Low dose Gemcitabine and Cisplatin in advanced non – small cell lung cancer

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Abstract

Aim: Evaluate safety & efficacy of gemcitabine at a low dose of 250 mg / m2 in 6 h prolonged infusion plus cisplatin in advanced non – small cell lung cancer (NSCLC) patients.

Patients & methods: Fifty – four patients with stage III B or IV NSCLC were enrolled, 39 males & 15 females, with a median age 53 years (range 18 – 65). A total of 33 patients (61%) had adenocarcinoma, 12 (22%) had squamous cell carcinoma, 2 (4%) had large cell carcinoma & 7 (13%) had other histopathological types.. Treatment consisted of 250 mg / m2 gemcitabine in a 6 h infusion on days 1 & 8, and cisplatin at 75 mg / m2 on day 2 of a 3 – week cycle. A total of 210 chemotherapy cycles were administered, with a median of 4 cycles per patient (range 1 – 6).

Results: The overall response rate was 39% (o CR, 22 patient PR). Median time to disease progression was 5.2 months & median overall survival time was 11.7 months. One – year survival time was 43%. Hematologic toxicity was mild where grade 3–4 neutropenia in 18.5% of patients, thrombocytopenia in 9.3%, and anemia in 5.5%. Grade 3 nausea / vomiting was one of the main nonhematological toxicities in 27.7% of patients, in addition to grade 1 – 2 alopecia in 62.9% and grade 1 – 2 skin rash in 18.4%.

Conclusion: Prolonged infusion of low dose gemcitabine & cisplatin is an effective treatment in NSCLC treatment. Toxicity, especially myelosuppression, is remarkably mild.

Introduction

Non small cell lung cancer (NSCLC) constitutes approximately 80% of all cases of lung cancer (1). It is the leading cause of cancer death in the world (2). It is the second most common malignancy after bladder cancer in men and breast cancer in women in Egypt (3). This high incidence is due to high smoking prevalence among Arab men (4). The standard treatment of advanced stage NSCLC is platinum doublet chemotherapy, as cisplatin is considered the most effective for NSCLC (5). The third generation agents, such as taxanes and yinorelbine, adminstered with a platinum derivative, have resulted in improved median and 1- year survival times when compared with either cisplatin alone or older platinum – based combinations in randomized trials (6, 7).

Gemcitabine (2', 2' – difluorodeoxy cytidine, dFdC), an analog of cytosine arabinoside (Ara-C), is a pyrimidine antimetabalite. Gemcitabine – Cisplatin regimen is considered as one of the most active regimens for advanced NSCLC, with an overall response rate (ORR) of 22 – 40.6% and median survival of 8.1 – 9.8 months in phase III trial (8).

A recent meta – analysis showed an absolute 1– year survival benefit of 3.9% for gemcitabine – cisplatin regimen when compared with other platinum – containing regimens (9).

Gemcitabine is usually administrated intravenously at a dose of 1000 – 1250 mg / m2 as a 30 – minute infusion on days 1 and 8 of a 21-day cycle or days 1, 8 and 15 of a 28-day cycle (10).

This standard gemcitabine infusion acts through the enzyme deoxycytidine kinase (dCK) which catalyzes the phosphorylation of gemcitabine into active gemcitabine triphosphate which then will be saturated (11).

Preclinical studies in human tumor cell lines and xenografts showed that intracellular accumulation of gemcitabine triphosphate (dFdCTP), the active metabolite of gemcitabine, is dependent on the total exposure time & rate of administration of gemcitabine (12), So, the brief 30 – minutes infusion of gemcitabine might not result in higher concentrations of its active metabolite (13). Therefore, prolonging the infusion time at lower dose levels of gemcitabine, such as moderately prolonged 100 min infusion (fixed dose rate 10 mg / m2 / min) (14) and the low dose infusion lasting for 3, 6, 24 hours have been studied in different clinical trials, and demonstrated good efficiency in different tumors, as it leads to the maintenance of plasma gemcitabine concentrations at levels at which dCK is saturated for prolonged periods of time which increases intracellular accumulation of gemcitabine triphosphate (15, 16, 17). This strategy was hypothesized to result in a higher antitumor activity of gemcitabine in patients (18, 19).Table 1 summarizes the different trials done using prolonged infusion of low dose gemcitabine.

On the basis of possible advantages of low – dose gemcitabine, this phase II study was done to evaluate the toxicity and response rate of a 6 h infusion of gemcitabine at a dose of 250 mg / m2 on days 1 and 8 plus cisplatin at 75 mg / m2 on day 2 as first – line chemotherapy for advanced NSCLC. Secondary end points were time to progression (TTP) and overall survival (OS).

Patients & Methods

Patient selection

Patients who were 18 – 65 years of age and who had histologically or cytologically

confirmed, locally advanced or metastatic stage III B or IV NSCLC were eligible for enrollment. Patients had to have at least one bidimensionally measurable indicator lesion. Other eligibility criteria included performance status of ≤ 2 according to Eastern Cooperative Oncology Group (ECOG); life expectancy ≥ 3 months, adequate bone marrows function (absolute neutrophil count ≥ 2 × 109 / L-1, platelet count ≥ 100 × 109 / L-1 , haemoglobin ≥ 10 g / dl). Adequate hepatic and renal functions (serum bilirubin ≤ 1.5 × upper normal limit, hepatic enzymes ≤ 2 × upper normal limit, serum creatinine × 1.5 upper normal limit). Written informed consent was obtained from all patients. Exclusion criteria were brain metastases, other malignant diseases except for carcinoma of the cervix uteri in situ and squamous cell carcinoma of the skin, severe comorbid diseases, active infections that could have interfered with the trial.

Treatment plan and dose adjustments

Gemcitabine (Gemzar, Eli Lilly and Company), 250 mg / m2 was administered as a 6 h. i.v. infusion on days 1 & 8 of a 21 day cycle. Cisplatin was given in a dose of 75 mg / m2 i.v. on day 2. All patients were scheduled to receive at least two cycles of therapy & up to 6 cycles of chemotherapy if there's no evidence of disease progression. Treatment was stopped early in cases of patient refusal, severe toxicity, documented progressive disease (PD) or pregnancy. Patients with PD after 2 or 4 cycles or with stable disease after 4 cycles were withdrawn from the trial. Full supportive therapy, corticosteroids, anticonvulsants and antibiotics were given as needed. Antiemetic premedication, in the form of 5 – HT3 antagonists was given. All patients were treated on an outpatient basis.

Dose adjustments during therapy were based on hematologic and nonhematologic toxicities. On day 1, if neutrophil count was < 1.5 × 109 / L-1 & / or platelet count was < 100 × 109 / L-1, chemotherapy was delayed (for up to 2 weeks) and doses were reduced by 25% until the count recovered. On day 8, if neutrophil count < 1.0 × 109 / L-1 & / or platelets < 75 × 109 / L-1, the gemcitabine was omitted, & the cycle continued with one gemcitabine dose not given.

If patient didn't recover from hematological toxicity (neutrophil count > 1.0 × 109 / L-1 and platelets > 75 × 109 / L-1) within 2 weeks, treatment is stopped & patient is withdrawn from the trial.

Patients who developed any grade 3 nonhematologic toxicity (excluding nausea, vomiting and alopecia), doses were reduced by 25% while treatment was discontinued for grade 4 or repeated grade 3 nonhematological toxicity.

Baseline & treatment assessments

Pretreatment evaluation included physical examination; ECOG – PS, brain, thoracic and abdominal computed tomography scan (CT scan); bronchoscopy (if not performed at the time of diagnosis); bone scan; electrocardiogram; complete blood count, liver & renal function tests. On days 1 & 8, a physical exam (including weight) was performed, and ECOG – PS and blood count were assessed. All measurable and evaluable lesions were assessed by the same method used at baseline. Treatment response was evaluated every 2 cycles by clinical & / or radiological tumor assessment, then every 2 months for patients who finished 6 cycles of chemotherapy.

Toxicity was recorded according to the National Cancer Institute (NCI – CTC, version 2.0). All patients who received at least one dose of treatment were included in the toxicity assessment.

Statisical analysis

Statistical analysis were performed using SPSS 11.0 for windows procedures (SPSS Inc, Chicago, IL, USA).

TTP was determined by measuring the time interval from the beginning of treatment until the first documentation of progression. OS was determined by measuring the time interval from the beginning of treatment to the date of death or last contact. Kaplan – Meier was used to calculate TTP and OS.

Results

Patient characteristics

From May 2005 to October 2008, a total of 54 patients were enrolled in this study. Patients characteristics are listed in table (2). Fifty one patients were assessable for response. Three patients didn't continue treatment after the first cycle due to unrelated causes.

The majority of patients were males (72%), with a median age 53 (range 18 – 65), performance status was 0 in 15%, 1 in 50% and 2 in 35% of patients. Eleven patients (20%) were stage III B & 43 patients (80%) were stage IV. Adenocarcenoma was the predominant pathology (61% of patients).

Efficiency

The overall response rate (ORR) was 39% including 22 partial responces and no complete responses. With a median follow – up time of 11.1 months, by the close out date, 9 patients (18%) were alive without progression & 42 patients (82%) had progressed, 17 patients (33%) were still alive and 34 (67%) had died. The median time to progression (TTP) was 5.2 months, median OS line was 10.7 months & 1 – year survival was 43%, and 2 – year survival was 20% (fig 1, 2).

Toxicity

Grade 3-4 hematologic toxicities were neutropenia in 10 patients (18.5%), thrombocytopenia in 5 patients (9.3%) and anemia in 3 patients (5.5%). Two patients required packed RBC transfusions and no patient needed platelets transfusion, neither bleeding episodes were recorded. Nonhematologic toxicity was mild. Grade 3 nausea / vomiting occurred in 15 patients (27.7%). Grade 3 alopecia in 2 patients (3.7%) and grade 1 – 2 alopecia occurred in 34 patients (62.9%). Reversible increased AST were observed in 6 patients (11.2%), 5 cases of grade 1 – 2 & one case of grade 3.

Grade 1–2 skin rash was encountered in 10 patients (18.4%). No serious adverse events were recorded during the study & no patients died from the toxicity. Although the protocol was to be repeated every 21 days, 196 cycles (93.3 %) were given within the 21-day period of the protocol. Twelve cycles (5.7%) were delayed for less than 7 days; 2 cycles (1%) were delayed for more than 7 days. Of these, 10 cycles (4.8%) were delayed for toxicity reasons.

Dose intensity

A total of 210 cycles of chemotherapy were administered, with a median of 4 cycles per patient (range 1 – 6). Seven patients (12.9%) received all 6 cycles, 6 (11.1%) received 5 cycles, 23 (42.6%) received 4 cycles, 11 (20.4%) received 3 cycles, 6 (11.1%) received 2 cycles & 1 (1.9%) received 1 cycle.

Discussion

In the last year, several clinical trials have tested the combination of gemcitabine & cisplatin in advanced NSCLC; in these trials, gemcitabine, at doses of 1000 – 1200 mg / m2 was administrated weekly for 2 – 3 weeks followed by 1 week rest (22, 23). Among the regimens, gemcitabine – cisplatin has proven to be well tolerated with response rates 22 – 40.6%, TTP 4.2 – 6.9 months, median OS 8.1 – 9.8 months & 1 – year survival rate 32 – 39% in several large phase III studies (7, 12, 23`). In all the trials, gemcitabine was administrated in a 30 min infusion.

In the current study, gemcitabine was given as a 6 h infusion at 250 mg / m2 on days 1 & 8 plus cisplatin. Overall response rate was 39%, with a median TTP of 5.2 months and median OS time of 11.7 months.

In this study, the most outstanding feature of this regimen is low – dose gemcitabine in prolonged infusion. The explanation for this phenomenon is the saturation of deoxycytidine kinase that occurs after short infusion at conventional doses. This enzyme is necessary to convert gemcitabine into gemcitabine triphosphate (active form). Prolonged infusion results in a higher intracellular concentration of the active metabolite,in contrast to the short infusion which leaves most of the drug unmetabolized. (11, 13).

Akrivakis et. al and Pollera et. al. demonstrated in their phase I trials that the MTD for gemcitabine in 6 h infusion is 250 – 300 mg / m2 (25, 26). In phase II trials, Schmid et. al and Khaled et. al confirmed the previous data with good efficiency and mild myelosuppression (26, 27). On the basis of these results, this study was conducted. In a similar study, conducted by Zwitter et. al., response rate was 45%, median progression – free survival was 6.3 months and median OS was 11.9 months, similar to the present trial.

Ceribelli et. al and Xu et. al., demonstrated the efficiency of gemcitabine in prolonged infusion at fixed dose rate (10 mg / (m2 min)) if used with cisplatin or carboplatin in NSCCC, with a response rate of 34 – 41%, median TTP of 5 – 8 months and OS of 11.5 – 13 months (13, 18). Tempero et. al., compared fixed dose rate infusion (10 mg / (m2 min)) with standard 30 min infusion of gemcitabine in pancreatic carcinoma and observed a longer median survival with the former. If gemcitabine was given in a large dose at a fixed dose rate infusion, all the randomized phase II trials, (15, 18, 28) indicated more hematologic toxicity in the fixed dose rate rather than in the 30 min infusion arms. In the current study, mild hematologic toxicity was encountered in the form of grade 3–4 neutropenia, thrombocytopenia and anemia that were 18.5, 9.3, 5.5%, respectively. Also, no patients had febrile neutropenia, platelet transfusion or bleeding episodes. Only two patients received packed RBC transfusion. This in contrast with higher rate of grade 3–4 neutropenia, thrombocytopenia & anemia 38.1 – 64%, 36.3 – 63.9%, and 11.9 – 30.9% respectively with regimens of conventional 30 min infusional gemcitabine plus cisplatin. Also, high rates of febrile neutropenia, platelet transfusions and packed RBCtransfusions up to 7, 20.4 and 37.7% respectively (5, 7, 12, 19, 23). Therefore, the lower rate of hematologic toxicity, in the present study, was due to low – dose gemcitabine in prolonged infusion.

The low hematologic toxicity encountered in this study coincided with that in Zwitter's study (20) where gemcitabine was given in similar way as the current study. Also, nonhematologic toxicity in the form of nausea & vomiting were the most commonly observed, in both trials followed by grade 1 – 2 alopecia, skin rash and increased AST.

Beside the advantage of lower hematologic toxicity, lower costs due to low dosing of gemcitabine in this study made it possible for more patients to continue their chemotherapy.

In conclusion, treatment with low dose gemcitabine in prolonged infusion plus cisplatin is feasible.

The good efficiency, mild hematologic toxicity and lower drug costs make it an attractive option for patients with NSCLC.

It is recommended to be studied in comparison with standard infusion of gemcitabine in a randomized study.

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Tables

Table 1: Trials of low dose gemcitabine in NSCLC

	Regimen Used	ORR %	OS	Side Effects
Zwitter et.al.(2005) [20]	Gemzar:250mg/m^{2}d1 Cisplatin:75mg/m^{2}d2/3Ws.	45%	11.9month	Mild neutropnia, thrombocytopenia N, V, alopecia, ,skin rash.
Xiong et .al.(2008) [21]	Gemzar:250mg/m^{2}d1 Cisplatin:75mg/m^{2}d2/3Ws	39.3%	10.5month	Mild neutropnia, thrombocytopenia N, V, alopecia, ,skin rash.

N:nausea,V:vomiting.

Table 2: Patient's Characteristics

	No. of patients	**%**
No. included	54	___
Median age (years)	53 (18 – 65)	___
Male / Female	39 / 15	72 / 28
ECOG performance status		
0	8	15
1	27	50
2	19	35
Stage		
III B	11	20
IV	43	80
Histology		
Squamous	12	22
Adenocarcinoma	33	61
Large cell	2	4
Others	7	13
Sites of metastases		
Lung	25	46
Liver	5	9
Bone	18	33
Nodes	13	24
Others	2	4
No. of metastasis sites		
1	33	61
2	18	33
3	3	6

Table 3: Toxicity profile by grade

Patients (n = 54)	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Hematologic toxicities				
Leucocytopenia	7 (12.9)	15 (27.7)	12 (22.2)	1 (1.9)
Neutropenia	5 (9.3)	14 (25.9)	9 (16.6)	1 (1.9)
Febrile Neutropenia	0	0	0	0
Anemia	23(42.6)	13 (24.1)	3 (5.5)	0
Thrombocytopenia	6 (11.1)	10 (18.5)	5 (9.3)	0
Nonhematologic toxicities				
Nausea / Vomiting	16 (29.6)	15 (27.7)	15 (27.7)	0
Danalea	2 (3.7)	0	0	0
Increased AST	4 (7.4)	1 (1.9)	1 (1.9)	0
Increased creatinine	3 (5.5)	0	0	0
Skin rash	7 (12.9)	3 (5.5)	0	0
Alopecia	15 (27.7)	19 (35.2)	2 (3.7)	0

Figures

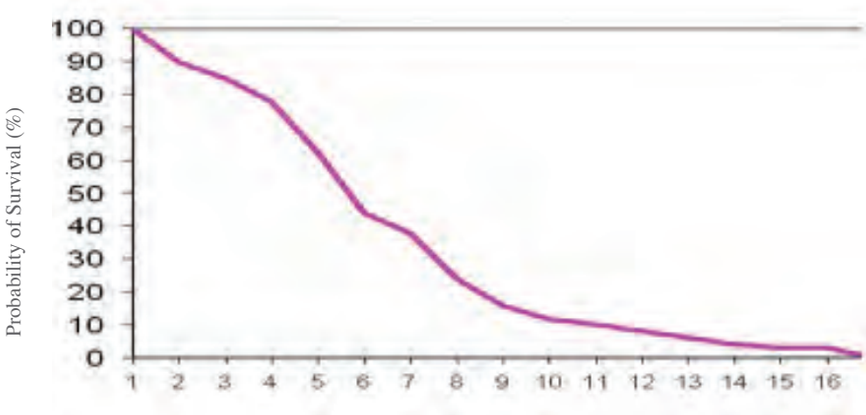

Fig 1.

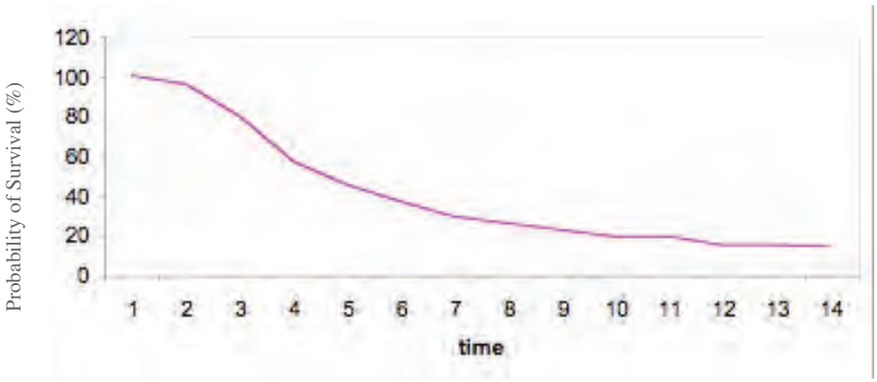

Fig 2.