PHASE II STUDY OF GEMCITABINE AND CISPLATIN IN ADVANCED NON-SMALL CELL LUNG CANCER

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Abstract- Cisplatin-based chemotherapy is the standard treatment for advanced non-small cell lung cancer (NSCLC). Many novel drugs have been used in combination with cisplatin in this setting. Of these drugs, gemcitabine is reported to have a high response rate and acceptable toxicity. The aim of this study was to evaluate the efficacy and safety of gemcitabine and cisplatin combination. Twenty-three patients with NSCLC were enrolled from January 2001 till September 2003. All of them were confirmed by histology and were in advanced stage, *i.e.* stage III_B or stage IV. Cisplatin with the dose of 70 mg/m^2 was given every 21 days, in combination with gemcitabine at a dose of 1250 mg/m^2 administered on days 1, 8 of a 21-day cycle. Of the 23 patients, 1 showed complete remission, 5 achieved partial remission and 7 had stable disease and 2 patients showed progressive disease, 8 patients were not evaluable for response. The overall response in 15 evaluable patients was 40% (95% CI.), median survival was 13.5 months (95% CI, 3.5-27.4 months), and median progression free survival was 11 months (95% CI, 1.04-20.9 months). Hematological toxicity's included anemia, neutropenia and thrombocytopenia. Non-hematological toxicities included nausea/vomiting, peripheral neuropathy, skin rashes, mild renal impairment and one case of acute respiratory distress syndrome; another case developed transient acute psychosis. The regimen of combined gemcitabine with cisplatin is safe and effective and well tolerated in patients. In this combination, a lower dose of cisplatin seems to have an efficacy similar to that seen in previous reports.

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Key words: Non small cell lung cancer, gemcitabine, cisplatin

INTRODUCTION

Lung cancer continues to be a major health problem worldwide. Lung cancer is the most common case of cancer-related death in men and women in the United States (1). Non small cell lung cancer (NSCLC) comprises 80% of lung cancers (2). Majority of the patients presenting with locally advanced cancer, either stage III_B or IV, can not be cured by current therapies; thus, prolongation of life and palliation of symptoms are the goals of treatment. Cisplatin-containing regimens have long been used and have shown to be of some benefit compared with the best palliative care (3, 4). A recent meta-analysis comparing cisplatin-based chemotherapy with the best supportive care had shown that chemotherapy could yield a 27% reduction in death risk, a 10% survival benefit at 1 year and an increase in median survival of 1.5 months (5). Although the cisplatin based regimens are considered to be an effective treatment for advanced NSCLC, they only have modest benefits.

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Recently, a number of novel agents with different mechanisms of action and lower toxicity profiles have been used in NSCLC, such as paclitaxel, docetaxel, vinorelbine and gemcitabine. Gemcitabine, a nucleoside analogue (2′, 2′-difluorodeoxycytidine) acts as a competitive nucleotide for incorporation into DNA, where it leads to chain termination (6). Single-agent treatment with gemcitabine has achieved response rates of 20% or more in some phase II trails (7-10). Synergistic interactions were found, both *in vitro* and *in vivo*, between gemcitabine and cisplatin (11). The NSCLC cell lines that express a high level of HER-2/neu are thought to have greater power for DNA repair. The gemcitabine and cisplatin combination was found to be more effective than etoposide and cisplatin against these cell lines (12).

The aim of this study was to evaluate the efficacy and safety of gemcitabine and cisplatin combination. Although some published studies had reported valuable results, there has been little work on patients receiving gemcitabine and cisplatin in the treatment of NSCLC in Iran.

MATERIALS AND METHODS

Patients with histologically confirmed NSCLC, stage III_B or IV, who met the below mentioned eligibility criteria were included in this study.

Patients were required to have complete medical history records, a physical examination, complete blood cell count, biochemical analysis profile, chest radiographs and computed tomographic (CT) scan of the thorax and brain. Eligibility criteria included a performance status scale (Karnofsky scale) > 70, a life expectancy of more than 12 weeks, no previous chemotherapy or radiotherapy for the assessable lung tumor and at least a two-dimensionally measured lesion. Others include granulocytes counts ≥ 1500/ml, platelet count ≥ 100/000/ml and hemoglobin level ≥ 10 g/dl, a serum creatinine level < 1.6 mg/dl, a serum bilirubin level < 1.5 times the upper normal limit, no history of other malignancies, no severe concomitant disease and no brain metastasis. Informed consent was obtained verbally from all the patients before they were enrolled. All of the patients who met the eligibility criteria were registered in the study after informed consent had been-given.

Gemcitabine at a dose of 1250 mg/m^2 (intravenous infusion, 30 min) was administered on days 1 and 8 of each 21-day cycle. Cisplatin at a dose of 70 mg/m^2 was given on day 1 of each 21 day cycle. Parental administration of $5\text{-}HT_3$ receptor antagonists plus corticosteroids preceded cisplatin infusion. Treatment was discontinued if disease progression or unacceptable side effects occurred.

In those patients who responded, a maximum of six cycles were given. The dose of gemcitabine and cisplatin was reduced by 75% if the granulocyte count was between 1000 and 1500/mL and/or the platelet count was between 75000 and 50000/mL. Chemotherapy was delayed until recovery if the granulocyte count was < 1000/mL and/or the platelet count was < 50000/mL. Granulocyte colony stimulation factor (G-CSF) was applied in patients who had suffered from neutropenic fever after chemotherapy.

The treatment response was recorded according to World Health Organization (WHO) criteria for the assessment of chemotherapy efficacy. Complete response was defined as the complete disappearance of all evidences of tumor. Partial response was defined as a ≥ 50% reduction in the sum of the products of the largest perpendicular diameters of all measured 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. Chest CT scans were performed after the third and sixth courses of chemotherapy.

The response was evaluated after three and six cycles of chemotherapy. Those patients with stable or responsive disease received further treatment until disease progression and a maximum of six cycles were given. After completion of six cycles of treatment, complete physical and chest X-ray examination were done each month and a chest CT scan was performed to evaluate if there was any change in the chest X-ray film.

Statistical analysis of data was performed with SPSS software, version 11.

RESULTS

From January 2001 to September 2003, 23 patients with NSCLC who met the inclusion criteria were enrolled. Their characteristics are listed in table 1. The median age of the patients was 57 years, range from 37 to 75. We enrolled 23 patients, 15 of them had received three or more courses of chemotherapy and were assessable patients for response. Eight of patients could not receive at least three courses of chemotherapy, because 5 of them had early death and 3 of them cut their therapy. Early mortalities in non-assessable patients were due to progressive disease in 3 cases and side effect of chemotherapy in 2 cases.

Of the 15 assessable patients for response (the patients who had received at least three courses of chemotherapy) 1 showed complete response, 5 achieved partial response, 7 patients showed stable disease and 2 (13%) had progressive diseases. The overall response (complete and partial response) was 40% (95% CI). The median time to disease progression for all patients was 11 months (95% CI, 1.04-20.9 months) (Fig. 1). The median survival was 13.5 months (95% CI, 3.5-27.4 months). The Kaplan-Meier curve for survival is shown in figure 2. After a median follow-up time of 334 days (11.5 months), 5 patients showed no disease progression, 6 patients were still alive and 2 patients had died. A total of 85 cycles of chemotherapy were given to the patients. The median number of cycles was 3.6 (range 1-6 cycles). Seven cycles were delayed owing to hematological toxicities. The chemotherapy dose was reduced to 75% in one cycle owing to combined leukopenia and thrombocytopenia.

Table 2 shows the hematological and non-hematological toxicities of treatment. Hematological toxicities, including WHO grade 3 and 4 anemia, neutropenia and thrombocytopenia, were seen in 10%, 7% and 2% of cases, respectively. Non-hematological toxicities included nausea and vomiting WHO grade 1 or 2 and peripheral neuropathy WHO grade 1or 2.

Table 1. Characteristics of enrolled patients

Characteristic	Number	Percent
Gender		
Male	17	74%
Female	6	26%
Availability		
Available patients (> 3 courses of chemotherapy were received)	15	65%
Non-available patients (< 3 of chemotherapy courses were received)	8	34%
Patients didn't continue chemotherapy	3	8%
Early death	5	21%
Due to progressive disease	3	8%
Due to side effects of chemotherapy	2	8%
Pathology		
Adenocarcinoma	14	61%
Squamous cell carcinoma	4	17%
Large cell carcinoma	1	4%
Bronchoalveolar carcinoma	4	17%
Stage		
III_B	3	13%
IV	20	87%
Responses (in available patients)		
Complete response	1	6%
Partial response	5	33%
Stable disease	7	46%
Progressive disease (after three courses of chemotherapy)	2	13%

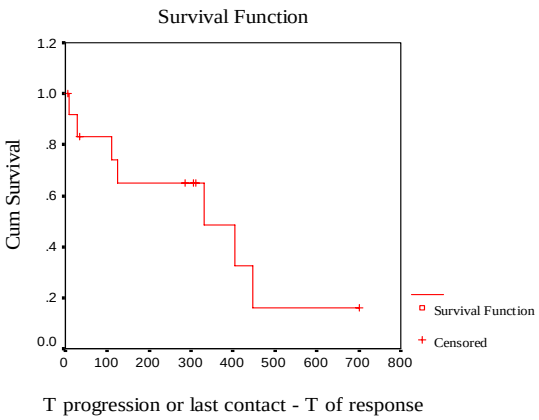

Fig. 1. Disease progression free survival in patients with response.

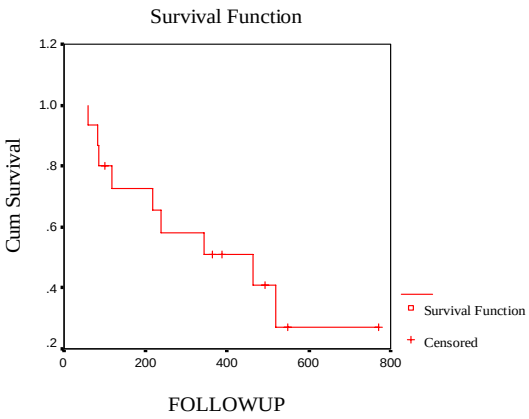

Fig. 2. Median survival (Kaplan-Meier curve) in patients under study.

DISCUSSION

Cisplatin is a cycle-specific agent, whereas gemcitabine is a phase-specific agent. They have different anti-cancer activities in NSCLC and their toxicity profiles do not overlap. The major toxicities of cisplatin are nephrotoxicity and neurotoxicity (13), while these side effects are rarely seen in treatment with gemcitabine. A regimen containing these two drugs would yield a better therapeutic result than either of them given alone.

Cisplatin kills tumor cells by binding to DNA and forming intra- and inter-strand DNA-DNA cross-links. The damaged DNA could undergo excision repair, causing the occurrence of resistance to cisplatin (14). The addition of gemcitabine offers many benefits. When gemcitabine is incorporated into the end of an elongating DNA strand, it makes the chain termination after a further deoxynucleotide is added. Gemcitabine blocks new DNA repair by depleting the deoxyribonucleotide and ribonucleotide pools (11). Table 3 shows the results of some phase II studies using a combined regimen of gemcitabine and cisplatin in different schedules. Different schedules of the combined regimen may offer different efficacies and side effects.

Table 2. Hematological and non-hematological toxicities

	WHO Toxicity Grade							
	1		2		3		4	
Toxicity	**No**	**%**	**No**	**%**	**No**	**%**	**No**	**%**
Hematological								
Anemia	15	8%	5	6%	10	12%		
Thrombocytopenia	2	2%	8	9%	2	2%		
Granulocytopenia Neutropenia	10	12%	2	2%	5	6%	1	1%
Non-hematological								
Renal	3	3%	-	-	-	-	-	
Peripheral Neurotoxicity	6	7%	-	2	2%	-	-	
Cutaneous	2	2%		6	7%	-	-	
Pulmonary	-	-	-	-	-	-	1	
Gastrointestinal	-	-	-	-	-	-	-	
Others								
Transient acute psychosis							1 case	
Sudden death (unknown)							1 case	

Table 3. Results of some phase II clinical trials

Study (Ref Number)	Schedule Administration	No	Response (%)	Survival (months)
Steward *et al.* [17]	GEM 1000 mg/m^2 on day 1, 8, 15 CDDP 100 mg/m^2 on day 15	43	42	10.2
Abratt *et al.* [7]	GEM 1000 mg/m^2 on day 1, 8, 15 CDDP 100 mg/m^2 on day 15	50	42	13
Einhorn [19]	GEM 1000 mg/m^2 on day 1, 8, 15 CDDP 100 mg/m^2 on day 1	30	37	8.1
Shepherd *et al.* [15]	GEM 1500 mg/m^2 on day 1, 8, 15 CDDP 30 mg/m^2 on day 1, 15	35	26	9.1
Lippe *et al.* [16]	GEM 1000 mg/m^2 on day 1, 8, 15 CDDP 35 mg/m^2 on day 1, 15	30	40	11.8
Present study	GEM 1250 mg/m^2 on day 1, 8, 15 CDDP 75 mg/m^2 on day 1	15	40	13.4

Abbreviations: GEM, gemcitabine; CDDP, cisplatin.

Shepherd *et al.* first gave gemcitabine 1000 mg/m^2 and cisplatin 30 mg/m^2 weekly on day 1, 8 and 15 of a 28-day cycle. They described a low response rate of 26% and a median survival of 11 months (15). Interestingly, with the same schedule, but with a higher dosage of cisplatin (35 mg/m^2), Lippe *et al.* reported a higher response rate of 40% and a longer median survival of 11.8 months (16). In two studies, gemcitabine was given 1000 mg/m^2 weekly for 3 weeks on days 1, 8 and 15 and cisplatin 100 mg/m^2 on day 15 of a 28-day cycle. The results were comparable in both studies with an overall response rate of 42%. The median survival was 10.2 months in a total of 43 patients described by Steward *et al.* (17) and the overall response rate was 52%. Median survival was 13 months in a total of 50 patients studied by Abratt *et al.* (18). In present study, we used gemcitabine 1250 mg/m^2 on day 1, 8 and cisplatin on day 1 of a 21-day cycle. Our result were similar to those described in the above two studies, with an overall response rate of 40%, median survival of 13.5 months and one year survival of 64%. Cisplatin may also be given in different schedules. In two studies, gemcitabine 1000 mg/m^2 was given on days 1, 8 and 15 and cisplatin on day 1 and a median survival of 8.4 months was achieved in 30 assessable patients (16, 19). Crino *et al.* gave cisplatin on day 2 in 48 patients and got a higher response rate of 54% and a median survival of 15 months (20). A re-evaluation report reviewing the data from previous phase II studies concluded that cisplatin given on day 15 rather than weekly is more beneficial (21). When cisplatin is administered on day 15, it provides the patient with a longer exposure to gemcitabine. Besides, it can be accompanied with the optimal dose intensity. Although no randomized study has been carried out comparing the efficacy and toxicity when cisplatin is used in different schedules (weekly or on day 15), the regimen of weekly gemcitabine and monthly cisplatin on day 15 is now more commonly used. Some authors also administered cisplatin on day 1 or day 20.

In this study hematological toxicity (grad 3, 4) was lower than those in other reports (17, 20, 21). The lower incidence of hematological toxicity in our patients than in previous reports may be due to a lower dose of cisplatin and better performance status of our patients. Nausea or vomiting are mainly due to the adverse effects of cisplatin but our patients showed lower grade of nausea and vomiting; grade 1, 2 occurred in 27 (31%) of all cycles and grade 3, 4 were not seen.

In conclusion, in the 15 assessable NSCLC patients with a combined regimen of gemcitabine plus cisplatin the response rate was 40%, the median survival was 13.5 months and one-year survival probability was 64%. This regimen is safe and effective in the treatment of NSCLC. In this combination, a lower dose of cisplatin shows to have an efficacy similar to previous reports.

Conflicts of interests

We have no conflict of interests.

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