survival from the median of three months without therapy.

Although an oral formulation of etoposide is available, it is not widely used. There is substantial variability in absorption between patients leading to unpredictable haematological toxicity. This is reflected in the results of randomised trials comparing oral and intravenous use of etoposide, which show increased toxicity and worse outcomes in patients receiving oral therapy.

In contrast to non-small cell lung cancer, there has been little change in the drugs used to treat small cell lung cancer in the past decade and the prognosis is poor (Table 3). Although all of the newer drugs used for treating non-small cell lung cancer also have activity in small cell lung cancer, they have not resulted in improved outcomes. Recently, irinotecan, a camptothecin widely used in the management of colorectal cancer, has been shown to improve survival in extensive small cell lung cancer when used in combination with cisplatin. The results of this single randomised trial are awaiting confirmation, and this regimen is not yet in widespread use.

Future directions

A large number of newer drugs are currently undergoing clinical trials for use in lung cancer. These drugs differ from conventional chemotherapy by targeting molecules involved in tumour growth including those responsible for intracellular signalling and new blood vessel growth (angiogenesis). Typically, they have fewer adverse effects than conventional chemotherapy, and generally may be administered orally. However, the evidence available from current studies suggests that they will need to be used in conjunction with chemotherapy rather than in place of it, but their exact place in management remains to be defined.

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Associate Professor Boyer serves on an advisory board for AstraZeneca, as well as Aventis Pharma.

Self-test questions

The following statements are either true or false (answers on page 119)

3. The best combination of drugs for chemotherapy of metastatic non-small cell lung cancer is unknown.
4. Modern chemotherapy regimens for metastatic non-small cell lung cancer increase the median survival by twelve months.