

## Gemcitabine and Cisplatin in the Treatment of Advanced Non-Small Cell Lung Cancer: National Cancer Institute Cairo Experience

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### ABSTRACT

**Aim of the work:** The aim of the present study is to document the antitumor activity of the combination of gemcitabine and cisplatin for the treatment of advanced NSCLC, assess the nature and severity of the side effects and elicit the impact of the combination chemotherapy on progression free survival and overall survival.

**Patients and methods:** From August 1997 to August 2001, we conducted a phase II study of gemcitabine and cisplatin in 60 chemo-naïve patients (21 stage IIIB and 39 stage IV). For the first 34 cases, gemcitabine was given at a dose of 1,000 mg/m<sup>2</sup> IV on days 1, 8 and 15 with cisplatin 100 mg/m<sup>2</sup> on day 15, every 28 days. In the following 26 patients, the regimen was modified to gemcitabine 1,250 mg/m<sup>2</sup> days 1 and 8 and cisplatin 80 mg/m<sup>2</sup> day 1, every 21 days.

**Results:** Patients included 53 males and 7 females [median age, 52 years (range, 28-69)]. Twenty-nine had adenocarcinoma, 18 large-cell carcinoma and 13 squamous-cell carcinoma. Thirty-one patients had a performance status (PS) of 2 and 22 presented with weight loss. All patients were evaluable for response. Three patients achieved a complete response (CR) and 22 had partial response (PR), giving an overall response of 41.7%, with a median duration of 10 months (range, 4-46 months). The time to progression (TTP) was 8 months (range, 2-46 months), with a median overall survival of 9 months (range, 2-46 months). The one-year survival rate was 30.3% for the entire study population, 44% for responders, and statistically improved in patients with a PS of 1 and those with no weight loss. A total of 255 cycles were administered (median, four cycles/patient). Myelosuppression was significant (but manageable) with grade 3/4 neutropenia in 32.6% of cases, anemia in 18.6% and thrombocytopenia in 20.4%. Nonhematologic toxicity was limited to grade 3/4 nausea and vomiting in 28.8% of cases and impaired liver enzymes in 13.6%.

**Conclusion:** In spite of the relatively poor prognostic characteristics in the study population, gemcitabine and cisplatin was an effective combination with tolerable, manageable toxicity in advanced NSCLC.

**Key Words:** NSCLC - Chemotherapy - Palliative therapy - Gemcitabine.

### INTRODUCTION

The management of non-small-cell lung cancer (NSCLC) has evolved considerably during the past decade. New drugs and combinations have provided a modest, genuine improvement in the survival of patients, including those with advanced unresectable disease [2].

Gemcitabine (Gemzar) has established itself as an active single agent in the treatment of advanced NSCLC, achieving a response rate of 20% with mild toxicity [1]. Gemcitabine monotherapy appears to be as active as, but at the same time much less toxic than, the combination of etoposide (vepesid) and cisplatin (platinol) as first-line chemotherapy for advanced NSCLC [16]. Gemcitabine is also effective in the palliation of tumor-related symptoms [21] in many cases, the patient's performance status (PS) is improved following gemcitabine therapy [21].

The encouraging response rates and modest toxicity suggested provide a rationale for the evaluation of gemcitabine in combination with other agents possessing activity against NSCLC. Cisplatin forms the backbone of most combination regimens used in NSCLC, due not only to

its single-agent activity, but its association with only modest myelosuppression. In vitro data suggested that cisplatin might share synergism with gemcitabine, possibly a result of interference with intracellular DNA repair mechanisms induced by cisplatin [13].

The combination of gemcitabine and cisplatin proved to be significantly more effective than single-agent cisplatin (response of 31% vs 12%) [18]. Also, when gemcitabine/cisplatin was compared with other standard regimens used in the treatment of NSCLC, e.g., mitomycin (Mutamycin), ifosfamide and cisplatin (MIC) therapy, Crino et al reported response rates of 40% for gemcitabine/cisplatin vs 28% for MIC ( $p = 0.03$ ) [6]. Castellano and colleagues demonstrated that the combination regimen of gemcitabine plus cisplatin administered every 3 weeks was well tolerated and resulted in a markedly high response rate of 65% [4].

In Egypt, most lung cancer patients who present in the late stages have a large tumor bulk disease and poor PS [10]. We report here the results of our expanded phase II trial of gemcitabine/cisplatin that was conducted at the National Cancer Institute (NCI), Cairo University, Egypt during the period between August 1997 and August 2001.

## PATIENTS AND METHODS

Inclusion criteria included histologically confirmed advanced NSCLC (stage IIIB and IV). Only stage IIIB patients with supraclavicular lymph node metastasis or malignant pleural effusion were included. Other criteria included: measurable disease, World Health Organization (WHO) PS of 0-2, age < 70 years, and normal organ function (renal, hepatic and cardiac). No previous chemotherapy was allowed. All patients gave informed consent according to the World Medical Association Declaration of Helsinki.

Pretreatment evaluation included a complete history and physical examination that included neurological evaluation, PS, laboratory assessment (full blood picture, electrolytes, liver enzymes, bilirubin, creatinine, creatinine clearance, total protein, albumin), electrocardiogram and tumor assessment. (Chest, abdomen and brain CT scan, bone scan and abdominal ultrasound were performed only if there was clinical suspicion of metastasis).

For the first 34 cases, gemcitabine was given at a dose of 1,000 mg/m<sup>2</sup> IV on days 1, 8 and 15, together with cisplatin 100 mg/m<sup>2</sup> on day 15, every 28 days. In the next 26 patients, the regimen was modified to gemcitabine 1,250 mg/m<sup>2</sup> days 1 and 8 plus cisplatin 80 mg/m<sup>2</sup> day 1, every 21 days. Gemcitabine was dissolved in 250 ml of 0.9% saline and infused over 30 minutes. Cisplatin was dissolved in 500 ml saline and administered IV over 2 hours. Patients received an IV hydration regimen and prophylactic parenteral antiemetics, consisting of a 5-HT<sub>3</sub> receptor antagonist plus dexamethasone, before cisplatin administration. A maximum of six cycles was planned.

Gemcitabine on day 8 or 15 was administered at a full dose only if the white blood cell (WBC) count was > 2 x 10<sup>9</sup>/l and platelet count > 100 x 10<sup>9</sup>/l. Seventy-five percent of the dose was given if WBC was 1-2 x 10<sup>9</sup>/l or if platelets were 50-100 x 10<sup>9</sup>/l. Before repeating a cycle, the requirements were: absolute neutrophil count ≥ 1.5 x 10<sup>9</sup>/l, platelets ≥ 100 x 10<sup>9</sup>/l, hemoglobin ≥ 9 g/dl, creatinine clearance ≥ 60 ml/min and normal liver function.

If hematologic, renal, or hepatic function did not meet these criteria, treatment was delayed until recovery for a maximum of 2 weeks. Patients went off study when treatment delays exceeded 2 weeks.

Patients were considered evaluable for response and survival after completion of at least 2 cycles.

A complete response (CR) was defined as a complete disappearance of all known disease determined by two observations not less than 4 weeks apart. A partial response (PR) was a 50% or greater reduction of the product of the perpendicular diameters of all measurable lesions. Stable disease (SD) defined less than a 50% response or less than a 25% increase in tumor size. Progressive disease (PD) was an increase of more than 25% in the product of the perpendicular diameters of all measurable lesions or the appearance of new lesions. Time to progression (TTP) was defined as the time elapsed from the start of treatment confirmed progression and survival from initiation of chemotherapy until death. In cases of PD, patients went off study. Toxicity was evaluated

according to National Cancer Institute Common Toxicity Criteria (NCI-CTC) grading system.

Analyses of efficacy included calculations of tumor response rates and 95% confidence intervals (CIs). Statistical tools included the Kaplan-Meier method for estimating the probability of survival and time to progression [15].

## RESULTS

### *Efficacy/Survival:*

Sixty patients were included in the study from August 1997 to August 2001. Table (1) summarizes the patients' characteristics. There were 53 males and 7 females, with a median age of 52 years (range, 28-69). Of the 60 patients diagnosed, 29 had adenocarcinoma, 18 large-cell carcinoma and 13 squamous-cell carcinoma. Twenty-one patients had stage IIIB disease and 39 had stage IV.

All 60 patients were evaluable for response and toxicity, and the efficacy data are enumerated in Table (2). Three patients achieved a CR and 22 had a PR, resulting in an overall response rate of 41.7% (95% CI, 29-53%). Responses were observed in patients with stage IIIB with 9 of 21 (42.9%) patients and stage IV with 16 of 39 (41.0%). The overall median duration of response was 10 months (range, 4-46 months).

The 1-year survival was 30.3% for the study group and 44% for patients exhibiting objective responses. As illustrated in Fig. (1), the median overall survival was 9 months (range, 2-46 months; 95% CI, 8-12 months). Of the factors

that influenced 1-year survival, there was a statistically significant difference between patients having a PS of 1 and 2 ( $p = 0.007$ ) and also for weight loss ( $p = 0.001$ ). These data are summarized in Table (3). At the last evaluation, PD was present in 11 patients (18.3%) and the median TTP was 8 months (range, 2-46 months; 95% CI, 7-10 months) (Fig. 2).

Relief of symptoms was observed in many patients during treatment: dyspnea 45%, cough 40%, pain 42% and hemoptysis 38%. The PS improved in 50% of the patients and this was noted with the first two treatment cycles.

### *Toxicity:*

A total of 255 cycles were administered, with each patient receiving a median of four cycles (range, two to six cycles). Delay or omission of scheduled treatment occurred in 54 cycles (21.6%).

The most significant toxicity was hematologic, as summarized in Table (4). Grade 3 neutropenia developed in 28.9% of patients, with grade 4 in 3.7%. However, only 3.6% of patients had febrile neutropenia requiring IV antibiotics. Approximately 20% of patients experienced grade 3/4 thrombocytopenia and 18.6% had grade 3 anemia.

The nonhematologic toxicity is enumerated in Table (5) and included grade 3/4 nausea/vomiting in 28.8% of cases. Viral hepatitis was reported in 6.6% of cases ( $n = 4$ ) following chemotherapy and grade 1/2 flu-like symptoms were encountered in 37.3%. Grade 1/2 neurotoxicity was present in 28.8% of patients.

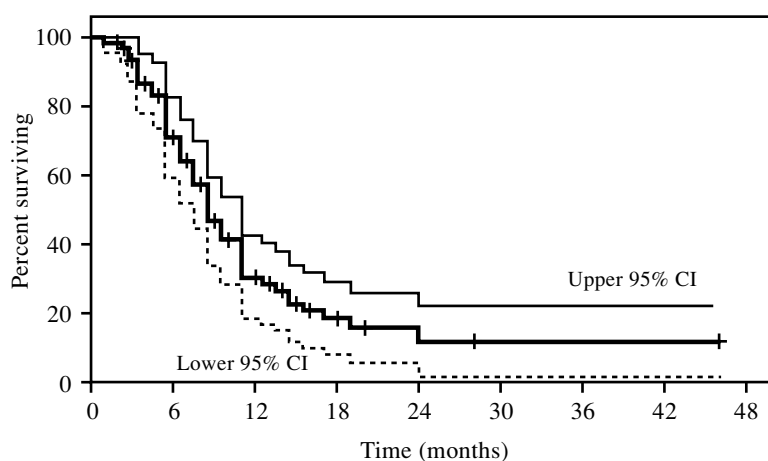


Fig. (1): Overall survival in non-small-cell lung cancer.

Fig. (2): Time to progression in non-small-cell lung cancer.

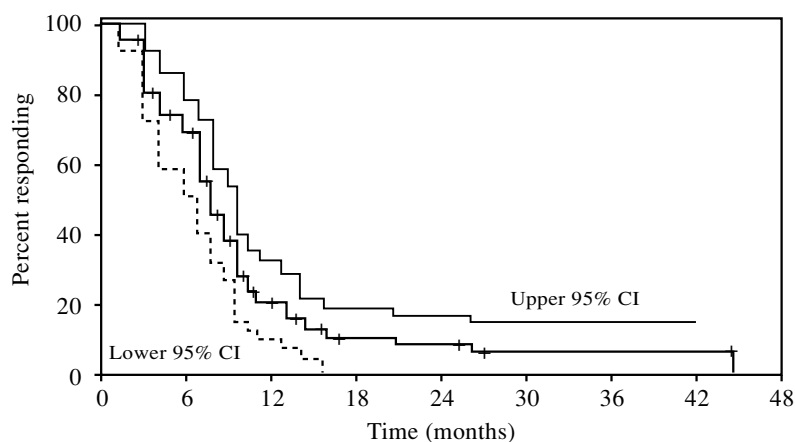


Table (1): Patient characteristics.

Number of patients		60
<i>Gender:</i>		
Male		53
Female		7
<i>Age, years:</i>		
Median		52.5
Range		28-69
↑ 60		47
<i>PS (ECOG):</i>		
1		29
2		31
<i>Pathology:</i>		
Adenocarcinoma		29
Large-cell carcinoma		18
squamous-cell carcinoma		13
<i>Grade:</i>		
Moderate		34
Poor		26
<i>Stage:</i>		
III B		21
IV		39
<i>Weight loss:</i>		
≥ 5%		22
< 5%		38

ECOG: Eastern cooperative oncology group.  
PS: Performance status.

Table (2): Efficacy response (n = 60 evaluable).

	Patient number	Percentage
Overall response	25	41.7 (95% CI, 29%-53%)
Complete response	3	5
Partial response	22	36.7
Stable disease	24	40
Progressive disease	11	18.3
Median duration of response	10 months (range, 4-46 months)	
Time to progression	8 months (range, 2-46 months; 95% CI, 7-10 months)	

CI: Confidence interval.

Table (3): Prognostic factors for 1-year survival.

	Survival (%)	p-value
<i>Age (years):</i>		
≤ 60	33.1	0.205
> 60	18.5	
<i>Gender:</i>		
Male	26.6	0.088
Female	57.1	
<i>Weight loss:</i>		
+	14.7	0.001
-	39.5	
<i>Pathology:</i>		
Adenocarcinoma	34.5	0.314
Large-cell carcinoma	20.6	
Squamous-cell carcinoma	33.9	
<i>Stage:</i>		
III B	30	0.582
IV	30.7	
<i>PS (ECOG):</i>		
1	44.8	0.007
2	15.2	

ECOG: Eastern cooperative oncology group.  
PS: Performance status.

Table (4): Hematologic toxicity (n = 60).

Toxicity parameter	Percentage of patients				
	NCI-CTC grade				
	0	1	2	3	4
Anemia	25.4	22.0	33.9	18.6	—
Leukopenia	30.5	15.3	32.2	18.6	3.4
Neutropenia	30.9	12.9	23.6	28.9	3.7
Thrombocytopenia	39.0	25.4	15.3	15.3	5.1

NCI-CTC; National Cancer Institute Common Toxicity Criteria.

Table (5): nonhematologic toxicity (n = 60).

Toxicity parameter	Percentage of patients				
	NCI-CTC grade				
	0	1	2	3	4
Nausea/vomiting	11.9	20.3	39.0	27.1	1.7
Diarrhea	78.0	8.5	13.6	0	0
Bilirubin	84.7	3.4	5.1	6.8	0
Transaminases	74.6	11.9	6.8	6.8	0
Renal	91.5	6.8	1.7	0	0
Skin	83.1	13.6	3.4	0	0
Neurologic	71.2	23.7	5.1	0	0
Flu-like symptoms	52.7	35.6	1.7	0	0
Edema	78.0	18.6	3.4	0	0

NCI-CTC; National Cancer Institute Common Toxicity Criteria.

## DISCUSSION

Lung cancer exhibits high morbidity and mortality due its high incidence and accompanying high fatality rate. A decade ago, the chemotherapeutic armamentarium for treating lung cancer was characterized by high toxicity and a detrimental impact on a patient's quality of life (QOL). More recently, newer agents positively impacted outcomes in patients with advanced NSCLC and include novel combinations/schedules of chemotherapeutic agents. This impact is manifested through prolongation of survival and palliation of symptoms that presumably improve QOL [2].

Single-agent gemcitabine has achieved significant activity in NSCLC and along with data obtained from studies combining it with cisplatin, it was registered for treatment of NSCLC in the United States. The combination of gemcitabine and cisplatin was active and the main toxicity was myelosuppression.

An early refinement was replacement of a 28-day cycle with a 21-day schedule. Elimination of day-15 administration also improved its tolerability [4]. Moreover, 21- and 28-day schedules of the combination of gemcitabine and cisplatin were similarly effective and considered current standard therapy in NSCLC [17]. Also, while initial studies employed the maximum

tolerated dose of cisplatin (100 mg/m<sup>2</sup>) in combination with gemcitabine, there was little evidence of a dose-response relationship. Reduction of the cisplatin dose to 60-80 mg/m<sup>2</sup> will thus likely preserve activity with decreasing toxicity [7]. In the study presented here, we employed the "classic" regimen for the first 34 patients and switched to a 21-day schedule, reducing the dose of cisplatin to 80 mg/m<sup>2</sup> in 26 successive patients. The response rate was 41.7%, with a median duration of 10 months. These data are in accordance with previous studies that reported response rates ranging between 32% and 54% [19].

When gemcitabine/cisplatin was compared with cisplatin/etoposide in a randomized phase III trial of the Spanish Lung Cancer Group (SLCG), the respective response rates were 41% vs 22% ( $p = 0.02$ ), with times to progression of 6.9 months vs 4.3 months ( $p = 0.01$ ) without impairment in QOL [3]. These data by Cardenal and co-workers are comparable to those reported herein (response, 41.7%; TTP, 8 months).

In a previous study of 72 NSCLC patients at our institution using a regimen of mitomycin/vinblastine (Velban)/cisplatin (MVP), we reported a response rate of 32% with relatively high toxicity [9]. On the contrary, carboplatin (Paraplatin)/etoposide was well tolerated, but the response was only 20%, with a median survival of 7 months [8]. In the present study, the comparative response and median survival were higher (41.7% and 9 months, respectively).

The Eastern Cooperative Oncology Group (ECOG) recently conducted a randomized phase III trial (E1594) that compared three third-generation platinum-based regimens with activity in NSCLC [gemcitabine/cisplatin, docetaxel (taxotere)/cisplatin, paclitaxel (taxol) / carboplatin] to a reference regimen of cisplatin and paclitaxel. Shiller et al., reported statistically increased TTP ( $p = 0.002$ ) for the gemcitabine/cisplatin arm compared with the reference group-the paclitaxel / cisplatin arm [20]. (A significant number of patients discontinued treatment on the paclitaxel/carboplatin arm due to disease progression). The respective median and 1-year survival rates were 8.1 months and 36%. These previously reported data are comparable to those described in the study presented here (9 months and 30.3 %).

In the ECOG study, the incidence of myelosuppression was significantly increased in the gemcitabine/cisplatin arm vs the reference arm ( $p < 0.05$ ). In fact, patients in the gemcitabine/cisplatin arm exhibited grade 3/4 thrombocytopenia (19/29) and anemia (28/1), possibly a result of the cisplatin dose (100 mg/m<sup>2</sup>) employed. The two other arms used cisplatin at a dose of 75 mg/m<sup>2</sup>.

In the present study, toxicity consisted primarily of grade 3/4 neutropenia (32.6% that was manageable and reversible (febrile neutropenia occurred in 3.6% of patients), Grade 3/4 anemia occurred in 18.6% of cases, with thrombocytopenia in 20.4%. Our study also confirmed the significance of good PS ( $p = 0.007$ ) and absence of weight loss ( $p < 0.001$ ) as prognostic factors for survival. However, during accrual, 31 patients presented with a poor PS of 2 and 22 had weight loss. As a result, data from these patients may have influenced the final survival data.

The Southern Italy Cooperative Oncology Group conducted a phase III study in advanced NSCLC randomizing cisplatin / gemcitabine / vinorelbine (PGV) with either cisplatin/gemcitabine (PG) or cisplatin/vinorelbine (PV). The PG regimen was more active than PV (30% vs 25%) and achieved increased median survival (42 weeks vs 35 weeks); these data influenced the deletion of the study arm with PV. Response in the PGV arm was 47%, with a median survival time of 51 weeks [5].

More recently, Van Meerbeek and colleagues from the European Organisation for Research and Treatment of Cancer (EORTC) conducted a randomized study comparing gemcitabine/cisplatin, gemcitabine/paclitaxel and paclitaxel/cisplatin [22]. Paclitaxel/cisplatin was considered the reference arm based on previous EORTC trial data comparing paclitaxel/cisplatin with cisplatin/teniposide (Vumon) where paclitaxel/cisplatin achieved similar survival but with better palliation [12]. Gemcitabine / paclitaxel was chosen as a study arm due to a reported response rate of 30% in phase II investigation [11]. Van Meerbeek et al reported no statistical differences in response in the study arms when compared to the standard, but noted that CRs were achieved exclusively in the gemcitabine/cisplatin arm. There was also a trend toward improved TTP in this arm, confirming previous

results. A statistically higher incidence of thrombocytopenia was reported in the gemcitabine/cisplatin arm, but there were no cases of bleeding and only one of toxic death (compared to 4 cases in the paclitaxel/gemcitabine arm and 3 in the standard arm).

Huisman and co-workers recently conducted an interesting phase II study with a new schedule of cisplatin 50 mg/m<sup>2</sup> days 1 and 8 plus gemcitabine 800 mg/m<sup>2</sup> days 2, 9 and 15-a schedule designed to optimize drug synergy and reduce toxicity due to high-dose cisplatin [14]. They reported an overall response rate of 58% and respective 1-year survival percentages of 90%, 23% and 42% for stage IIIA, IIIB and IV patients. Toxicity was tolerable (mainly myelosuppression), with frequent omission of gemcitabine on day 15, a limitation of the study schedule. It appears likely that fractionation of cisplatin might reduce toxicity.

To our knowledge, the study reported herein is the first prospective, expanded study from the Middle East using the gemcitabine/cisplatin combination in NSCLC. The data demonstrated that the combination of gemcitabine and cisplatin is effective and relatively well tolerated, even in patients with advanced and large-tumor bulk NSCLC. Based on the analysis of the significance of prognostic factors, this regimen should be used in patients presenting with a PS of 0-1 and with no weight loss.

The combination of gemcitabine and cisplatin is recommended for neoadjuvant therapy prior to surgery or radiotherapy in earlier stages of NSCLC. Modifications in the dosing schedule to reduce toxicity are also of value for future investigation.

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