

## Weekly Chemotherapy with Cisplatin and Paclitaxel in Inoperable Non-small Cell Lung Cancer: An Extended Phase II Study\*

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**Abstract.** *Background:* A phase II study of a cisplatin/paclitaxel combination given on a weekly schedule in the front-line treatment of non-small cell lung cancer (NSCLC) is reported. *Patients and Methods:* Treatment consisted of an intravenous infusion of cisplatin, 25 mg/m<sup>2</sup>, and paclitaxel, 80 mg/m<sup>2</sup>, every week. Chemotherapy was continued until completion of a 22-week treatment plan, disease progression, persistent toxicity, or patient refusal. *Results:* Seventy-nine patients entered the study. The median number of infusions per patient was 14 (range 0-22). The median dose-intensity was 75% of that projected. Toxicity was generally acceptable, and never life-threatening. Seven complete responses (pathologically documented in 4 patients) and 27 partial responses were observed for an overall response rate of 43%. The estimated median survival and median time to progression was 55 (95% CI: 38-71) and 37 weeks (95% CI: 31-44), respectively. *Conclusion:* In our experience, the weekly combination of cisplatin and paclitaxel is well tolerated, active and associated with remarkably long survivals.

Today, lung cancer represents a major public health concern worldwide, accounting for about 12% of all new cancers in both sexes (1-3). Non-small cell lung cancers (NSCLC), including the varieties of adenocarcinomas, squamous cell and large cell carcinomas of the bronchus, represent 75-80% of all histotypes of lung cancer. Most of the patients with NSCLC present an incurable stage of disease, and 5-year survival across all stages is about 12%

(4). Patients with locally advanced (Stage III) or metastatic disease (Stage IV) (5) receive chemotherapy, since first-line platinum-based combinations improve survival, palliate symptoms and ameliorate quality of life (6-9). Unfortunately, there is no consensus on which drug combination or treatment schedule should be recommended in everyday practice (10). Randomized trials seem to support the use of two-drug combinations, containing at least one new agent, such as vinorelbine, gemcitabine, or the taxanes (11).

Paclitaxel was the first identified member of a new class of anticancer drugs known as the taxanes, which also includes docetaxel. Paclitaxel promotes the polymerization of tubulin, producing extraordinarily stable and malfunctioning microtubules. This effect provokes the disruption of the normal microtubule dynamics required for cell division and cell death (12). Paclitaxel is indicated as a first-line treatment in patients with NSCLC in combination with cisplatin (13). One of the most important clinical questions regarding the taxanes is the issue of the optimal schedule. A preliminary analysis of weekly administration schedules suggests that this approach yields equivalent efficacy, maintains dose intensity and is associated with lower toxicity (14).

Herein, the final results of an extended phase II study of a weekly cisplatin/paclitaxel (C/P) combination in chemotherapy-naïve patients with inoperable or recurrent NSCLC are reported (15).

### Patients and Methods

**Eligibility.** All patients seen, between December 2001 and April 2004, at the Pulmonary Unit of the "S. Croce e Carle" Hospital, Cuneo, Piedmont, Italy, were eligible for study if they had a cytologically or pathologically documented NSCLC (16). Mixed tumors were acceptable if only non-small cell components were identified. A 70-year age limit was established. Patients relapsing after complete tumor resection or patients incompletely resected were also eligible. Patients had to have had either a measurable or an assessable disease. An Eastern Cooperative Oncology

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Group (ECOG) performance status (17) of 2 or less was required. Laboratory values at study entry included a leukocyte count higher than 4,000/mm<sup>3</sup>, platelet count higher than 100,000/mm<sup>3</sup>, and creatinine and bilirubin blood levels less than 1½ times the upper range of normal. Patients were given all the information they wished to receive about their clinical status and the available treatment options, and were encouraged to consult their relatives for a final decision. Signing of a formal informed consent sheet was required.

Ineligible patients were those with a history of a second or third cancer (unless surgically removed and in apparently complete remission). Other criteria of ineligibility included mental instability or impairment, pre-existing moderate/severe peripheral neuropathy and previous chemotherapy (including neo-adjuvant or adjuvant treatments).

**Treatment.** Paclitaxel (Taxol®, Bristol-Meyers-Squibb, Princeton, NJ, USA) was given weekly at the dose of 80 mg/m<sup>2</sup> for a maximum of 22 weeks of treatment. Paclitaxel was diluted with 100 mL normal saline and infused intravenously over 60 minutes, followed by 250 mL normal saline. Cisplatin (Platinex®, Bristol-Meyers-Squibb) was administered at the weekly dose of 25 mg/m<sup>2</sup>, after the paclitaxel infusion.

A standard protocol of premedication and hydration was used (18). Premedication consisted of ondansetron (Zofran®, Glaxo SpA, Verona, Italy) 8-16 mg in 100 mL normal saline, 12 mg dexamethasone (Soldesam®, Laboratorio Farmacologico Milanese srl, Milan, Italy), clorphenamine 10 mg (Trimeton®, Shering-Plough, Madison, NJ, USA) and 50 mg ranitidine (Zantac®, Glaxo-Wellcome SpA) given by slow intravenous infusion 30 minutes prior to the administration of paclitaxel. Dose adjustments were based on the results of blood counts, hepatic/renal function tests and the clinical assessment of toxicity, made on the day of treatment. Reductions of 25%, 50% and 75% of the planned dose were applied for a toxicity grade ranging 0-2 (19). For higher levels of toxicity, the treatment was withheld and the patient reconsidered 1 week later.

All patients received full supportive care, including blood product transfusions, hematopoietic growth factors, antibiotics, antiemetics, laxatives and analgesics as appropriate. Palliative irradiation to painful bone metastases, or brain secondary localizations was permitted at any time, and could be concurrent to chemotherapy. Areas treated with radiotherapy were not assessed for tumor response.

Chemotherapy was discontinued on disease progression, patient refusal, or severe toxicity persisting for more than 2 consecutive weeks. Otherwise, it was continued for a maximum of 22 weekly courses.

**Staging and follow-up.** At study entry, each patient was required to have a baseline clinical work-up, which included medical history, physical examination, blood counts and serum biochemistry, chest X-rays, computed tomography (CT) of the thorax, abdomen and brain, bronchoscopy with cell and tissue biopsies. In addition, all patients were assayed for their plasmatic levels of carcinoembryonic antigen (CEA) and cytokeratin 19 fragments (Cyfra 21-1) (20-22). Additional imaging tests and tumor biopsies were not mandatory, but requested as clinically indicated. Based on the results of such evaluation, a clinical stage of disease was obtained (23).

During treatment, patients underwent 3 types of follow-up examinations. The first was a weekly pre-treatment toxicity assessment and consisted of a patient interview undertaken by the oncology nurse, hematological counts and serum biochemistry. Every 3 weeks, a preliminary re-evaluation of the tumor status was made by a physician on the basis of the medical history, physical examination, body weight and ECOG performance status assessments, the standard chest radiogram and the plasmatic measurement of CEA and Cyfra 21-1. Finally, a complete restaging evaluation was made in the 12th week of treatment and repeated during the 21st week of treatment. Restaging consisted of the same diagnostic procedures used during the baseline pretreatment evaluation except for bronchoscopy, which was optional.

**Toxicity and response evaluation.** The patients' responses were evaluated by CT scan comparisons and, thus, only at the time of the two protocol-planned restaging evaluations. This choice increased the quality of the objective response assessment, but had the negative effect of reducing the number of observations (to be assessable, patients had to be followed-up until the 12th week of treatment at least).

Toxicity was graded every week prior to the administration of the cytotoxic drugs, using standard criteria (19). In addition to the response categories of complete remission (CR), partial remission (PR), stable disease (SD) and progressive disease (PD) as they are conventionally defined (19), an intermediate category called "minor regression" was interposed between PR and SD. Minor regression (MR) was defined as a tumor shrinkage of between 25% and 49% of the pre-treatment size (as measured by the sum of the products of the longest perpendicular diameters of all measurable lesions). In non-measurable assessable lesions, analogous percent changes were used to classify a response as MR. Given our follow-up schedule, tumor responses were considered confirmed by a second evaluation made 3 weeks apart.

**Study flow and statistical analysis.** In total, 79 eligible patients were registered. Five patients withdrew their consent before starting the planned treatment, and 9 patients incurred a rapid deterioration of clinical status. Thus, 14 patients were not treated at all or were inadequately treated, having received less than 4 weeks of chemotherapy. These 14 patients could not be evaluated for response at the restaging evaluation time. Another 3 patients were lost to follow-up before their first restaging evaluation. Therefore, a total of 74 patients were assessable for toxicity, but only 62 patients for response.

This was an extended phase II clinical study with the following end-points: treatment dose intensity, treatment toxicity, objective response rate, time to treatment failure and survival. Survival and time-to-treatment failure were recorded from the day of registration. End-points for survival times were death or the last follow-up contact for patients alive at the closure of the study. End-points for treatment failure were the day of the first clinical documentation of PD or the day of death; for patients alive at the closure of the study and for whom PD was not documented, the end-point for treatment failure was the day of the last follow-up visit. Kaplan-Meier curves were used to display data (24). To control for the effect of potential confounders, a multivariate analysis, based on Cox's proportional hazards regression model (25), was performed.

Table I. Patient demographics and follow-up information.

Clinical characteristics at registration	Median	Range	Frequency
Age (yr)	64	43-70	
Sex (m/f)			64/15
ECOG PS (0/1/2)			7/46/26
Weight loss (°)	-4%	+6% / -17%	
Tumor cell type (E/A/L/M)			28/37/5/9
Serum tumor markers:			
CEA (ng/ml)	5	1-841	
Cyfra 21-1 (ng/mL)	4	0-494	
Stage of disease (IIIA/IIIB/IV)			10/23/42 (§)
TNM staging factors:			
T factor (0/1/2/3/4)			4/8/26/4/37
N factor (0/1/2/3)			28/4/33/14
M factor (0/1)			37/42
Prior surgical treatment (L/ET)			4/1
Follow-up information	Median	Range	Frequency
Post-chemotherapy surgical treatment (L/P/AR/ET)			7/4/2/1
Additional chemotherapy programs at progression (0/1/2/4)			65/11/2/1
Disease status (progressed/not progressed)			38/41
Patient status (dead/alive)			36/43

(°) percent body weight loss in 6 months; (§) four additional patients had an intrathoracic recurrent disease.

Abbreviations: ECOG PS=Eastern Cooperative Oncology Group performance status; yr=years; m=male; f=female.

Tumor cell type: E=epidermoid-squamous cell cancer; A=adenocarcinoma; L=large cell anaplastic cancer; M=mixed carcinoma; CEA=carcinoembryonic antigen; Cyfra 21-1=cytokeratin 19 fragments.

Surgical treatment: L=lobectomy; P=pneumonectomy; AR=atypical resection; ET=explorative thoracotomy.

## Results

**Characteristics of the study cohort.** The clinical characteristics of the 79 patients are depicted in Table I. The characteristics are summarized according to the main end-points of clinical interest (*i.e.*, at study registration and at the closure of the study). The patients were more often males (81% of the cohort) and in good performance status (67% of the patients had ECOG performance 0-1). Tumor markers were only slightly elevated, on average, confirming the overall fairly good prognostic trait of the cohort (26). Cell types were typically distributed, with a clear prevalence of adenocarcinomas (47% of the whole series). The distribution of the stage of disease at study entry was advanced in 23 (stage IIIB, 29%) and metastatic in another 42 subjects (stage IV, 53%). Four patients entered the study for a recurrent disease after lobectomy or following an intervention of exploratory thoracotomy. Based on the results of the first restaging evaluation, 14 subjects (18%) were considered downstaged to a condition of technical operability, were suspended from chemotherapy for at least 2 weeks and operated upon. Fourteen other patients were further treated with different regimens of chemotherapy, after the study treatment failed (Table I).

**Treatment delivery and objective response.** The duration and intensity of chemotherapy and the reasons for interruption are summarized in Table II. Sixty-six patients received more than 3 C/P courses, which we consider the smallest amount for a valid therapeutic test; the median number of infusions per patient was 14 (range 0-22). The dose intensity was lower than expected (75%) with significant dose reductions (Table II). The main reason for stopping treatment was completion of the treatment plan (51%), followed by progression of disease (19%).

Seven complete responses (pathologically documented in 4 patients after pulmonary resection) and 27 partial responses were observed with an overall response rate of 43% (on an intent-to-treat basis), and 54% (34 of the 62 patients assessable for response). Most of the objective responses were already visible at the 12th week of treatment (32/62, 52%), however continuing treatment produced a remarkable increase in the rate of complete remission (from 2 to 7, Table II).

A summary of the clinical characteristics of the 7 patients who benefited from a documented complete response is provided in Table III.

Table II. Summary of treatment administration and tumor response.

Clinical characteristics	Median	Range	Frequency
Chemotherapy courses (0/1/2/3/4/5/6 or more)	14	0-22	2/5/3/3/2/3/61
Reasons for stopping chemotherapy (C/R/D/P/O)			40/5/8/15/11
Cisplatin/Taxol median dose intensity (percent of projected)			75%
Cisplatin/Taxol dose reductions (no.of courses at 0/25/50/75/100% of projected)			19/6/28/70/101
Toxicity assessment (no.assessable/no.of registered)			74/79
Response assessment (no.assessable/no.of registered)			62/79
Objective response at the 1st CT-scan evaluation (CR/PR/MR/SD/P)			2/30/15/6/9
Objective response at the 2nd CT-scan evaluation (CR/PR/MR/SD/P)			3/13/2/8/4
Pathological complete remissions at operation (yes/no)			4/10
Best response evaluation (CR/PR/MR/SD/P)			7/27/13/5/10
Percent best response evaluation (assessable patients)			54.8%
Percent best response evaluation (registered patients)			43.0%

**Abbreviations:**

Reasons for stopping chemotherapy: C=completion of the schedule of 22 weeks treatment; R=patient refusal; D=clinical deterioration; P=progression; O=other reasons.

CT-scan=computed tomography.

Objective responses: CR=complete remission, PR=partial remission, MR=minor regression, SD=stable disease, P=progression.

Table III. Clinical characteristics of completely responding patients.

Pre-treatment data								Treatment & post-treatment data				Follow-up data		
Patient initials	Sex (M/F)	Age (years)	ECOG PS	CEA (ng/ml)	Cyfra 21-1 (mg/ml)	Tumor cell type (E/L)	Stage of disease	Type of surgery	Pathological stage	OR (1st restaging)	OR (2nd restaging)	Duration of response	Additional treatments	Overall survival (wks)
G.C.	M	64	1	3	4.7	E	IIIA	Lingulectomy	T0N0	PR	PR	85	2nd line CT	93 +
B.B.	M	65	2	12	13.8	E	IIIA	Left Lower Lobectomy	T0N0	PR	-	64 +	/	64 +
P.M.	F	57	1	1	1.7	E	IIIB	Right Lower Lobectomy	T0N0	PR	-	58 +	/	58 +
G.V.	M	65	1	3	0.9	L	IIIB	/	/	CR	CR	34+	/	34+
C.F.	M	70	2	35	6.5	L	IIIA	Left upper Lobectomy	T0N0	PR	-	36+	/	36+
G.B.	M	56	1	2	0.9	E	IIIB	/	/	PR	CR	30+	Thoracic RT	30+
R.C.	M	65	2	2.1	0.4	L	IIIB	/	/	CR	CR	19+	/	19+
Median	/	65	1	3	2	/	/	/	/	/	/	38 +	/	38 +

**Abbreviations:** M=male, F=female; ECOG PS=Eastern Cooperative Oncology Group performance status; wks=weeks; OR=objective response CEA=carcinoembryonic antigen; Cyfra 21-1=cytokeratin 19 fragments; CT= chemotherapy; RT= radiotherapy.

Tumor cell type: E=epidermoid-squamous cell cancer; L=large cell anaplastic cancer.

Objective responses: CR=complete remission; PR=partial remission.

**Toxicity.** Toxicity was measured each week, during treatment, for a total of 1560 observations (Table IV).

Leukopenia (17%, never associated with life-threatening infections), anemia (16%) and neuropathy (11%, never severe) were the most common toxicities (Table IV). Grade 3 or 4 toxicity (except alopecia) was found in only 90/1560 observations (6%). There were no documented toxic deaths. Anemia was in general mild and not necessarily treatment-related (Table IV). Other common non-alarming toxicities were alopecia (51%), nausea-vomiting (15%), hypersensitivity

reactions, including dermatitis and flu-like symptoms (15%), stomatitis (10%) and diarrhea (5%) (Table IV).

**Time-to-treatment failure and survival.** Until September 2004, 36 patients died. The median follow-up time was 32 weeks (range 1-138). The estimated median survival and the median time to progression was 55 weeks (quartile range: 31-not reached) and 37 weeks (quartile range: 24-59), respectively. The Kaplan-Meier estimates for time to progression and overall survival are outlined in Figures 1 and 2. A Cox's multivariate analysis showed that the duration of

Table IV. Toxic events (1560 pre-infusion assessments).

Toxicity grade (ECOG scale)	0		1		2		3		4		Total
	no.	%	no.	%	no.	%	no.	%	no.	%	
Hemoglobin	1290	83.2%	182	11.7%	54	3.5%	20	1.3%	4	0.3%	1550
Leukocytes	1302	84.0%	110	7.1%	90	5.8%	24	1.6%	22	1.4%	1548
Platelets	1526	98.4%	12	0.8%	6	0.4%	0	0.0%	6	0.4%	1550
Renal (creatinine)	1540	99.4%	8	0.5%	2	0.1%	0	0.0%	0	0.0%	1550
Nausea-vomiting	1323	85.4%	199	12.8%	32	2.1%	0	0.0%	0	0.0%	1554
Diarrhea	1467	94.6%	62	4.0%	18	1.2%	4	0.3%	0	0.0%	1551
Stomatitis	1400	90.3%	150	9.7%	2	0.1%	0	0.0%	0	0.0%	1552
Hypersensitivity reactions	1437	92.7%	96	6.2%	12	0.8%	6	0.4%	0	0.0%	1551
Water retention	1441	93.0%	92	5.9%	18	1.2%	0	0.0%	0	0.0%	1551
Alopecia °	758	48.9%	174	11.2%	324	20.8%	304	19.5%	0	0.0%	1560
Local reaction at the site of intravenous injection	1550	100.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1550
Neuropathy	1384	89.3%	160	10.3%	8	0.5%	0	0.0%	0	0.0%	1552
Respiratory infections with leukopenia	1487	95.9%	64	4.1%	0	0.0%	0	0.0%	0	0.0%	1551
Bronchodynamic toxicity	1473	95.0%	48	3.1%	26	1.7%	4	0.3%	0	0.0%	1551

(°) partially due to the concurrent brain irradiation given to 3 patients

Abbreviations:

ECOG= Eastern Cooperative Oncology Group

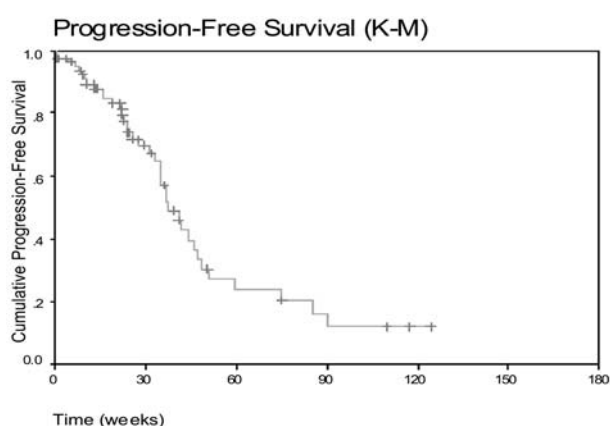


Figure 1. Kaplan and Meier estimate of treatment failure for the whole group of cisplatin/paclitaxel patients.

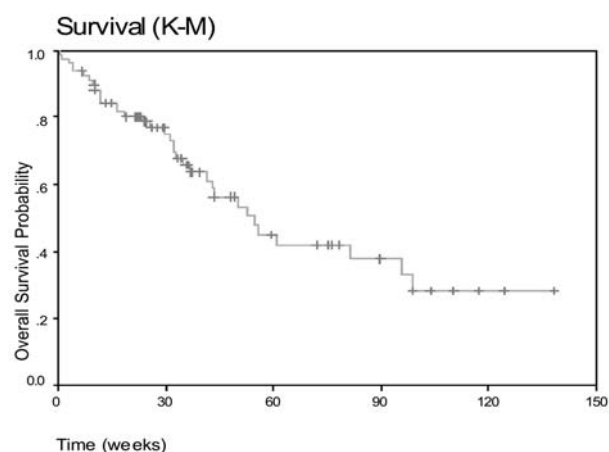


Figure 2. Kaplan and Meier estimate of survival for the whole group of cisplatin/paclitaxel patients.

chemotherapy was the most powerful predictor of survival, independent of the performance status and the extent of disease (Table V). Another important prognostic factor was the delivery of a second-line chemotherapy after the first-line treatment (Table V).

## Discussion

The goal of this report was to assess the activity and toxicity of a new weekly schedule of cisplatin/paclitaxel for the front-line treatment of clinically inoperable NSCLC patients.

Platinum-based chemotherapy is the standard for the front-line therapy of young, well-performing patients with metastatic NSCLC (6, 27). By the end of the nineties, most authors, including ourselves, regarded the doublet cisplatin/vinorelbine (C/V) as a standard chemotherapy regimen (28-32). Between January 1997 and October 2001, we treated 75 patients with a C/V combination (32), at the same dosages and schedule of administration demonstrated effective a few years before, in a large European multi-institutional study (33). Thirty-five patients responded, with 8 complete responses, for an overall response rate of 47%. The overall median survival of our patients was 60 weeks (Figure 3) (32). After the closure of that



Table IV. Factors independently influencing survival : results of a Cox's multifactorial analysis including all the variables described in Table I\*.

Variables	Statistic	Relative risk	95% C.I.	p-value
Treatment duration	33.1236	0.9224	0.8973- 0.9481	0.0000
ECOG performance status	10.5405	1.7832	1.2576-2.5284	0.1211
Stage of disease	9.7279	1.6456	1.2033-2.2505	0.0018
Age	7.2762	0.9600	0.9319-0.9889	0.0070
Other chemotherapies	6.5226	0.5138	0.3082-0.8586	0.0107
Carcinoembryonic antigen	3.6080	0.9997	0.9993-1.0000	0.0575

\*74 cases included; global Chi-square = 65.309;  $p=0.0000$

study in December 2001, we decided to start a new weekly combination of cisplatin/paclitaxel, with the intent to compare it with our previous C/V chemotherapy.

Weekly paclitaxel was initially used to exploit the radio-sensitizing properties of the drug. However, the improvement in therapeutic index with this regimen encouraged further use of weekly regimens, with and without radiotherapy, either as a single agent or in combination with other drugs. Weekly paclitaxel has been combined with carboplatin and vinorelbine in two-drug combinations and with cisplatin plus gemcitabine and cisplatin plus vinorelbine in three-drug regimens (34). Between 2003 and 2004, the activity/toxicity of weekly paclitaxel combined with cisplatin were reported in 3 consecutive studies (35-37). A regimen of weekly low-dose paclitaxel/cisplatin was reported by Kim *et al.* (35). Paclitaxel ( $40 \text{ mg/m}^2$ ) and cisplatin ( $20 \text{ mg/m}^2$ ) were administered weekly, without interruption, in 22 chemotherapy-naïve patients with NSCLC. With a median of 16 weekly cycles of chemotherapy, the objective response rate was 40.9% (95% CI, 18.6-63.2%). Stable diseases and progressive diseases accounted for 40.9 and 18.2%, respectively. The median duration of response was 3 months (1-12 months). Myelosuppression was not noted, and non-hematological toxicities were mild. This study used a schedule similar to our schedule, but the dose of paclitaxel was half of ours (35).

More recently, Yoshimura and co-workers conducted a phase I/II trial to determine the maximum-tolerated dose (MTD) and the recommended dose (RD) of paclitaxel administered weekly with a fixed dose of cisplatin, and to assess the toxicity and activity of this combination (37). In this study, patients with stage IIIB/IV NSCLC were eligible. Paclitaxel, at a starting dose of  $40 \text{ mg/m}^2/\text{week}$  on days 1, 8, and 15, was combined with a fixed dose of cisplatin  $80 \text{ mg/m}^2$  on day 1. Chemotherapy was given in a 4-week cycle. Thirty-eight patients were enrolled. Dose-limiting toxicities (DLT) were leukopenia, thrombocytopenia,

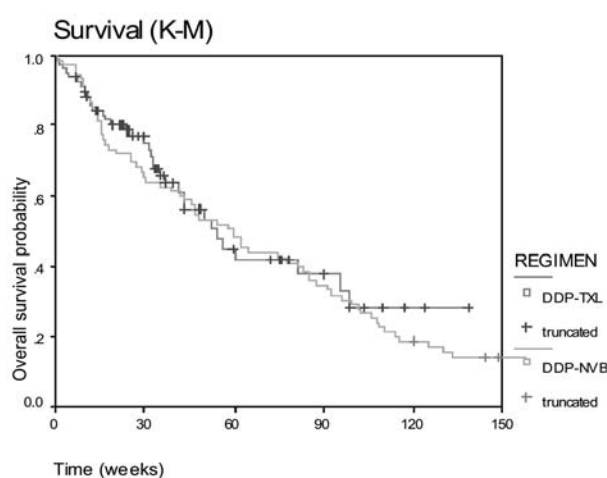


Figure 3. Kaplan and Meier estimate of survival for patients on cisplatin/paclitaxel (DDD-TXL) – as compared to cisplatin/vinorelbine (DDP-NVB) – treated patients. (Log rank  $p=0.6129$ ; Breslow  $p=0.6443$ ; Tarone-Ware  $p=0.6481$ ).

fatigue and febrile neutropenia. The MTD for paclitaxel was estimated to be  $70 \text{ mg/m}^2$ . Of the 37 assessable patients, 23 had a partial response and 1 had a complete response. Overall, the response rate was 62.1% (95% CI: 46.5-77.7%). The progression-free survival, the median survival time and the 1-year survival rate were 5.5 months, 13.7 months and 56.9%, respectively. This study was less comparable with ours, especially because of the timing and fractionation of cisplatin. However, it was similarly tolerated and even more active. The authors suggested that its efficacy should be confirmed in a phase III study (37).

Shortly thereafter, a phase III study comparing weekly paclitaxel plus cisplatin vs. vinorelbine plus cisplatin in 140 chemo-naïve NSCLC patients was reported (36). The treatment dose was paclitaxel  $66 \text{ mg/m}^2$  on days 1, 8 and 15 and cisplatin  $60 \text{ mg/m}^2$  on day 15, or vinorelbine  $23 \text{ mg/m}^2$

on days 1, 8 and 15 and cisplatin 60 mg/m<sup>2</sup> on day 15, every 4 weeks (36). There were 26 partial responses and 1 complete response (overall 38.6%) in the paclitaxel arm, and 27 partial responses (overall 38.6%) in the vinorelbine arm. Myelosuppression was more common in the vinorelbine arm ( $p < 0.001$ ). Peripheral neuropathy and myalgia were more common in the paclitaxel arm ( $p < 0.001$ ). The median time to disease progression was 6 months in the paclitaxel arm and 8.4 months in the vinorelbine arm ( $p < 0.05$ ). The median survival time was 11.7 months in the paclitaxel arm and 15.4 months in the vinorelbine arm ( $p = \text{NS}$ ). Also in this trial, the cumulative doses of paclitaxel and cisplatin were significantly less than ours, and the weekly scheduling of the combination was partial.

Our study used a complete weekly fractionation of the total amount of paclitaxel/cisplatin delivered, which, on average, was the highest so far. With this schedule, we have shown that the combination of cisplatin/paclitaxel is an effective therapeutic option, which is associated with low toxicity. Sixty-two of the 79 registered patients could be reassessed at the first planned restaging time and were assessable for response. In this group, the weekly regimen was highly effective (overall response rate: 55%) and well comparable to the best results reported so far (62%) (37). As in the previously discussed reports, toxicity was mild and manageable, with no major toxicity event. Importantly, the survival duration of the whole group of 79 patients was the most favorable reported so far.

Comparing retrospectively the results obtained with the C/V (32) and C/P chemotherapy protocols adopted in our institution in the last 8 years, several considerations can be made: a) both treatments may represent a valid therapeutic option for non-resectable NSCLC; b) they may be used in young, good performance status patients who have no significant co-morbidity; c) the duration of chemotherapy, in both studies, was the most powerful predictor of survival, independent of any other important and classic prognostic factors (including performance status and the extent of disease); and d) there was no statistically significant difference between the two arms, regarding both the objective response rate (47% vs. 43%) and the survival time (60 vs. 55 weeks) (Figure 3). The only substantial difference between the two types of combinations regards toxicity: the cisplatin/paclitaxel schedule, in fact, was associated with a lower toxicity as compared to the cisplatin/vinorelbine schedule. Neuropathy (11% vs. 31%), leukopenia (17 vs. 29%) and anemia (16% vs. 28%) occurred more frequently in the C/V regimen. Grade 3 or 4 toxicities (except alopecia) were also more frequent in the C/V arm (21% vs. 6%).

Based on the most recent evidence (30) and our present data, it seems that we have reached a plateau in chemotherapeutic effectiveness.

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