REVIEW ARTICLE

Chemotherapy for advanced non–small-cell lung cancer: role of paclitaxel and gemcitabine

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Objective. To review the role of chemotherapy in advanced non–small-cell lung cancer, focusing on cisplatin-based regimens and two new drugs: paclitaxel and gemcitabine.
Data sources. *Medline* search of the relevant English literature.
Study selection. Open and randomised comparative (phases II and III) studies, and meta-analyses of cytotoxic drugs/regimens used to treat advanced non–small-cell lung cancer.
Data extraction. The following factors were studied and compared: symptomatic response rates; tumour response rates; median survival time and 1-year survival rates; and side effects of cisplatin-, paclitaxel-, and gemcitabine-based regimens.
Data synthesis. Using cisplatin-based chemotherapy achieves significant relief of disease-related symptoms of advanced non–small-cell lung cancer and a slight improvement in the median survival time (by approximately 1.5 months). New cytotoxic drugs that are effective and have good safety profiles include paclitaxel and gemcitabine. When used as single agents, these two drugs give response rates of approximately 25%. When used with cisplatin/carboplatin, response rates increase to 45% to 62% and 1-year survival rates increase to 40% to 60%.
Conclusion. Paclitaxel, gemcitabine, and other drugs such as decetaxel and vinorelbine are promising new chemotherapeutic agents in the treatment of advanced non–small-cell lung cancer. These drugs can palliate disease symtoms and improve the median survival time. The optimal dose and treatment schedules, however, are yet to be defined.

HKMJ 1999;5:180-6

Key words: Antineoplastic agents/therapeutic use; Carcinoma, non–small-cell lung/drug therapy; Cisplatin; Deoxycytidine/analogs & derivatives; Paclitaxel; Survival rate

Introduction

Lung cancer is the most common cause of cancer death in Hong Kong and accounted for 29% of all cancer deaths in 1995.[1] Of the four major histological subtypes of lung cancer, small-cell carcinoma is the most responsive to chemotherapy and radiotherapy. In contrast, squamous cell carcinoma, adenocarcinoma, and large cell carcinoma are relatively resistant to chemotherapy and radiotherapy. These three disease types are collectively referred to as non–small-cell lung cancer (NSCLC) and account for approximately 80% of all primary lung cancers.[2]

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The treatment of NSCLC depends on the stage of the disease, as denoted by the tumour-node-metastasis (TNM) staging system,[3] which is used internationally. Stage IIIB disease is locally advanced disease and stage IV disease indicates that metastasis has occurred; these two stages account for approximately 60% of all cases of lung cancer on presentation.[2] Stage IIIB and IV diseases are advanced diseases that are incurable. The primary goals of therapy are to palliate symptoms and, if possible, to prolong survival. Traditionally, treatment has been only symptomatic and supportive by giving palliative radiotherapy, pleurodesis for pleural effusion, or analgesics for pain.

The use of chemotherapeutic agents

In the late 1970s and 1980s, commonly used drugs to treat NSCLC included cyclophosphamide, mitomycin, methotrexate, adriamycin, etoposide, fluorouracil,

Table 1. Symptoms improved by chemotherapy

Symptom	Treatment		
	MVP*[8,11]	PV + M or I†[9]	MIP‡[10]
Cough	66%-71%	45%	70%
Haemoptysis	-	91%	92%
Pain	60%-63%	47%	77%
Dyspnoea	59%-65%	78%	46%
Anorexia	-	50%	58%

* MVP mitomycin/vinblastine/cisplatin
† PV + M or I cisplatin/vindesine + mitomycin or ifosfamide
‡ MIP mitomycin/ifosfamide/cisplatin

vincristine, vinblastine, bleomycin, nitrosoureas, and cisplatin. Subsequent reviews showed that, of the conventional cytotoxic drugs, only the following five gave an objective response rate of 12% or more in patients with advanced NSCLC when used as single agents: mitomycin (22%), cisplatin (21%), ifosfamide (20%), vinblastine (18%), and vindesine (12%).[4] Typical combination chemotherapy in the late 1980s and early 1990s included cisplatin-based regimens such as cisplatin in various combinations with etoposide, adriamycin/epirubicin, vindesine/vinblastine, and mitomycin and cylophosphamide/ifosfamide.[5-7]

Does chemotherapy palliate symptoms of advanced non–small-cell lung cancer?

One of the aims of chemotherapy for advanced NSCLC is to alleviate disease symptoms, and many clinicians are concerned that the toxic chemotherapeutic agents may adversely affect patients' quality of life and performance status. This is certainly true for older agents, particularly alkylating agents, but not the newer cisplatin-based regimens. A few studies have addressed the effect of chemotherapy on disease-related symptoms, such as cough, pain, haemoptysis, and breathlessness (Table 1).[8-11] The studies show that giving cisplatin-based chemotherapy could alleviate symptoms in 45% to 92% of patients with NSCLC.[8-11] Even modest doses of mitomycin, vinblastine, and cisplatin combination therapy were able to cause complete or substantial symptomatic relief in 69% of patients; only one course of chemotherapy was needed by 61% of patients and two courses by 96% (patient response rate, 20% to 30% [n=120]).[11]

Although previous studies show that modern chemotherapy can achieve the first goal of therapy in metastatic lung cancer—namely, the palliation of symptoms—many of the studies involved relatively small numbers of patients; thus, the evidence is not conclusive. Nevertheless, the availability of new, powerful anti-emetics[12,13] and haemopoietic growth factors[14] can help decrease the toxicities and morbidities associated with chemotherapy. Haemopoietic colony-stimulating factors, for example, have been used to treat febrile neutropenia induced by a prior chemotherapy cycle; the treatment avoids infectious complications and maintains the dose-intensity of the chemotherapeutic drugs in subsequent treatment cycles, when chemotherapy dose-reduction is not appropriate.[14]

Elaborate test methods to measure the quality of life in patients with lung cancer are now available (eg the Lung Cancer Symptoms Scale, the Quality of Life Questionnaire of the European Organisation for the Research and Treatment of Cancer, the Rotterdam Symptom Checklist, the Functional Living Index-Cancer, and the Daily Diary Card).[15,16] The quality of life is increasingly becoming integrated as part of clinical trials.[16]

Does chemotherapy prolong survival?

Advanced stages (IIIB and IV) of lung cancer have a poor prognosis and a median survival time of only 6 to 8 months.[17] Use of the older, toxic alkylating agents might actually result in shortened survival time.[18] A recent meta-analysis of trials using long-term therapy of alkylating agents suggested a detrimental effect of chemotherapy, and obtained a hazard ratio of 1.26 (P=0.095).[18] Whether cisplatin-based chemotherapy prolongs survival significantly in patients with NSCLC remains debatable.[19,20] At least five recent meta-analyses of a large number of randomised controlled studies have compared chemotherapy and best supportive care alone in advanced NSCLC.[18,21-24] The earlier meta-analyses analysed six to eight studies and show that cisplatin-based chemotherapy prolongs survival in patients with advanced NSCLC by approximately 2 months. The most recent large-scale meta-analysis used updated data on individual patients from 52 randomised clinical trials involving in 9387 patients, that took place between 1970 and 1988.[18] Of the advanced disease group, data were available from 11 trials (1190 patients). The absolute survival difference was calculated by comparing survival rates of patients in the control arm of cisplatin-based trials with that of each treatment arm at given points in time. The results show that compared with the best supportive care, the patients in the cisplatin-based chemotherapy arm gained an absolute improvement in survival of 10% at 1 year and an increase in median survival of 1.5 months (P<0.0001).[18]

While such survival gains may be considered small and unimportant to some clinicians, they are of great

importance to the patients.[25] The patients must be fully informed of the facts and be allowed to take part in the decision of whether or not to use chemotherapy and if so, which type.

Recommendations on chemotherapy

From the above brief review, it is apparent that cisplatin-based chemotherapy can result in the palliation of symptoms and prolongation of survival time of patients with advanced NSCLC. The initial performance status is an important prognostic factor, and patients who have an initial Karnofsky performance status of 80 to 100 (on a scale of 1 to 100) have an increased major objective response rate and survival.[26] Cisplatin-based chemotherapy may be offered to patients who have a satisfactory performance status,[26] have recently lost less than 5% of their body weight,[27] have evaluable tumour lesions, or have significant tumour-related symptoms that would not be readily relieved by medication or radiotherapy. The response to treatment should be assessed and therapy should be discontinued early if it proves ineffective. Patients should fully understand the aims, side effects, and limitations of chemotherapy and should be fully motivated about their treatment.

It must be realised, however, that the role of cisplatin-based chemotherapy in NSCLC has remained uncertain and controversial.[19,20,28] More large-scale prospective studies such as the Big Lung Trial[28] are needed to elucidate the effects of cisplatin-based treatment.

New chemotherapeutic agents

In the past few years, many new cytotoxic agents have been developed that demonstrate improved response rates of 14% to 38% (mean, approximately 25%) when used as single agents in the treatment of NSCLC (Table 2).[29-33] Some of these are analogues of agents with known mechanisms of action; examples are gemcitabine (a derivative of cytarabine), vinorelbine (a synthetic vinca alkaloid), and edatrexate (a derivative of methotrexate). Some of the new drugs have new mechanisms of action—for example, the taxanes promote microtubule assembly and inhibit their depolymerisation, and topoisomerase I inhibitors prevent DNA replication (Table 2). Paclitaxel and gemcitabine are briefly reviewed below.

Table 2. New drugs for advanced non–small-cell lung cancer[29-33]

Class	Drug	Response rate as single agent (%)
Taxane	Paclitaxel	21-38
	Docetaxel	23-38
Antimetabolite	Gemcitabine	17-28
Vinca alkaloid	Vinorelbine	14-36
Topoisomerase I inhibitor	Irinotecan	32-34

Paclitaxel

Paclitaxel was first reported to have a beneficial activity in patients with advanced NSCLC in 1993.[34,35] Initial studies used a 24-hour infusion schedule to reduce the incidence of hypersensitivity reactions. With the demonstration that the triple premedication schedule (corticosteroid, antihistamine, H_2-receptor antagonist) was effective in alleviating hypersensitivity reactions, short infusion schedules (1-hour or 3-hour) were used and were found to produce equivalent efficacy and less myelosuppression.[30] Currently, 3-hour short infusion schedules are mainly used.

Paclitaxel as a single agent

Single-agent activity of paclitaxel to treat NSCLC has now been confirmed.[30] Despite a variety of doses (175 mg/m^2 to 250 mg/m^2) and different schedules (1-hour, 3-hour, 24-hour, 3-weekly infusions), 10 studies involving 316 patients have demonstrated a superior mean response rate of 27%, which is similar to the response to standard drug combinations of the early 1990s, such as cisplatin and etoposide; or mitomycin, vindesine, and cisplatin.[5-7] The median survival time was 37 weeks and the 1-year survival rate was 41%.[30] A recent study in which paclitaxel 175 mg/m^2 was given as an intravenous infusion over 3 hours weekly for six consecutive weeks of an 8-week cycle (using standard antihypersensitivity premedication) showed partial responses in 14 (56%) of 25 patients.[36] The median duration of response was 6.5 months and the 1-year survival rate was 53%. The marked activity and accepted toxicity (mainly neurological) of paclitaxel, if confirmed, would represent an improved schedule of administration.

Paclitaxel plus cisplatin

There have been at least seven reported studies of paclitaxel used in combination with cisplatin in the treatment of advanced NSCLC.[30] Response rates between 31% and 52% (mean, 42%) were observed in a total of 219 patients; the median survival was 45 weeks and the 1-year survival rate was 39%.[30] In contrast, existing cisplatin-based chemotherapy regimens typically give objective response rates of less than 40% in cases of advanced NSCLC, the treatment rarely results in a median survival beyond 25 to 30 weeks or a 1-year survival rate of greater than 20% to 25%.[30] The paclitaxel/cisplatin regimen

Table 3. Comparison of existing cisplatin- and paclitaxel-based chemotherapy

Treatment	Response rate (%)		Median survival time (weeks)	1-year survival rate (%)
	Complete	Partial		
Current cisplatin-based chemotherapy	-	≤40	25-30	20-25
Paclitaxel as single agent[30]	-	27	37	41
Paclitaxel/cisplatin regimen[30]	-	42	45	39
Paclitaxel/carboplatin[38]	9	53	53	54

is well tolerated, and neurotoxicity (mainly paraesthesia) is the dose-limiting toxicity.

Paclitaxel plus carboplatin

The rationale of combining paclitaxel with carboplatin rather than with cisplatin is that carboplatin is both more convenient (no hydration needed) and less toxic than cisplatin.[37] Langer et al[38] have reported the use of paclitaxel at an initial dosage of 135 $mg \cdot m^{-2} \cdot d^{-1}$ by 24-hour infusion, a sequential dose increase by 40 mg/m^2 per cycle to a maximum of 215 mg/m^2, and the co-administration of carboplatin on day 2 at a targeted area under the concentration-time curve (AUC) of 7.5 using the Calvert formula.[38] Treatment was repeated at 3-week intervals for six cycles and subcutaneous granulocyte colony-stimulating factor was given during the second and subsequent cycles. The objective response rate to this regimen was 62% (33/53); five (9%) were complete responses. The median survival was 53 weeks and the 1-year survival rate was 54%.[38] These results are compared with existing cisplatin-based chemotherapy regimens in Table 3.

The paclitaxel/carboplatin regimen has subsequently been modified in schedules by other groups. Greco and Hainsworth[39] administered paclitaxel 225 mg/m^2 by 1-hour infusion, followed immediately by carboplatin at an AUC of 6.0, using a repeating 21-day cycle; 38 (40%) of 94 patients had objective responses (3 complete and 35 partial responses) and the median survival and 1-year survival rate were 8 months and 42%, respectively. DeVore et al[40] obtained an overall response rate to paclitaxel/carboplatin infusion of only 25%; they noted different toxicity profiles and greater myelosuppression after 24 hours of paclitaxel treatment as well as more neurotoxicity and arthralgia/myalgia due to the 1-hour infusion. Langer et al[41] have studied the following modified schedules: (1) paclitaxel 175 mg/m^2 given in 1 hour with an intrapatient dose escalation of 35 mg/m^2 per cycle to a maximum of 280 mg/m^2, plus carboplatin at an AUC of 7.5 every 3 weeks; and (2) paclitaxel 135 mg/m^2 with an intrapatient dose escalation of 40 mg/m^2 per cycle, to a maximum dose of 215 mg/m^2, plus the same carboplatin dosage as in regimen (1). For the cohort using regimen (1), the objective response rate was 55%, but the incidence of neurotoxicity was intolerable and dose-limiting when the paclitaxel dose exceeded 215 mg/m^2. In contrast, for the cohort using regimen (2), which used lower doses of paclitaxel, treatment was more tolerable but gave a lower response rate of 26%.[41] The optimal dose schedule remains to be defined.[42]

Gemcitabine

Gemcitabine is a pyrimidine nucleoside analogue that is related to cytarabine; gemcitabine acts as an antimetabolite.

Gemcitabine as a single agent

The single-agent activity of gemcitabine in advanced NSCLC has now been confirmed.[32,43,44] Using a dosage of 1000 to 1250 mg/m^2, administered as a 30-minute infusion once weekly for 3 weeks followed by a week of rest, four studies involving 398 evaluable patients have demonstrated a mean response rate of 21% and a median survival of 34 weeks. Comparative studies have shown that single-agent gemcitabine is, like paclitaxel, at least as effective as the combination of cisplatin/etoposide in the treatment of advanced NSCLC and has a better toxicity profile.[45,46]

Table 4. Phase II clinical trials of gemcitabine and cisplatin combination therapy

Study	No. of evaluable patients	No. of CRs*	No. of PRs†	Response rates (%)	Median survival time (months)
Natale,[44] 1997	52	1	21	42	9.8
Abratt et al,[47] 1997	50	2	24	52	13.0
Crino et al,[48] 1997	48	1	25	54	14.4
Einhorn,[49] 1997	27	0	10	37	8.4

* CRs complete response
† PRs partial response

Gemcitabine plus cisplatin or carboplatin

At least four phase II trials of gemcitabine/cisplatin in advanced NSCLC have been reported (Table 4).[44,47-49] The overall response rate of 177 evaluable patients was 47.5% (range 37.0%-54.0%); there were four complete responders. The 1-year survival rate was 61% in a South African study.[47] Dose-limiting toxicities were primarily haematological. Grade 3/4 granulocytopenia and thrombocytopenia were observed in up to 58% and 52% of treated patients, respectively. Febrile neutropenia was rare and there were no episodes of serious bleeding. Nausea and vomiting were common, as was expected with a cisplatin-containing regimen. Other toxicities, such as elevation of liver transaminase levels, rashes, and lethargy, were generally mild and reversible. These results appear to be encouraging, and further phase II/III studies are warranted. Studies of the gemcitabine/carboplatin regimen are underway,[50] and results are awaited with interest.

Symptomatic benefit and elderly patients

Thatcher et al[51] have examined the effect of gemcitabine therapy on patients' symptomatic relief and change in performance status. The results showed that symptom improvement occurs in a significant proportion of patients with moderate to severe symptoms (73% for cough, 100% for haemoptysis, 37% for pain, 51% for dyspnoea, and 38% for anorexia). In addition, 52% of patients had improvement in their performance status, and in about one third of patients treated with gemcitabine, palliative radiotherapy was no longer required.[51]

Gemcitabine has a mild toxicity profile and has thus been administered to elderly patients older than 65 years.[52] Gemcitabine's activity and tolerability in the elderly group is similar to those in the younger age group (aged <65 years); the study concluded that gemcitabine should be considered as an alternative for the treatment of elderly patients with advanced NSCLC.

Pulmonary toxicity of gemcitabine

The safety profile of gemcitabine is good. Myelotoxicity is the major dose-limiting toxicity, but very few patients (<1%) have required discontinuation of therapy.[29,32,43,44,53] Other side effects include mild to moderate nausea and vomiting, influenza-like symptoms, mild skin rash, reversible elevation of serum transaminases levels, fever, and dyspnoea; therapy is seldom discontinued, however.[53-55] A recent report has drawn attention to a life-threatening pulmonary toxicity in three patients who developed tachycardia, marked hypoxaemia, and interstitial infiltration, symptoms which are consistent with non-cardiac pulmonary oedema.[56] Two of the patients died and post-mortem examination confirmed acute respiratory distress syndrome, which was consistent with drug-induced pulmonary toxicity.[56] Withdrawing gemcitabine early and starting a course of corticosteroids and diuretics are recommended for averting a fatal outcome. This special pulmonary toxicity is similar to that observed during cytarabine therapy.[57-59]

Gemcitabine/paclitaxel as salvage therapy

The subsequent treatment of patients with NSCLC whose condition has relapsed or for whom initial cisplatin-based chemotherapy was unsuccessful is difficult. A phase II study of paclitaxel/gemcitabine combination therapy has been conducted among patients with NSCLC who had failed first-line cisplatin-based chemotherapy or docetaxel therapy.[60] Of the 26 patients evaluated, two (8%) gave complete responses and five (21%) gave partial responses; the median duration of response was 2.5 months and the median survival was 8 months.[60] The regimen is therefore well tolerated. This preliminary result is encouraging and further studies are warranted.

Conclusion

Paclitaxel, gemcitabine, and other drugs such as docetaxel and vinorelbine are promising new chemotherapeutic agents in the treatment of advanced NSCLC. Their use seems to achieve the two aims of therapy—namely, to palliate disease symptoms and to improve the median survival rate. There are currently no data to show a survival benefit from using these new drugs over cisplatin-based chemotherapy, but comparative studies are underway.[30,44,61,62] Although the toxicities of these two new drugs are tolerable, the optimal dose and treatment schedules are yet to be defined. Efforts to identify new active agents and to determine optimal combinations and dose schedules of existing regimens must continue.

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