Original Article

Phase II Trial of Gemcitabine and Cisplatin Sequentially Administered in Asian Patients With Unresectable or Metastatic Non-small Cell Lung Cancer

D Poon,[1] *MBBS, M Med (Int Med), MRCP (UK)*, KF Foo,[1] *MBBS, M Med (Int Med), MRCP (UK)*, L Chew,[2] *BSc, MSc*, SS Leong,[1] *MBBS, M Med (Int Med), MRCP (UK)*, J Wee,[3] *MBBS, FRCR*, EH Tan,[1] *MBBS, M Med (Int Med), MRCP (UK)*

Abstract

Introduction: The aim of this study was to assess toxicity and response in the sequential administration of gemcitabine followed by cisplatin in unresectable or metastatic non-small cell lung cancer. Materials and Methods: Twenty-three patients were enrolled in this study. Gemcitabine was given at 1250 mg/m² on days 1 and 8, for four 21-day cycles, followed by cisplatin 40 mg/m² on days 1, 8 and 15, for three further 28-day cycles. Results: There were 4 patients with partial responses, 5 patients with stable disease and 10 patients with progressive disease, giving a response rate of 21%. The median time to disease progression was 3.3 months. The median overall survival was 14.6 months. Toxicities graded 3 or 4 included anaemia (13.0%), neutropaenia (13.0%), supraventricular tachycardia (4.3%), and nausea and vomiting (4.3%). Conclusion: Although these results show similar efficacy to single-agent treatment regimens, the low toxicity profile and promising survival outcome with this regimen are important points for consideration.

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Key words: Anaemia, Neutropaenia, Supraventricular tachycardia

Introduction

Lung cancer is the most common cause of cancer-related death worldwide. It ranks first among males and third among females in the incidence of cancers in Singapore.[1] Non-small cell carcinoma (NSCLC) comprises 88% of the patients with lung cancer in Singapore. The majority of patients present with locally advanced or stage IV disease that precludes treatment with curative intent. Therefore, palliation of symptoms and prolongation of life are the standard aims of treatment. Compared to best supportive care, cisplatin-based regimens have been shown to be of benefit with modest survival gain.[2,3] Relatively newer agents such as gemcitabine, docetaxel, paclitaxel and vinorelbine are gaining primacy in dual-drug cisplatin-based combination regimens. Gemcitabine, a nucleoside analogue (2', 2'-difluorodeoxycytidine), acts as a competitive nucleotide for incorporation into deoxyribonucleic acid (DNA), where it leads to chain termination.[4] Single-agent treatment with gemcitabine yielded a response rate of 20% or more in some phase II trials.[5,6] Synergistic interaction was found, in vitro and in vivo, between gemcitabine and cisplatin.[7] Various phase II trials[8-13] of combination gemcitabine and cisplatin had reported response rates of between 26% and 54%, with median overall survival (OS) ranging from 8.4 to 15 months. Furthermore, the toxicity profile with sequential single-agent use is likely to be more tolerable compared to that in concurrent dual-drug regimens. This latter fact is of utmost importance in the palliative treatment of advanced lung carcinoma. In our study, we investigated the sequential use of gemcitabine and cisplatin in advanced lung cancer to achieve equivalent clinical outcome and a more favourable toxicity profile, compared to historical results with the concurrent use of gemcitabine and cisplatin therapy.

Materials and Methods

Eligibility Criteria and Pretreatment Evaluation

Eligibility criteria included histological diagnosis of incurable stage IIIB or IV NSCLC, a performance status of Eastern Congress Oncology Group (ECOG) scale of 0 to 2, a life expectancy of more than 12 weeks, no previous chemotherapy, no prior radiotherapy to site(s) of measurable

[1] Department of Medical Oncology
[2] Oncology Pharmacy
[3] Therapeutic Radiology Department
National Cancer Centre, Singapore
Address for Reprints: Dr Tan Eng-Huat, Department of Medical Oncology, National Cancer Centre, 11 Hospital Drive, Singapore 169610.
Email: dmoteh@nccs.com.sg

disease, at least a two-dimensionally measurable lesion, adequate haematological, renal and liver function using standard laboratory measurements, no history of other malignancy, and no severe concomitant disease. Presence of brain metastases did not render a patient ineligible as long as cranial irradiation had been administered and disease control was satisfactory at point of enrolment. Computed tomography (CT) scans were used as baseline and follow-up assessments of all measurable and evaluable disease sites after every 2 cycles of treatment. Whole-body radionuclide bone scan was performed only if bone metastasis was suspected. Written informed consent was obtained from all patients who met the eligibility criteria prior to enrolment in this study.

Treatment Regimens and Dose Modification

Gemcitabine at a dose of 1250 mg/m^2 (intravenous 30 minutes) was administered on days 1 and 8 of each 21-day cycle for 4 cycles, followed by cisplatin 40 mg/m^2 on days 1, 8 and 15, for 3 further 28-day cycles. Parenteral administrations of 5HT3 receptor antagonists plus corticosteroids preceded cisplatin infusion. Treatment was discontinued if disease progressed or unacceptable side effects occurred. Chemotherapy was delayed until recovery if the granulocyte count was <1000/μL and/or the platelet count was <100,000/μL. Prophylactic granulocyte-colony stimulating factor was not allowed in this study.

Response and Toxicity Evaluation

The treatment response was evaluated according to World Health Organization (WHO) criteria for the assessment of chemotherapy efficacy. A complete response was defined as the complete disappearance of all clinical evidence of tumour. A partial response was defined as a ≥50% reduction in the sum of the products of the largest perpendicular diameters of all measurable lesions for at least 4 weeks. Stable disease was defined as a decrease of <50% or an increase of <25% in well-outlined lesions for at least 4 weeks. Progressive disease was defined as an increase of >25% in the cross-sectional area of one or more lesions or the occurrence of new lesions. Toxicity was evaluated using the WHO toxicity grading scale. CT scan evaluation of measurable lesions (at least >2 cm) was done pre-treatment as baseline, and subsequently, after every 2 cycles of chemotherapy. Those patients with stable disease or responsive disease received further treatment until disease progression or maximum planned total of 7 cycles of chemotherapy.

Statistical Analysis

Sample size was calculated using Simon's optimal two-stage design[14] – a lower activity (p0) of 0.20 and a target activity level (p1) of 0.40. A maximum sample size of 54 patients were required to test this hypothesis (type I error 0.05, type II error 0.10). At the end of the first stage, at least 5 responses had to be found in 19 patients before continued accrual. Time to disease progression was defined as the time from the date of initial treatment to the date of progression. These analyses were performed using SPSS® version 11.5 software. OS was estimated using the Kaplan-Meier method.

Results

Patient Characteristics

From March 1999 to December 1999, 23 patients with NSCLC who met the eligibility criteria were enrolled. Their characteristics are listed in Table 1. There were 13 male and 10 female patients. The median age was 59 years (range, 41 to 75). There were 20 patients with stage IV disease, 2 patients with unresectable stage III disease and 1 patient with unresectable locally advanced recurrent disease. Six patients (26.0%) had liver metastases, 13 patients (56.5%) had lung metastases, 8 patients (34.8%) had bone metastases and 7 patients (30.4%) had brain metastases. Nine patients (39.1%) had multiple sites of involvement.

Response

Best overall objective response results and best responses

Table 1. Characteristics of Enrolled Patients

Characteristic	No. of patients (n = 23)	%
Gender		
Male	13	56.5
Female	10	43.5
Age (y)		
Median	59	
Range	41-75	
Pathology		
Adenocarcinoma	16	69.6
Squamous cell carcinoma	4	17.4
Large cell carcinoma	3	13.0
Stage		
IIIB	2	8.7
IV	20	87.0
Recurrent metastatic disease	1	4.3
Performance status by ECOG* grade		
1	16	69.6
2	7	30.4
Sites of metastases		
Brain	7	30.4
Lung	13	56.5
Liver	6	26.0
Bone	8	34.8

* ECOG: Eastern Cooperative Oncology Group
Higher numerical grade denotes worse performance status.

Table 2a. Best Overall Objective Response

	No. of patients	%
Number of patients evaluable	19	100
Complete response	0	0
Partial response	4	21.0
Stable disease	5	33.3
Progressive disease	10	52.6
Disease control (partial response and stable disease)	9	47.4

Table 2b. Best Objective Response After Each Phase

	No. of patients (gemcitabine phase)	No. of patients (cisplatin phase)
Number of patients evaluable respective phase	19	9
Complete response	0	0
Partial response	9	4
Stable disease	0	5
Progressive disease	10	0
Disease control (partial response and stable disease)	9	9

achieved after each chemotherapy agent was administered are summarised in Tables 2a and 2b, respectively. Of the 19 patients who could be evaluated, there were 4 patients with partial response, 5 patients with stable disease and 10 patients with progressive disease, giving a response rate of 21%. Median follow-up duration was 15.0 months (range, 5.0 to 30.8). All these patients had relapsed. The median time to progression (TTP) was 3.3 months (95% CI, 1.0 to 7.1). The majority of patients (52.6%) had disease progression after completing 4 cycles of gemcitabine. Sixteen patients died, 15 due to disease-specific causes and 1 from probable pulmonary embolism. Three patients defaulted follow-up upon disease progression in our centre. Survival at 1 year was 63%. The median OS was 14.6 months (95% CI, 13.5 to 15.7). The progression-free and OS Kaplan-Meier plots are depicted in Figures 1 and 2, respectively. Further accrual to this trial was terminated due to failure to satisfy optimal design stage I pre-mandated response rate.

Treatment Compliance, Delay and Toxicity

A total of 83 cycles of chemotherapy were administered. The median number of cycles was 4 (range, 1 to 7). One, 8 and 2 cycles were delayed due to abnormal liver function test, neutropaenia and thrombocytopaenia, respectively. Four patients were withdrawn from the study. One patient requested to be withdrawn from the trial after 1 cycle of gemcitabine because of grade 1 rash and non-neutropaenic fever. The investigators terminated the other 3 patients' participation after they developed idiosyncratic adverse reactions to a single dose of gemcitabine; 2 developed grade 2 truncal pruritic maculopapular rash, and 1 had an

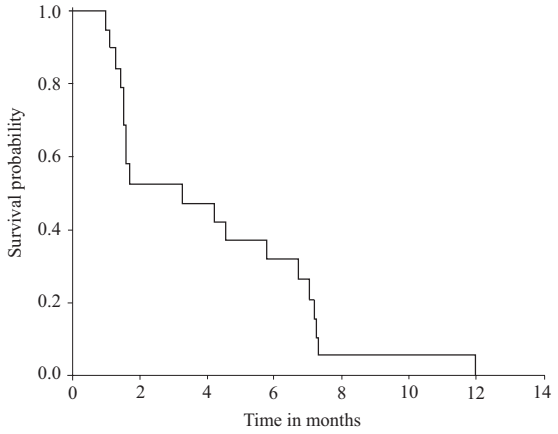

Fig. 1. Kaplan-Meier plot depict progression free survival.

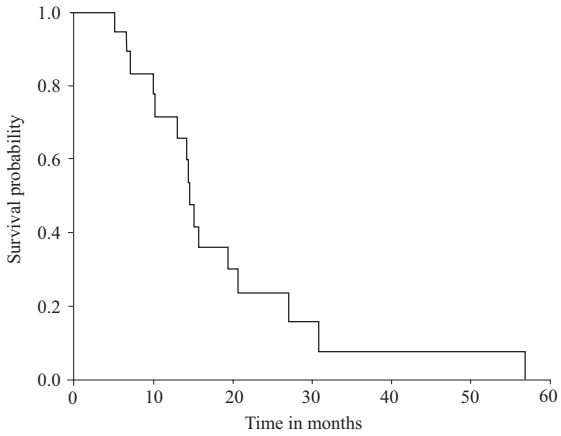

Fig. 2. Kaplan-Meier plot for overall survival.

episode of grade 3 supraventricular tachycardia. Table 3 summarises the haematological and non-haematological toxicities. All other severe adverse effects occurred during the cisplatin phase, and included grade 3/4 anaemia (13%), grade 3 neutropaenia (13%) and grade 3 nausea and vomiting (4%). Ten (52.6%) patients received second-line treatment after disease progression during the trial. Only 2 (10.5%) patients proceeded to receive third-line treatment after progression on second-line therapy. The second- and third-line chemotherapy regimens used in these subsequent lines are detailed in Table 4. Such diverse subsequent combinations and single-agent usage did not allow for any meaningful analysis and comparison of TTP and OS between different regimens.

Discussion

The possible explanation for the modest response rates with the treatment design as used in this study is that the full potential of the synergistic effects of gemcitabine and cisplatin combination would not be realised. When used concurrently, gemcitabine may block DNA repair by

Table 3. Chemotherapy-related Toxicity Occurrence

	World Health Organization (WHO) grade (n = 23)							
	1		2		3		4	
	No.	%	No.	%	No.	%	No.	%
Haematological								
Neutropaenia	3	13.0	5	21.7	3	13.0	0	0
Anaemia	6	26.0	3	13.0	2	8.7	1	4.3
Thrombocytopaenia	1	4.3	2	8.7	0	0	0	0
Infection								
Neutropaenic fever	0	0	0	0	0	0	0	0
Non-neutropaenic	1	4.3	1	4.3	0	0	0	0
Metabolic								
Liver transaminases increase	0	0	1	4.3	0	0	0	0
Gastrointestinal								
Nausea	1	4.3	0	0	1	4.3	0	0
Vomiting	1	4.3	0	0	1	4.3	0	0
Dermatological								
Alopecia	1	4.3	1	4.3	0	0	0	0
Rash	1	4.3	2	8.7	0	0	0	0
Neurological								
Peripheral neuropathy	1	4.3	1	4.3	0	0	0	0
Cardiovascular								
Supraventricular tachycardia	0	0	0	0	1	4.3	0	0

Table 4. Second- and Third-line Chemotherapy Regimens Used

	No. of patients (second line)	No. of patients (third line)
Combination		
Paclitaxel 175 mg/m^2, and carboplatin AUC 6, every 21 days	4	0
Vinorelbine 25 mg/m^2, days 1, and 8, and cisplatin 70 mg/m^2 on day 1 only, every 21 days	1	0
Single agent		
Vinorelbine 25 mg/m^2, days 1, 8 and 15, every 28 days	2	2
Docetaxel 30 mg/m^2, days 1, 8 and 15, every 28 days	1	0
Pacliataxel 30 mg/m^2, days 1, 8 and 15, every 28 days	0	1
Gemcitabine 1000 mg/m^2 days 1, 8 and 15, every 28 days (repeat use six months after initial good response to gemcitabine while on trial)	2	0

depleting the deoxyribonucleotide and ribonucleotide pools, thereby enhancing cisplatin-induced DNA damage by intra-strand and inter-strand cross-linkages.[15]

Disease response to our study treatment naturally contributed to the identification of those patients with relatively longer TTP. All those with partial response had a median TTP of 7.0 months compared to the overall median of 3.3 months. The median TTP of 3.3 months is consistent with phase II trial results with gemcitabine as a single agent in previously untreated advanced NSCLC.[16] Despite the fact that 30.4% of enrolled patients had brain metastases at enrolment, the median OS of 14.6 months compared favourably with historical data on the combined use of gemcitabine and cisplatin. Typically, the median survival in these historical studies[8-13] was 8.4 to 15.0 months. In this trial, most patients upon disease progression were offered second-line chemotherapy. Despite the low response rate and short TTP, the median survival and 1-year survival rate in this cohort of patients did not appear compromised. This is probably attributable to effective second-line treatment although we cannot exclude the effect of patient selection. This observation raised an important question: will the use of different cytotoxic agents in a sequential manner be similar in efficacy to the concurrent use that is currently in vogue? The advantage of sequential use is the ability to deliver a higher dose of the individual agents at a lower toxicity rate. This latter advantage is of utmost importance in the palliative setting.

Only a properly conducted randomised phase III study will be able to answer this question.

One of the main flaws of our study protocol is not allowing our patients to proceed to the cisplatin-phase when they progressed while on the gemcitabine treatment phase. Such patients were taken off the study and treated according to the attending physician's recommendations. Hence, this study was unable to assess the sequential use of active chemotherapeutic agents effectively.

Conclusion

Although there was a modest response rate, the sequential combination of gemcitabine and cisplatin to treat advanced NSCLC was well tolerated and did not seem to compromise on the survival outcome of the patients. More studies of better design are required to assess the sequential use of cytotoxic agents in patients with advanced NSCLC.

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