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Fixed Dose Rate versus Standard Dose Rate Infusion of Gemcitabine and Cisplatin in Advanced Stage Non-Small Cell Lung Cancer

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Abstract

Background: Comparing the efficacy and safety of gemcitabine at a fixed-dose rate (FDR) infusion (10 mg/m²/min) with the standard dose rate infusion in patients with locally advanced and metastatic non-small squamous cell carcinoma (NSCLC). Methods: The study randomized 60 patients with confirmed diagnosis of NSCLC to receive gemcitabine at a dose of 1000 mg/m² on days 1 and 8 given as a 30-min infusion (Arm A) or at a rate of 10 mg/m²/min (Arm B). Cisplatin 75 mg/m² was administered intravenously on day 2 in both arms. Results: No difference in overall response rate (46.6% versus 43.3%). Median time to progression for Arm A was 7 months (95% CI, 6.207 - 7.793 months), versus 6 months for Arm B (95% CI, 4.990 - 7.010 months). Median survival time was comparable [12 months (95% CI, 8.588 - 15.412 months) versus 11 months (95% CI, 9.066 - 12.934 months)] respectively. Two-year survival (18% versus 11%, p = 0.38) was detected. No treatment related deaths occurred. Main hematological toxicities were grade I and II neutropenia, in 36.7% and 53.3% respectively (p = 0.044). Grade III anemia was observed in 10% and 6.7% in both arms respectively (p = 0.024). Grade I and II nausea and vomiting was observed in 50% and 46.7%. Conclusions: FDR gemcitabine in combination with cisplatin had equivalent efficacy and more severe hematologic toxicities compared to the standard 30-min gemcitabine infusion with cisplatin in patients with advanced NSCLC.

Keywords

Non-Small Cell Lung Cancer, Gemcitabine, Fixed-Dose Rate, Toxicities

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1. Introduction

Lung cancer is the leading cause of cancer death in the United States. An estimated 226,000 new cases of lung and bronchus cancer will be diagnosed in 2012, and 160,000 deaths are estimated to occur due to the disease [1]. In Egypt, lung cancer is the sixth most common cancer, accounting for about 5% of all new cases. It is the fourth most common malignancy in males (7.5%) and the ninth among females (2.3%) [2].

Advanced Non-Small Cell Lung Cancer (NSCLC) encompasses metastatic disease (Stage IV) as well as locally advanced disease (Stage IIIB) that due to tumor or patient characteristics cannot be approached with curative intent [3]. Chemotherapy is the main treatment for patients with advanced NSCLC as it improves survival according to a meta-analysis based on individual patient data [4]. Among numerous chemotherapy regime ns, gemcitabine and cisplatin combination have been proved effective and tolerable [5].

Gemcitabine is taken up into the cell via human nucleoside transporters (hNTs) and is intracellulary phosphorylated by deoxycytidi ne kinase (dCK) to its monophosphate and subsequently into its main active triphosphate metabolite 2', 2'-difluorodeoxycytidine triphosphate (dFdCTP), which is incorporated into DNA and inhibits DNA synthesis. In addition, gemcitabine is extensively deaminated to 2', 2'-difuorodeoxyuridine, which is largely excreted into the urine [6].

Prolonged infusion of gemcitabine at a fixed dose rate (FDR) of 10 mg/m^2 per minute was associated with a higher intracellular accumulation of dFdCTP, and a higher response rate than with the standard 30-minute infusion of gemcitabine. The explanation for this phenomenon lies in the saturation of deoxycytidine kinase which occurs after short infusion at conventional doses. This enzyme is needed to convert gemcitabine into its active form gemcitabine triphosphate. While short infusion leaves most of the drug unmetabolized, prolonged infusion results in a higher intracellular concentration of the active metabolite, thus enhancing the e agent's efficacy [7]. The improved survival in patients with pancreatic adenocarcinoma, who received FDR infusion in a randomized phase II clinical trial [8], encouraged many researchers to investigate the feasibility and efficacy of FDR gemcitabine in NSCLC patients [9]-[14]. However, controversial results have been drawn from these trials.

In light of this information, we conducted this phase III prospective clinical trial to compare the efficacy and safety of FDR infusion (10 mg/m^2/min) with the standard dose rate infusion of gemcitabine in patients with locally advanced and metastatic NSCLC.

2. Material and Methods

2.1. Eligibility Criteria

Chemonaive patients with histologically or cytologically confirmed locally advanced or metastatic stage IIIB or IV NSCLC according to the American Joint Committee on Cancer staging system (AJCC, 2002) [3], who were not amenable to surgery or radiation therapy with curative intent , were eligible for this study. Other eligibility criteria included the presence of at least one bi-dimensionally measurable lesion; at least 18 years old but not more than 60 years, Eastern Cooperative Oncology Group performance status (ECOG-PS) ≤ 2; life expectancy $\geq$ 3 months; adequate bone marrow function (absolute neutrophil count $\geq 1.5 \times 10^3$/ml, platelet count $\geq 100 \times 10^3$/ml, hemoglobin $\geq$ 10 g/dL); adequate renal and hepatic function (serum creatinine $\leq$ 2 mg/dl, hepatic enzymes $\leq 2.5\times$ upper normal limit, bilirubin $\leq$ 2 mg/dl). 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 hepatic or renal impairment, and active infections or other severe co-morbid diseases that could have interfered with the trial. Written informed consent was obtained from all patients. The trial was approved by the Ethics and Scientific Committees at Faculty of Medicine, Ain-Shams University.

2.2. Treatment Protocol

Eligible patients were randomly assigned to receive gemcitabine at a dose of 1000 mg/m^2 on days 1 and 8 given as a 30-min infusion (Arm A) or at a rate of 10 mg/m^2/min (Arm B). Cisplatin 75 mg/m^2 was administered intravenously on day 2 in both groups of patients. Cycles were repeated every 3 weeks. Before cisplatin administration, patients received intravenous hydration with 1500 mL of normal saline supplemented with 20 mEq of potassium chloride over 90 minutes followed by 250 mL of mannitol 20% solution and 1000 mL of normal saline, given over 2 hours. Cisplatin infusion was preceded by intravenous administration of a 5-HT3 receptor antagonist plus corticosteroids; prophylactic antiemetic steroids were not routinely administered d on the day of

gemcitabine administration. Dose adjustments during the treatment were based on hematologic and non-hematologic toxicities.

In case of grade III toxicities except anemia, alopecia and local toxicities, chemotherapy was held for a maximum of two weeks from the planned d date of i infusion until resolution to grade < 1, then given if the patient is medically appropriate with possibility of 25% dose reduction. If grade IV toxicity occurred, except anemia, the patient was planned to go off protocol l. All patients were scheduled to receive at least 2 cycles of therapy, and up to 6 cycles if there was no evidence of disease progression. Treatment was stopped early in cases of patient refusal, severe toxicity, progressive disease (PD), for which they were excluded from being evaluated.

2.3. Evaluation of Response and Toxicity

Pretreatment evaluation included the physical examination; ECOG-Performance Status (PS); chest X-ray; brain, thoracic and abdominal computer tomography scan (CT scan); bone scan; electrocardiogram ram; complete blood count t and blood chemistry with liver function tests and creatinine clearance. Response to therapy was assessed for every 2 cycles with CT-based radiological evaluation according to the response evaluation criteria in solid tumors (RECIST) [15]. Patients who finished 6 cycles of chemotherapy were assessed every 2 months. Toxicity was recorded according to the Common Toxicity Criteria of the National Cancer Institute (NCI-CTC, Version 3.0) [16].

2.4. Statistical Analysis

The primary objective of our study was to evaluate overall response rate (ORR), and toxicity of the fixed dose rate gemcitabine in comparison to the standard infusion dose rate. Secondary end points were time to determine progression (TTP) and overall survival (OS). Due to the paucity of patients who presented with advanced stage NSCLC to our department, a maximum number of 60 patients could be recruited. This study could be considered as an exploratory study. No sample size was calculated.

Data collected were revised, coded and introduced to the computer system where statistical manipulation and analysis were conducted. The Kaplan Meir survival analysis was used to illustrate the progression free survival and the overall survival. The Chi-squared test was used to compare the overall response rates in both treatment arms.

Hematologic and non-hematologic toxicities were analyzed using the Chi-squared test and the Fisher Exact in case of small number observations. The *p*-value was always set at 0.05. All statistical analyses were performed using the 15th version of SPSS (Statistical Package for Social Sciences).

3. Results

3.1. Patient and Tumor Characteristics

From June 2009 to June 2011, a total of 60 patients were enrolled in this trial. Patients' characteristics were balanced between the two arms. Thirty patients were included in each arm. In arm A, the majority of patients were males (90%), age was below 60 years in 73.3%, PS was 0 - 1 in 70%, and 60% of patients had stage IIIB disease. In arm B, 83.3% of patients were males, 60% of patients were below 60 years, PS was 0 - 1 in 63.3%, and 46.7% had stage IIIB disease. Patients' and tumor characteristics at baseline are listed in **Table 1**.

3.2. Response and Survival

A total of 60 patients were eligible for assessment on intent to treat analysis. The median follow up period was 13 months (range 3 - 24 months). In arm A, only one patient achieved complete response (3.3%), 43.3 (13 patients) achieved partial response, giving an overall response rate of 46.6%, 40% (12 patients) were stationary, and 13.3% (4 patients) progressed. The median TTP was 7 months (95% CI, 6.207 - 7.793 months), median OS time was 12 months (95% CI, 8.588 - 15.412 months) and 1-year survival was (50% versus 34%, $p = 0.4$). In arm B, complete response was recorded in one patient (3.3%), 40% (12 patients) achieved partial response, giving an overall response rate 43.3%, 43.3% (13 patients) were stationary and 13.3% (4 patients) progressed. The median TTP was 6 months (95% CI, 4.990 - 7.010 months), median OS time was 11 months (95% CI, 9.066 - 12.934 months) (**Figure 1**) and 1-year survival was 34% (**Figure 2**). The difference between the 2 arms of the study, in terms of ORR, TTP, and OS, was statistically non-significant (**Table 2**).

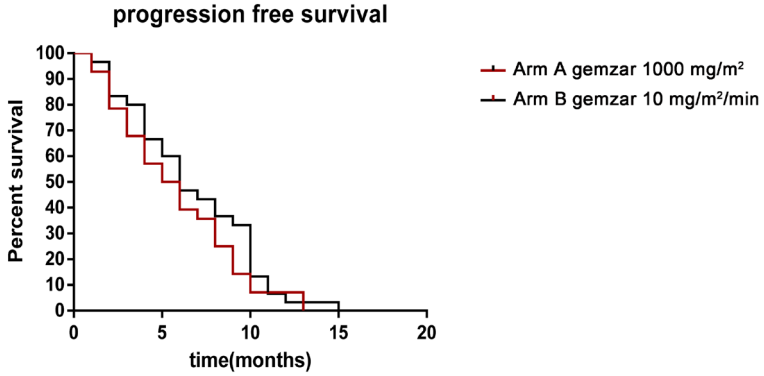

Figure 1. The time to disease progression in both Arm A and B.

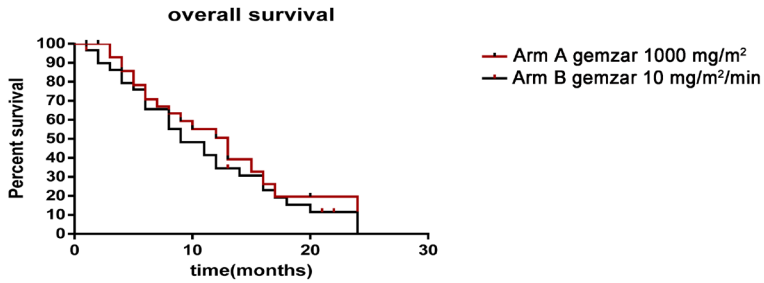

Figure 2. The overall survival in both Arm A and Arm B.

Table 1. Description and comparison between two study groups as regard patient and tumor characteristics.

		Arm A (N = 30)	Arm B (N = 30)	p^* (Chi square)	Sig.
Age Groups	<60 years	22 (73.3%)	18 (60%)	0.243	NS
	≥60 years	8 (26.7%)	12 (40.0%)		
Sex	Male	27 (90.0%)	25 (83.3%)	0.448	NS
	Female	3 (10.0%)	5 (16.7%)		
Performance status	0	5 (16.7%)	8 (26.7%)	0.403	NS
	1	16 (53.3%)	11 (36.7%)		
	2	9 (30.0%)	11 (36.7%)		
Pathology	Squamous	27 (90%)	26 (86.7%)	0.707	NS
	Large cell	3 (10%)	4 (13.3%)		
TNM Stage	IIIB	18 (60%)	14 (46.7%)	0.301	NS
	IV	12 (40%)	16 (53.3%)		
Site of metastases	Lung	7 (23.3%)	5 (16.7%)	0.519	NS
	Bone	13 (43.3%)	11 (36.7%)	0.598	NS
	Liver	7 (23.3%)	5 (16.7%)	0.519	NS
	Suprarenal	3 (10%)	1 (3.3%)	0.301	NS
	Scalp	1 (3.3%)	0 (0.0%)	0.313	NS

Table 2. Response to treatment in both arms of the study.

Response	Arm A (N = 30)	Arm B (N = 30)	*p*	Sig.
CR	1 (3.3%)	1 (3.3%)	0.994	NS
PR	13 (43.3%)	12 (40%)		
SD	12 (40%)	13 (43.3%)		
PD	4 (13.3%)	4 (13.3%)		

3.3. Toxicity

All 60 patients were evaluable for toxicity. No serious adverse events were reported d during the study and none of the patients died from the toxicity. Hematologic toxicities were more prominent in arm B. Main hematological toxicities were neutropenia , mainly grade I and II, observed in 36.7% and 53.3% in arm A and B respectively (p = 0.044). Grade III neutropenia was equally recorded in 13.3% in each arm. The incidence of grade I and II anemia was 40% and 70% in arm A and B respectively, while grade III anemia was observed in 10% and 6.7% in both arms respectively (p value = 0.024). As regards thrombocytopenia, it was mild in most cases, with grade I and II thrombocytopenia in 23.4% in arm A and 40% in arm B. Grade III thrombocytopenia was reported in 3.3% in each arm. Only one patient (3.3%) in each arm developed grade IV hematological toxicity, in the form of neutropenia. Non hematologic toxicities were almost comparable in both arms. Grade I and II Nausea and vomiting was observed in 50% and 46.7% in arm A and B respectively, while grade III was recorded in 26.7% and 30% in both arms respectively. Grade I and II neurotoxicity was noted in 30% in arm A and in 23.3% in arm B. The hematologic and non-hematologic toxicities are described in **Table 3** and **Table 4**.

In total, 273 cycles were administered (138 cycles in arm A and 135 cycles in arm B), with a median of 5 cycles per patient (range 2 - 6). Of all the planned infusions, there were 23 dose modifications (8.4% of cycles), 11 dose reductions (4.02% of cycles) in arm A and 12 dose reduction s (4.39% of cycles) in arm B, all of them were candidate for chemotherapy dose modification due to encountered toxicities and continue d their planned therapy. Also there was 10 dose omissions (5.2% of cycles) for gemcitabine, 3 dose omissions (1.56% of cycles) in arm A and 7 dose omissions (3.46%) in arm B. Fourteen patients (23.3% of patients) had cycle delays (7 patients in each arm) for less than 2 months.

4. Discussion

Prolonged infusion of gemcitabine at a fixed dose rate (FDR) of 10 mg/m^2 per minute, as compared to commonly used 30-minute infusion , has shown promising results in phase I and II clinical trials for the treatment of pancreatic adenocarcinoma [8] and NSCLC [9] [11].

The current phase III randomized clinical trial was conducted to compare the efficacy and tolerability of the standard (arm A) versus the FDR (arm B) infusion of gemcitabine and cisplatin in patients with advanced NSCLC.

Table 3. The hematologic toxicities distribution between Arm A (n = 30) and Arm B (n = 30).

	Neutropenia	Anemia	Thrombocytopenia
Grade 1 Arm A	6/30 (20%)	3/30 (10%)	5/30 (16.7%)
Arm B	10/30 (3.3%)	13/30 (43.3%)	8/30 (26.7%)
Grade 2 Arm A	5/30 (16.7%)	9/30 (30%)	2/30 (6.7%)
Arm B	6/30 (20%)	8/30 (26.7%)	4/30 (13.3%)
Grade 3 Arm A	4/30 (13.3%)	3/30 (10%)	1/30 (3.3%)
Arm B	4/30 (13.3%)	2/30 (6.7%)	1/30 (3.3%)
Grade 4 Arm A	1/30 (3.3%)	0	0
Arm B	1/30 (3.3%)	0	0

Table 4. The non-hematologic toxicities distribution between Arm A (n = 30) and Arm B (n = 30).

	Nausea and Vomiting	Neurosensory	Mucositis	Renal Toxicity	Fatigue
Grade 1 Arm A	10/30 (33.3%)	8/30 (26.7%)	2/30 (6.7%)	2/30 (6.7%)	10/30 (33.3%)
Arm B	9/30 (30%)	6/30 (20%)	5/30 (16.7%)	3/30 (10%)	7/30 (23.3%)
Grade 2 Arm A	5/30 (16.75)	1/30 (16.7%)	1/30 (3.3%)	1/30 (3.3%)	3/30 (10%)
Arm B	5/30 (16.7%)	1/30 (3.3%)	0	0	3/30 (10%)
Grade 3 Arm A	8/30 (26.7%)	0	0	0	0
Arm B	9/30 (30%)	0	0	0	0
Grade 4 Arm A	0	0	0	0	0
Arm B	0	0	0	0	0

Both treatment arms had almost equal ORR, 46.6% and 43.3% in arm A and arm B respectively. In other clinical trials that used FDR infusion of gemcitabine (10 mg/m^2/min), ORR ranged between 20% and 47% [9]-[14]. The one-year survival rates in the present study were 50% versus 34%, $p = 0.4$ in the standard arm and the FDR arm respectively. The median TTP was 7 months and 6 months in both arms respectively, while the median OS time was 12 months and 11 months in the standard arm and the FDR arm respectively. In other similar studies, the one-year survival rates ranged from 36% to 52%, median TTP ranged from 4 - 12 months, and median OS ranged between 5 months and 11 months [9]-[14]. The superior results of our study reflects better patients' characteristics, as 60% and 46.7% of patients in the standard arm and FDR arm respectively, were stage IIIB disease. In other studies about 80% of patients were stage IV disease [9] [11]-[14] and enrollment of patients with brain metastases was allowed in four of these trials [9]-[12]. Ceribelli and colleagues included 24% of patients with brain metastases in their study [9]. In Cappuzzo *et al*. trial, 66% of patients were stage IV disease, but they used single agent gemcitabine at a dose of 1500 mg/m^2 d1, 8 every 21 days in both arms [12]. Also, two studies used carboplatin instead of cisplatin [11] [13]. In the trial conducted by Soo *et al*., they used gemcitabine at a lower dose (750 mg/m^2 over 75 minutes) in the FDR arm [11].

The equivalent efficacy of both standard 30-min infusion and FDR 10 mg/m^2/min infusion is in consistence with Qui *et al*. recently published meta-analysis of six randomized controlled trials, involving 867 patients , which compare d standard rate infusion with FDR infusion in patients with advanced NSCLC [17].

Analysis of toxicity in the current study showed that both schedules were well tolerated and had acceptable toxicity profiles. However, FDR arm was associated with more significant hematologic toxicities, as neutropenia (all grades) was reported in 70% of patients in the FDR as opposed to 53% in the standard dose arm. However, GIII-GIV neutropenia was equivalent in both arms at a rate of 16.6%. Anemia (GI-GIII) was recorded in 77% and 50% in the FDR arm and the standard arm respectively. Thrombocytopenia was mild and occurred in 43% and 27% in the FDR arm and standard arm respectively, however, it was mostly GI-II. Apart from alopecia GI-II, which was more prominent in the FDR arm (47%) as compared to the standard dose arm (33%), non-hematologic toxicities were comparable in both arms. Nausea and vomiting GI-III was recorded in 77% of patients in both arms, while neurotoxicity GI-II was documented in 23.3% and 30% of patients in the FDR arm and standard infusion arm respectively. These findings are in agreement with previous reports that gemcitabine infusion over a prolonged time is usually associated with increased hematologic toxicities [8] [18] [19]. Also, our results are consistent with Qiu *et al*. meta-analysis, in which FDR infusion was associated with more Grade III-IV hematologic and non-hematologic toxicities [17]. Previous studies in NSCLC that investigated ted gemcitabine/cisplatin regimens with FDR gemcitabine reported GIII-IV neutropenia in the range of 15% - 26% in the standard arm as compared to 30% - 395% in the FDR arm, GIII-IV thrombocytopenia in the range of 3% - 19% in the standard arm and 13% - 18% in the FDR arm, while GIII-IV anemia ranged between 2% - 8% in the standard arm and 11% - 13% in the FDR arm [9] [12] [14]. Other regimens that used carboplatin instead of cisplatin had more severe GIII-IV hematologic toxicities [11]-[13].

5. Conclusion

FDR administration of gemcitabine in combination with cisplatin had equivalent efficacy to the standard 30-min gemcitabine infusion with cisplatin in patients with advanced NSCLC. However, the FDR infusion protocol was associated with more severe hematologic toxicities and its administration in elderly patients or those with poor performance status should be with caution. Further studies are recommended to evaluate different infusion protocols of gemcitabine particularly in the elderly patients above 65 years who represent more than 50% of all patients with NSCLC at diagnosis. The low-dose prolonged infusion of gemcitabine at a dose of 250 mg/m^2 over 6 hours showed promising results in treatment of NSCLC.

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