Paclitaxel Plus Gemcitabine in Advanced Non-small Cell Lung Cancer Patients with Low Performance Status

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Abstract. *Background: The aim was to determine the efficacy and safety of a platinum-free regimen combining gemcitabine and paclitaxel for the treatment of patients with advanced non-small cell lung cancer (NSCLC) and a low performance status (PS). Patients and Methods: Patients with histologically confirmed unresectable NSCLC, no previous chemotherapy, measurable lesion and a PS of 2 or 3 according to the Eastern Cooperative Oncology Group (ECOG) scale were elegible. Chemotherapy consisted of paclitaxel 200 mg/m^2 on day 1 plus gemcitabine 1000 mg/m^2 on days 1 and 8, every 3 weeks, for a maximum of 8 cycles. Results: Twenty-nine consecutive patients were enrolled. PS was 2 and 3 in 93% and 7% of patients, respectively. A total of 149 courses of chemotherapy were delivered (median 4.6). Responses: complete response 1 (3.4%), partial response 11 (37.9%), stable disease 12 (41.3%), progressive disease 5 (17.2%) (response rate 41.3%, 95% CI: 23.5% to 61.6%). Median time to progression was 8.3 months (range 2.9-31.7); median overall survival was 13.6 months (range 3.2-31.7). Grade 3 leukopenia occurred in 3% of patients, while grade 3 thrombocytopenia was observed in 25% of patients. Conclusion: Reasonable response rates and a satisfactory clinical benefit can be obtained with a platinum-free regimen in NSCLC patients with a low PS.*

Seventy-five percent of patients with lung cancer present inoperable, locally advanced or metastatic disease and are therefore candidates for some form of systemic chemotherapy (1). Even though chemotherapy has a modest survival benefit compared to best supportive care (2), patients with advanced, non-small cell lung cancer (NSCLC) have a poor outcome, with a typical survival time of approximately 4 to 6 months (1). Platinum-based treatment is recommended for the treatment

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of advanced NSCLC in patients with a good performance status (PS 0-1 ECOG) (3); however, recent studies have shown that such treatment has reached a plateau and new strategies are necessary (4). The 1995 meta-analysis, comparing best supportive care to cisplatin-based combination chemotherapy in advanced NSCLC, showed a modest (10%) improvement in the 1-year survival rate (2); however, the side-effects that accompany cisplatin administration, including nephrotoxicity, ototoxicity and cumulative myelosuppression, often outweigh its palliative benefits. In another meta-analysis, the effects of single agent *versus* platinum-based combination chemotherapy on response rate, toxicity and survival of patients with advanced NSCLC were explored. The platinum-based regimen improved the objective response rates compared with single-agent chemotherapy, but again toxicity was significant with a 3.6-fold increase in the risk of treatment-related death (5).

Performance status has long been known to be one of the most important prognostic factors for patients with advanced NSCLC (6), irrespective of the treatment given. Patients with a performance status of ≥ 2, representing approximately 20% of the NSCLC population, may have no survival benefit from chemotherapy (7). In fact, a multifactor analysis performed on a database of 612 patients with inoperable NSCLC treated with chemotherapy showed that performance status 2 patients might not benefit from cisplatin-based chemotherapy (8) and that the toxicity of chemotherapy may outweigh the benefits offered by such treatment for symptom palliation. In fact, in the past such patients have been excluded from all forms of chemotherapy. There is little data regarding the benefits of chemotherapy in patients with a low performance status, therefore new drug regimens with low toxicity profiles and high antitumor activity, capable of giving a clinical benefit, are needed for this category of patients.

Fortunately, during recent years a number of new chemotherapeutic compounds, active against NSCLC, including gemcitabine, vinorelbine, paclitaxel and docetaxel, have been introduced into clinical practice. These new drugs are being used in the hope of increasing response rates with respect to platinum-based regimens (2), decreasing toxicity and

permitting ambulatory administration in the treatment of advanced NSCLC patients. Single-agent paclitaxel, currently considered one of the most active drugs in the treatment of advanced NSCLC, has produced overall response rates of 20% to 42% in chemotherapy-naïve patients with advanced disease, giving 1-year survival rates of approximately 40% (9-11). Paclitaxel has been compared to best supportive care in 157 patients with advanced NSCLC. A statistically significant improvement in survival was observed in the group of 78 patients randomized to paclitaxel plus supportive care, compared to the group receiving supportive care alone (two-sided $p=0.037$) (median survival = 6.8 months *versus* 4.8 months) (12). Gemcitabine (2'-deoxy-2',2'-difluorocytidine monohydrochloride), a nucleoside antimetabolite, has a wider spectrum of activity than its parent compound ara-C and high tolerability (13). When evaluated clinically, gemcitabine has proven antitumor activity in NSCLC, pancreatic, bladder, breast and ovarian tumors with a mild toxicity profile, and is well tolerated even at high dosage (14). As a single agent, gemcitabine has produced a response rate greater than 20% in the treatment of NSCLC, with median survival exceeding 8 months (10-12). Moreover, gemcitabine as a single agent has given similar response and survival rates and decreased toxicity compared to a cisplatin/etoposide combination (13). Paclitaxel and gemcitabine combinations have a favorable metabolic fate, as their pharmacokinetics are independent; moreover, paclitaxel increases the intracellular accumulation of the active metabolite gemcitabine triphosphate, enhancing the antitumor activity of gemcitabine (14).

The primary objective of the present phase II study was to evaluate the efficacy and safety profile of a platinum-free chemotherapeutic regime combining gemcitabine with paclitaxel in previously untreated patients with advanced NSCLC and a low performance status and, secondly, to establish the clinical benefit of treatment with this drug combination in such patients.

Patients and Methods

Eligibility criteria. Patients with histologically or cytologically confirmed stage IIIB or IV NSCLC were entered into this phase II study. Accrual in this trial was limited to patients with a performance status of 2 or 3 (ECOG scale). No prior chemotherapy or thoracic radiotherapy was permitted. Other eligibility criteria included: bidimensionally measurable or assessable disease, age ≤78 years and an anticipated life expectancy of >3 months. Patients were required to have adequate hematological (neutrophils $>2 \times 10^9$/L, platelets >100 $\times 10^9$/L, hemoglobin >10 g/dl, hematocrit >30%), hepatic (total bilirubin level of ≤1.5 mg/Dl, aspartate aminotransferase [AST] and alanine aminotransferase [ALT] <3 times the upper limit of normal), renal (serum creatinine level <2 mg/dL) and cardiac functions. Prior use of erythropoietin and blood transfusions were permitted. Patients with any history of invasive cancer or concurrent malignancies, or with active cardiovascular disease, were excluded. All patients had to sign a consent form approved by the Ethical Committee of the Civilian

Table I. *Characteristics of patients.*

Characteristics	No	%
Patients		
entered	29	100
evaluable for toxicity	29	100
evaluable for responce	29	100
Sex		
males	25	86
females	4	14
Age, years		
medium	68	
range	49-78	
Performance status		
2	27	93
3	2	7
Stage		
IIIB	8	28
IV	21	72
Histology		
squamous	21	72
poorly-differentiated squamous	2	7
adenocarcinoma	6	21
Grading		
grade 1	1	3
grade 2	11	38
grade 3	17	59
Metastatic sites*		
Brain	6	21
Bones	13	45
Controlateral lung	7	24
Liver	1	3
Nodes	14	48
Pleura	4	14
Thyroid	1	3
Adrenals	2	7

*14 patients had 2 or 3 metastatic sites

Hospital of Avezzano, Italy, and of the other participating institutions, in adherence with provisions set forth in the Helsinki Agreement.

Treatment. Outpatient treatment consisted of paclitaxel 200 mg/m^2 administered in 500 ml 5% dextrose in water over three hours on day 1, followed by gemcitabine 1000 mg/m^2, administered at an infusion rate of 10 mg/m^2/min on days 1 and 8. Standard antiallergic and antihemetic therapy was administered before each treatment cycle. Cycles were repeated every 3 weeks provided the absolute neutrophil count was $>2 \times 10^9$/L and platelet count was $>100 \times 10^9$/L. In order to maximize the synergistic mechanism of action of the two drugs, paclitaxel was administered as the first agent, to increase the intracellular concentration of gemcitabine triphosphate, the active metabolite of gemcitabine, thus enhancing the antitumor activity of gemcitabine (17). In turn, gemcitabine, which exhibits elevated activity on dividing cells, was administered on day 8 when it would be most
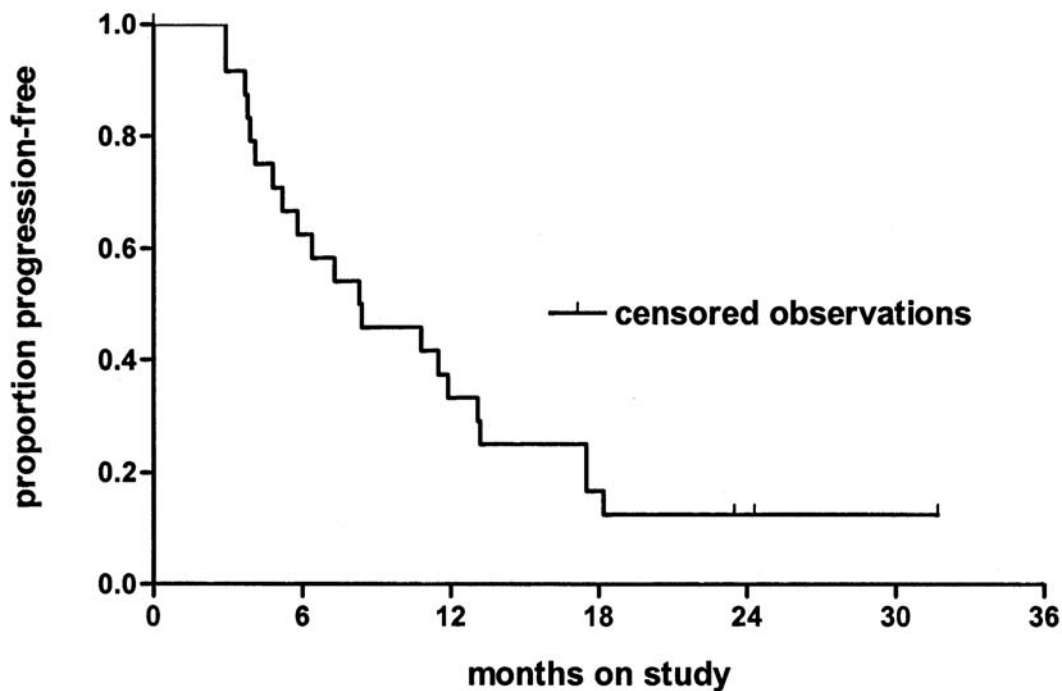
Figure 1. *Time to progression. Events 26, (89.6%), censored 3, (10.4%) median time to progression 8.3 months.*

Table II. *Clinical benefit.*

Parameter	No. of assessable patients	Patients improved	
		No.	%
Overall	29	22	73
Pain	8	6	75
Paraneoplastic syndrome	2	2	100
Dyspnea	11	8	73
Cough	10	8	80

active against these cells. Administration of drugs was reduced on day 8 or delayed for one week on day 21 in the case of toxicity, according to the protocol dosage adjustment criteria: in the case of an absolute neutrophil count from 1.0 to 1.5 x 10^9/L and/or platelet count from 75 to 99.9 x 10^9/L on day 8, 80% of the full doses of both drugs were given; chemotherapy was not administered for a lower neutrophil and platelet count. Stage IIIB patients, with a partial response after the 6 courses of chemotherapy, were treated with radiotherapy (5000 CGY given in daily fractions of 180 CGY), or surgery, as indicated. Stage IV patients received radiotherapy for palliation of symptoms, as necessary. Patients with complete response, partial response, or stable disease received a maximum of 8 courses of therapy. Patients exhibiting evidence of disease progression were removed from the study.

Pre-treatment evaluation included a medical history, clinical examination, complete blood cell count, assessment of plasma urea and creatinine levels, electrolyte measurement, a liver function test and serum carcinoembryonic antigen assessment. Electrocardiogram, computed tomographic (CT) scan of the chest and upper abdomen and X-rays of abnormal areas of bone scan uptake were also performed. CT scanning was carried out to evaluate hepatic lesions. Before each subsequent course of treatment, all patients had a blood cell count and plasma urea, electrolytes, serum creatinine, ALT, AST, alkaline phosphatase and bilirubin measurements taken. In addition, a blood cell count was repeated weekly. Patients were assessed for toxicity and response on an intent-to-treat basis, using standard World Health Organization (WHO) criteria (15), after two courses of therapy or sooner if the patient appeared to have disease progression. Parameters for the evaluation of clinical benefit included pain, paraneoplastic syndrome, dyspnea and cough.

Statistical methods. Using Simon's optimal two-stage design (18), 13 responders out of 29 patients were required during the first stage. For the response rate, exact binomial 95% confidence intervals (CI) were calculated. Time to progression and overall survival were defined as the time from initiation of chemotherapy to the time of progression and death, respectively. Both were assessed using the Kaplan and Meier product-limit method (18). Analysis of data was performed on February 28, 2004.

Results

Patient characteristics. Twenty-nine consecutive patients (25 males and 4 females), with a median age of 68 years (range: 49-78) and a poor performance status, were entered in this

Table III. *Toxicity according to WHO criteria.*

| | WHO grade | | | | | | | | | | | |
| | 0 | | 1 | | 2 | | 3 | | 4 | | Total | |
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Hematological												
Leukopenia	15	52	6	21	7	24	1	3	0	0	29	100
Neutropenia	12	41	4	14	5	17	6	25	2	7	29	100
Thrombocytopenia	19	66	1	3	1	3	8	28	0	0	29	100
Anemia	12	41	8	28	8	28	1	3	0	0	29	100
Infection	26	90	0	0	3	10	0	0	0	0	29	100
Gastrointestinal												
Oral	14	48	28	28	7	24	0	0	0	0	29	100
Nausea and vomiting	14	48	28	28	7	24	0	0	0	0	29	100
Diarrhea	28	97	0	0	1	3	0	0	0	0	29	100
Hepatic	27	93	7	7	0	0	0	0	0	0	29	100
Neurotoxicity	28	97	3	3	0	0	0	0	0	0	29	100
Cutaneous												
Alopecia	14	48	0	0	8	28	7	24	0	0	29	100

study from February 2000 to February 2002. Table I presents baseline patient characteristics. The majority (72%) of patients had stage IV disease. Twenty-one patients had squamous histology, which was poorly-differentiated in 7% of instances. Ninety-three percent of patients had a performance status of 2, while 7% had a performance status of 3. The most common sites of metastases were in the nodes, brain, bone and controlateral lung.

Dose administration. All 29 patients received a total of 149 courses of chemotherapy. The median number of courses administered per patient was 4.6 (range: 3 to 8 courses). Ten (7%) courses of chemotherapy were delayed for one week due to myelosuppression. Three patients omitted the day-8 dose of gemcitabine due to neutropenic fever. The planned dose-intensity of docetaxel and gemcitabine were, respectively, 66 and 660 mg/m^2/week. The delivered dose-intensities for paclitaxel and gemcitabine were 96% and 98% of the initial planned doses, respectively.

Response. After a minimum follow-up of 24 months, all patients were evaluated for response based on an intent-to-treat analysis. There was 1 (3.4%) complete response and 11 (37.9%) partial responses, giving an overall response rate of 41.3%, (95% CI: 23.5% to 61.0%). The response rate according to stage was as follows: 5 out of 8 patients with stage IIIB disease and 7 out of 21 patients with stage IV responded to treatment. Stable disease was observed in 12 patients (41.3%) and progressive disease in 5 patients (17.2%). Clinical benefit responses were as follows: pain improved and analgesic

consumption decreased in 6 out of 8 patients; cough and dyspnea, present in 10 and 11 patients, improved in 80% and 73% of instances, respectively; 2 patients presenting hypercalcemia and acanthosis nigricans had a complete resolution of these symptoms (Table II).

Time-to-event. Median time to disease progression was 8.3 months (range: 2.9-31.7+ months) and median overall survival was 13.6 months (range:3.2-31.7+ months). The 1-year survival rate was 51% for all patients, and 70% and 30% for patients with stage IIIB and stage IV disease, respectively ($p < 0.05$-log-rank test). As of 28 February 2004, 4 patients (14%) were alive and 3 (10.4%) were progression-free between 29.4 and 31.7 months after initiating treatment (Figure 1 and Figure 2). One stage IIIB patient underwent curative-intent radiation therapy after 6 courses of chemotherapy administered after palliative surgery. This patient is disease-free after 29.4 months from the start of chemotherapy. Three patients underwent surgery after 6 courses of chemotherapy.

Toxicity. All patients were evaluated for toxicity. The major hematological toxicities encountered in this study were neutropenia, leukopenia, thrombocytopenia and anemia (Table III). No treatment-related death was observed and no treatment was interrupted due to toxicity. Grade 4 neutropenia was observed in 2 patients and grade 3 thrombocytopenia in 8 patients. Grade 3 and grade 2 anemia occurred in 1 and 8 patients, respectively. The median WBC and platelet nadir occurred on day 14 (range: 4 to 18), with a median hematological recovery observed by day 21. Neutropenic fever
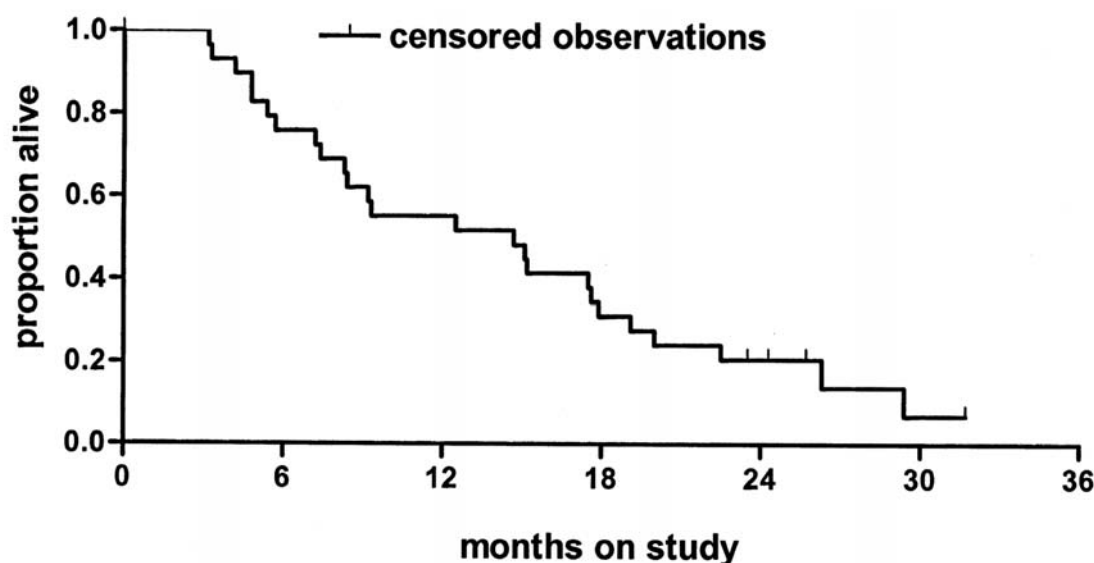
Figure 2. *Overall survival. Events 25, (86%), censored 4, (14%) median overall survival 13.6 months.*

was observed in 3 patients. Only one patient required blood transfusion for a hemoglobin value <7 g/dL.

Non-hematological toxicity was minimal. Nausea and vomiting were important (grade 2) in only 7 patients (24%) due to the appropriate administration of 5-HT3 antagonists and dexamethasone. Grade 2 and 3 alopecia occurred in 8 and 7 patients, respectively. Two patients exhibited a transient elevation in the concentration of liver enzymes. One patient developed an allergic reaction to paclitaxel.

Discussion

The use of a platinum-based chemotherapy is considered the standard treatment for NSCLC patients with a good performance status, but it is doubtful whether patients with PS of 2 benefit from such therapy. In a randomized study comparing single agent vinorelbine with vinorelbine-cisplatin and vindesine-cisplatin, a significant advantage was observed for the cisplatin-vinorelbine combination, but was limited to patients with a good performance status. The group of patients with a performance status of 2 had a median survival of 18 weeks, significantly lower than that of patients with a PS of 0 to 1 (median survival of 43, 36, 33 weeks, respectively, in the three arms) (20). In a phase II study (21), we reported that a combination of vinorelbine and ifosfamide with the less toxic drug carboplatin, instead of cisplatin, was active in the treatment of advanced NSCLC, achieving a response rate of up to 45%, with a 1-year survival rate approaching 48%. However, hematological toxicity, observed mostly in patients with a lower performance status, occurred in 60% of the 247 treatment cycles administered and required hospitalization in

14 patients. In a further phase II study, a platinum-free, three-drug chemotherapy regimen, including ifosfamide, gemcitabine and vinorelbine was tested for the treatment of NSCLC (22). Substantial hematological toxicity was observed in over 60% of patients. Such toxicity would be not acceptable for lung cancer patients with a performance status ≥ 2. In recent years, several randomized trials of platinum-free *versus* platinum-based chemotherapy for advanced NSCLC have been carried out (23-26). Platinum-containing regimens showed a worse toxicity profile, compared to the platinum-free regimens; however, patients with a PS of 2 treated with a platinum-free schedule had a comparable survival rate.

Since taxanes have been introduced in clinical practice, several studies have been conducted in patients with NSCLC. In a phase II study, a combination of docetaxel and vinorelbine was evaluated in 46 chemotherapy-naïve patients with NSCLC (27). A response rate of 36.6% was achieved, with a median time to progression and a median survival time of 5 months; however, toxicity was considerable in this study with 43% of patients requiring hospitalization for infectious complications, despite 8 days of administration of granulocyte-colony stimulating factor. Docetaxel and vinorelbine have been combined in a phase II study (28). Thirty-nine patients had a response rate of 23% and a 1-year survival rate of 31%, with grade 4 neutropenia in 92% of patients. Paclitaxel and gemcitabine have been combined in a cohort of 89 untreated NSCLC patients (29). In this study, 86% of patients with a good performance status had a median survival of 10.2 months, while patients with a performance status of 2 survived only 4.8 months. The dose-intensity of paclitaxel and gemcitabine were 75 mg/m^2/week and 1000 mg/m^2/week, respectively. In the

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present study aimed at determining the safety and effectiveness of gemcitabine and paclitaxel in the treatment of chemotherapy-naïve patients with advanced NSCLC and low PS, the dose-intensity of paclitaxel was 66 mg/m^2/week, while that of gemcitabine was 660 mg/m^2/week, which is similar to the active dose reported by other authors (20). At a higher dose-intensity, gemcitabine may result in more severe toxicity without improving clinical benefit. A response rate of 41.3%, median survival of 13.6 months and a 1-year survival rate of 51%, in a cohort of patients with a poor performance status, are encouraging data. Moreover, this regimen was not only successfully administered to 2 patients with a performance status of 3, but also determined a significant clinical benefit, with improvement of symptoms such as pain, cough, dyspnea and paraneoplastic syndromes in 76% of patients. Symptom palliation is especially meaningful in chemoresistant tumors such as gastrointestinal cancers or NSCLC, where non-surgical management cannot significantly improve survival.

In conclusion, the combination of gemcitabine and paclitaxel has been shown to be active in the treatment of chemotherapy-naïve patients with advanced NSCLC and low performance status. A randomized trial of this regimen *versus* best supportive care is planned in the same category of patients.

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