Phase II study of Gemcitabine and Cisplatin Regimen in Advanced Non-Small Cell Lung Cancer (NSCLC).

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Abstract
Background: Cisplatin-based chemotherapy is the standard treatment for advanced non-small cell lung cancer (NSCLC). Many novel drugs, including gemcitabine, vinorelbine, paclitaxel and docetaxel 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 & cisplatin combination.
Methods: Twenty-three patients with NSCLC, who met inclusion criteria, were enrolled from January 2001 till September 2003. All of them were confirmed by histology and were in advanced stages, i.e. stage III_B or stage IV. Cisplatin with a dose of 70mg/m^2 was given every 21 days, in combination with gemcitabine at a dose of 1250mg/m^2 administered on days 1and 8 of a 21-day cycle.
Results: of the 23 patients, 1 showed complete remission, 5 achieved partial remission, 7 had stable disease and 2 patients showed progressive disease, while 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 (PFS)was 11 months (95% CI, 1.04-20.9 months).
Hematological toxicities included WHO grade 3, 4 anemia, neutropenia and thrombocytopenia 10%, 7% and 2% respectively. Non-Hematological toxicities included nausea/vomiting WHO grade 1,2 & peripheral neuropathy WHO grade 1,2. Skin rashes were mild.Six patients developed grade 2 toxicity. Renal impairment was mild. One case developed Acute Respiratory distress syndrome (ARDS) after first dose of chemotherapy, another case developed transient acute psychosis under therapy.
Conclusions: The regimen of combined gemcitabine with cisplatin is safe and effective and well tolerated in patients. Some rare but important toxicity such as ARDS may occur occasionally. In this combination, a lower dose of cisplatin seems to have an efficacy similar to that of in previous reports.

Key words: Non small cell lung cancer (NSCLC),.Gemcitabine

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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 USA.[1] NSCLC comprises 80% of lung cancers.[2] The majority of the patients presenting with locally advanced cancer, either stage III_B or IV can not be cured by current therapies, thus, prolonged life and palliation of symptoms are the goals of treatment. Cisplatin-containing regimens have long been used & have proven 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 can yield a 27% reduction in death risk, a 10% survival benefit after 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, but they only have modest benefits.

Recently, a number of novel agents, with different mechanisms of action and lower toxicity profiles, such as paclitaxel, docetaxel, vinorlebine and gemcitabine have been used in NSCLC.Gemcitabine, a nucleoside analogue (2′, 2′-difluorodeoxycytidine) acts as a competi-

tive 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 & cisplatin.[11] The NSCLC cell lines that express a high level of Her2/neu are thought to have greater power for DNA repair. The Gemcitabine and cisplatin combination was found to be more effective than etoposide & cisplatin against these cell lines.[12]

In this prospective study of a combined regimen of gemcitabine & cisplatin, Gemcitabine was administered on days 1and 8 and cisplatin was given on day 1 of a 21-day cycle. Although some published studies had reported valuable results, there has been little work in Iran concerning gemcitabine and cisplatin in the treatment of NSCLC.

Patients and Methods

Eligibility criteria and pretreatment evaluation of patients with histologically confirmed NSCLC, stage III_B or IV, who met the below-mentioned eligibility criteria.

Patients were required to have complete medical history records, a physical examination, complete blood cell count, biochemical analysis profile, chest radiographs, computed tomographic (CT) scan of the thorax and brain. Eligibility criteria including 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, at least a two-dimensionally measured lesion. Others include granulocytes counts≥1500/ml, platelet count≥100/000/ml & 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.

Treatment Regimen & Dose modifications: Gemcitabine at a dose of 1250mg/m2 (iv. 30 min) was administered on days 1and 8 of each 21-day cycle. Cisplatin at a dose of 70mg/mL was given on day 1 of each 21 day cycle. Parental administration of 5-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 50,000/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.

Response and Toxicity Evaluation

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 was done each month and a chest CT scan was performed if there was any change in the chest X-ray film.

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. We enrolled 23 patients,15 of them

Table 1: Characteristics of enrolled patients

Characteristic		
Gender	Number	percent
Male	17	74%
Female	6	26%
Total	23	100%
Age (years)		
Median	57	
Range	37-75	
Eavaluable patients (had recived≥3 courses chemotrapy)	Number 15	percent 65%
CR(complete response)	1	6%
PR(partial response)	5	33%
SD(stable disease)	7	46%
Progressive disease(after three courses of chemotherapy)	2	13%
Non –evaluable patients (had recived<3 courses of chemptherapy)	Number 8	percent 34%
-Early death 1. Rekated to progressive disease 2. Related to chemotherapy to chemotherapy side effects - the patients did not continue their chempthepy	5 3 2 3	21.7% 13% 8% 13%
Pathology	Number	percent
Adenocarcinoma Squamus cell carcinoma Large cell carcinoma Bronchoalveolar carcinoma	14 4 1 4	61% 17% 4% 17%
Stage	Number	percent
III_B IV	3 20	13% 87%

Table 2: Hematological toxicity; WHO Toxicity grade

	1		**2**		**3**		**4**	
	No	%	No	%	No	%	No	%
Anemia	15	8%	5	6%	10	12%	-	
Thrombocytopenia	2	2%	8	9%	2	2%	-	
Granulocytopenia Neutropenia	10	12%	2	2%	5	6%	1	1%

had received three or more courses of chemotherapy.They were evaluble patients for response. Eight of them could not receive at least three courses of chemotherapy, because 5 of them had an early death and 3 of them stopped their therapy. Early mortalities in non-evaluable patients were due to progressive disease in 3 cases and side effect of chemotherapy in 2 cases.

Response: Of the 15 assessable patients for response (The patients who had received at least three course of chemotherapy) 1 showed CR 5 achieved PR, 7 patients showed stable disease and 2 (13%) had progressive diseases. The overall response (CR and PR) 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.

Compliance with Treatment: 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.

Toxicities: Table 2 and 3 show the hematological and non-hematological toxicities of treatment. Hematological toxicities included WHO grade 3, 4 anemia, neutropenia and thrombocytopenia 10%, 7% and 2% respectively. Non-hematological toxicities included nausea, vom-

Table 3: Non-Hematological toxicity, WHO toxicity grade

	1		2		3		4	
	No	**%**	**No**	**%**	**No**	**%**	**No**	**%**
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)								1case

iting WHO grade 1, 2 and peripheral neuropathy WHO grade 1, 2.

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 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 terminate after a further deoxynucleotide is added. Gemcitabine blocks new DNA repair by depleting the deoxyribonucleotide and ribonucleotide pools.[11]

Table 4 shows the results of some phase II studies using a combined regimen of gemcitabine & cisplatin in different schedules. Different schedules of the combined regimen may offer different efficacy and side effects. Shepherd et al,[15] first gave gemcitabine 1000mg/m^2 and cisplatin 30mg/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. Interestingly, with the same schedule, but with a higher dosage of cisplatin (35 mg/m^2), Lippe et al.[16] reported a higher response rate of 40% and a longer, median survival of 11.8 months.

In two studies, gemcitabine was given 1000mg/m^2 weekly for 3 weeks on days 1, 8 and 15 and cisplatin 100mg/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 this study, we used gemcitabine 1250mg/m^2 on day 1and 8 and cisplatin on day 1 of a 21-day cycle. Our results 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 1000mg/m^2 was given on days 1,8 and 15, cisplatin on day 1 and a median survival of 8.4 months was achieved in 30 evaluable patients. Crino et al[20] gave cisplatin on day 2 in 48 patients and got a higher response rate of 54% and a median survival of 15 months.

A re-evaluation report [21] reviewing the data from previous phase II studies concluded that cisplatin given on day 15 rather than weekly is more beneficial. 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 (grade 3,4) was lower than those in other reports.[17,20 ,21]

The lower incidence of hematological toxicity in our patients compared to 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 oc-

curred in 27 (31%) of all cycles and grade 3, 4 were not seen.

In conclusion, in the 15 evaluable 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 seems to have an efficacy similar to previous reports.

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