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Carboplatin and Weekly Paclitaxel in Non-small Cell Lung Cancer Patients Unfit for or Pretreated with Chemotherapy

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Abstract. *Background: Carboplatin-Paclitaxel is one of the most active regimens in non-small cell lung cancer (NSCLC). We assessed the administration of weekly Paclitaxel as second-line chemotherapy, or as first-line chemotherapy in unfit patients. Patients and Methods: Forty-eight patients received Carboplatin at the dose of 6 x area under the concentration-time curve (AUC) on day 1 and Paclitaxel 100 mg/m^2 on days 1, 8, 15 every 28. Thirty-two had received a prior platinum-based treatment, while 16 were chemotherapy-naive, unfit patients. Results: Grade 3-4 neutropenia occurred in 16 patients (33%); grade 3-4 thrombocytopenia in 7 (15%); grade 1-3 peripheral sensory neuropathy in 35 (73%). Nineteen patients (39.6%; 95% C.I.: 25.8% – 53.4%) achieved an objective response without any difference between the first-line and second-line group. One-year survival was 39.5% (95% CI: 25.4% – 53.6%). Conclusion: The impressive activity of this regimen makes it suitable for further investigation in the second-line setting. Toxicity seen in the unfit population mandates some modification of the regimen.*

The treatment of choice for patients with non-small cell lung cancer (NSCLC) relapsed after platinum-based chemotherapy is single-agent Docetaxel or Alimta. This treatment is able to improve survival and quality of life compared to best supportive care, despite a response rate below 10% (1, 2). Patients unsuitable for platinum-based doublets are also candidates for single-agent chemotherapy: Vinorelbine (3), Gemcitabine (4), Paclitaxel (5) and Docetaxel (6) all present improved clinical outcome in comparison with best supportive care. Response rates are in the range of 10 to 20%. In phase II studies, weekly Paclitaxel was shown to be one of the most active first-line treatments, with response rates ranging from 30% to 39% and a favorable therapeutic index (7, 8). Even when applied to a population of unfit patients at the dose of 80 mg/m^2/week, the response rate was 38% and the toxicity unremarkable (9). While in the first-line setting platinum-based doublets are definitely better than single-agent chemotherapy, the same is not proved in the second-line setting, at least when survival is considered the main end-point (10). However, combination chemotherapy may result in higher response rates, more tumor shrinkage and better symptom palliation, as shown in other diseases (11). A phase I study has shown that Paclitaxel at the dose of 100-125 mg/m^2/week could be safely combined with Carboplatin administered every 21 or 28 days (12). These results were confirmed in a large randomized phase II trial (13), in which the same schedule tested in our study had the best therapeutic index among three schedules. We applied this regimen to patients pre-treated with platinum-based chemotherapy or considered unfit for standard platinum-based regimens. Our aim was to prove that this combination is both feasible and active in patients usually selected only for single-agent treatments.

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Patients and Methods

Patients with histologically or cytologically proven advanced NSCLC, with a WHO Performance Status (P.S.) of 0 to 2, aged over 18, and with disease progression after at least three courses of a platinum-based treatment, were eligible for the study. Patients not pre-treated with chemotherapy but considered unable to receive a full dose, Cisplatin-based regimen were also included. Patients were considered unfit because of age ≥70, P.S. 2 or one of the following concomitant conditions: symptomatic heart failure, peripheral arteriopathy, peripheral neuropathy (due to diabetes, alcohol toxicity, amiloidosis, neurotoxic drugs or paraneoplastic), calculated creatinine clearance <60 ml/h. Exclusion criteria included: leukocytes <3,000/μL, platelets <100,000/μL, calculated

Table I. *Patients' characteristics.*

	N.	%
Median age (range)	67 (43-78)	
Sex (M/F)	37/11	
Median P.S. (range)	1 (0-2)	
Histology:		
Squamous	17	35%
Adenocarcinoma	16	33%
Large cell	1	2%
NSCLC	14	29%
Weight loss >5%	3	1%
Stage: III	15	31%
IV	33	69%
II-line CT	32	67%
Time from previous CT (months): median (range)	13.7 (0.5-53)	
PD after treatment for metastatic disease	24	75%
PD after CT/RT for stage III disease	8	25%
First-line regimen:		
Cisplatin – Gemcitabine	19	59%
Cisplatin – Vinorelbine	7	22%
Carboplatin – Gemcitabine	3	9%
Other Cisplatin-based regimens	3	9%
Response to previous CT:		
PR/CR	15	47%
SD	3	9%
PD	11	34%
NV	3	9%
I-line CT, unfit pts	16	33%
Age ≥70	7	44%
Associated conditions	9	56%

creatinine clearance <30 ml/h, serum transaminase >twice the upper normal limits, total bilirubin level above normal limits, active infections, cardiovascular events within the last 6 months, uncontrolled diabetes mellitus and any medical or psychiatric condition that could compromise the patient's ability to receive chemotherapy.

Treatment. Carboplatin was administered on day 1 at the dose of 6 x area under the concentration-time curve (AUC) diluted in normal saline, in 30 minutes. Carboplatin AUC was predicted using the calculated creatinine clearance through the Cockroft-Gault formula (14). Paclitaxel, at the dose of 100 mg/m^2, was given as a 1-hour infusion on days 1 (before Carboplatin), 8 and 15. Treatment was repeated every 28 days until disease progression, toxicity or patient refusal. At the first Paclitaxel administration, a standard prophylactic regimen was administered (Ranitidine 50 mg, Diphenidramine 25 mg, Dexamethasone 20 mg). If no hypersensitivity reaction (HSR) occurred, only Dexamethasone 8 mg was given subsequently (together with Metoclopramide as antiemetic prophylaxis).

Treatment modifications. Chemotherapy was administered on day 1 if neutrophils were >1,500/μL and platelets >100,000/μL. If these values were not reached, treatment was delayed until recovery.

On days 8 and 15, Paclitaxel was not given in case of neutrophils <1,000/μL or platelets <50,000/μL. In case of febrile neutropenia, grade 4 neutropenia lasting for more than 7 days or grade 4 thrombocytopenia, the dose of Paclitaxel was reduced to 80 mg/m^2. In the case of grade 3 peripheral sensory neuropathy, grade 2 motor neuropathy or any other grade 3-4 non-hematological toxicity, treatment was interrupted.

Response and toxicity evaluation. Baseline evaluation before study entry included clinical history and physical examination, complete blood count, biochemical profile, ECG, chest X-rays, chest and abdomen CT scan. Other radiological examinations were performed when clinically indicated. Before each cycle, patients underwent toxicity assessment, complete blood count and biochemical profile. A complete blood count was repeated weekly. At each hospital visit a history of active symptoms was taken and variations of their intensity were recorded by physicians according to a simple classification: worsening, no change, partial recovery, complete recovery. Toxicity was graded according to the National Cancer Institute's Common Toxicity Criteria (version 2.0), and response was assessed according to WHO standards. Tumor response was assessed every two courses and in case of withdrawal. Time to progression was calculated from study entry to the first objective evidence of disease progression or death. Survival was calculated from study entry to the date of death. Time to progression and survival were estimated using the Kaplan-Meier method. Patients were considered assessable for response if they completed 2 courses and were re-evaluated. Patients who were withdrawn from the trial during the first 4 weeks as a result of clinically evident tumor progression were considered non-responders. All patients who received at least one dose of Paclitaxel were included in the toxicity evaluation.

Statistical design. The target accrual was calculated using response rate as the primary end-point. Assuming a response rate of 20% in patients treated with single-agent chemotherapy (p0), we considered a response rate lower than 35% (p1-p0 = 15%) insignificant. Using the optimal two-stage Simon design for phase II trials, with an α error of 5% and a β error of 80%, 19 responses should have been detected among 72 patients in order to exclude the null hypothesis. We performed this analysis when 19 responses had been confirmed.

Results

Forty-eight patients met the eligibility criteria and entered the study. Baseline patients' characteristics are shown in Table I. Thirty-two (67%) were pretreated with platinum-based chemotherapy and 16 (33%) were unfit patients treated with chemotherapy for the first time. Among the pretreated patients, 78% had received the first-line treatment for metastatic disease while 22% had been treated with chemotherapy as part of an integrated treatment of stage III disease (induction chemotherapy before surgery or radiation). Patients enrolled for the first-

Table II. *Toxicity.*

	Grade 1-2		Grade 3-4	
	N	%	N	%
WBC	15	31%	14	29%
Ne	12	25%	16	33%
HGB	34	71%	4	8%
PLT	8	17%	7	15%
Nausea	26	54%	3	6%
Vomiting	20	42%	2	4%
Asthenia	36	75%	9	19%
Arthralgias	24	50%	-	-
Fever	9	19%	-	-
Stomatitis	22	46%	-	-
Diarrhoea	19	40%	3	6%
Alopecia	10	21%	28 (g3)	58%
Neuropathy – sensory	33	69%	2 (g3)	4%
Neuropathy – motor	18	37%	-	-
HSR	1 (g2)	2%	-	-

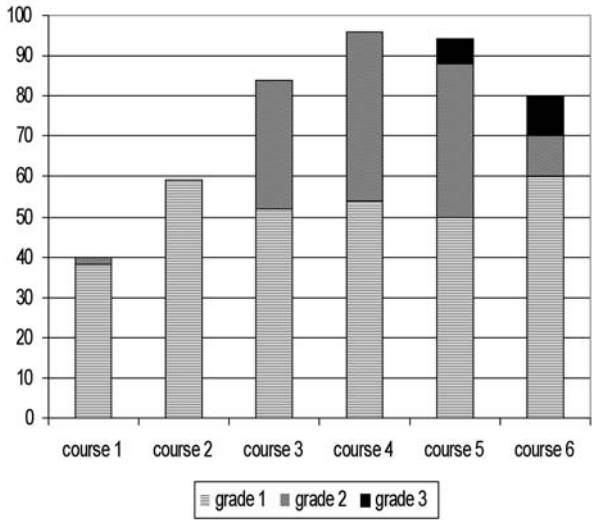

Figure 1. *Sensory neurotoxicity. Incidence and grade of peripheral neuropathy during each chemotherapy course. It should be noted that, in case of grade 3 neuropathy, patients did not undergo the subsequent chemotherapy course.*

line treatment had associated conditions other than elderly age in 9 cases: history of myocardial infarction or heart failure (3); history of pulmonary embolism (1); creatinine clearance <60 ml/h (2); respiratory failure with right cardiac overload (3). Pain was the most frequent symptom (43% of patients: 33% thoracic pain and 10% bone pain due to skeletal metastases); cough was indicated by 37.5% of the patients and dyspnea by 25%.

Compliance to treatment. Overall, 171 courses were administered (median 4, range 1-6). While the median number of administered courses was 4 in the second-line setting, it was only 2.5 in the unfit setting. Reasons for stopping treatment before the sixth course were disease progression in 7 patients (14.5%) and toxicity in 14 (29.1%) (neutropenia in 4 and peripheral neuropathy in 10). Other causes of early withdrawal were: treatment-unrelated death (4), worsening general conditions (7), refusal (1), disease-unrelated complications (2); 2 patients with stage IIIb disease due to supraclavicular nodes were given palliative radiation on residual disease after response to 3 courses. According to the protocol rules, Paclitaxel was not given on day 8 in 14 courses (8.1%) or on day 15 in 35 courses (20.4%). A one-week delay was necessary in 27 courses (15.7%). The most common reason for treatment modification was neutropenia. The dose of Paclitaxel was reduced to 80 mg/m^2 in 3 patients due to grade 4 neutropenia.

Toxicity. Toxicities are shown on Table II. Grade 3-4 neutropenia occurred in 33% of the patients and was complicated by fever in 4 cases (8.3%). One of these patients died from pneumonia during neutropenic fever. Twenty-two patients with anemia were given epoietin and 6 needed packed red cells. Using the simplified prophylactic regimen, clinically definite HSR occurred in only one patient at the second course and consisted of spontaneously reversible symptomatic hypotension, sweating and tachycardia. Asymptomatic hypotension was detected in 25 courses (14.6%). Three cases of deep venous thrombosis occurred during treatment. One female patient, with multi-site deep venous thrombosis at diagnosis, died after the second course from stroke, with disease in partial response. Peripheral neuropathy (Figure 1) was recorded in 35 patients (73%) and was the most common cause of withdrawal from treatment. At the end of the first course, 40% of the patients complained of symptoms of neuropathy, and at the fourth course this adverse event was almost universal. However, grade 3 sensory toxicity was recorded only after the fourth course, and grade 3 motor neuropathy did not occur. The median number of courses to onset of grade 2 neuropathy was 5, and the cumulative proportion of patients with grade 2 neuropathy at the sixth course was 60%.

Activity. Six of the 48 patients were not evaluable for response due to the following reasons: one had disease evaluable only with PET scan; 5 were withdrawn from

treatment after 1 or 2 courses before disease evaluation (1 for refusal, 1 for febrile neutropenia followed by long-lasting grade 2 neutropenia, 3 for P.S. worsening). A confirmed objective response was demonstrated in 19 patients (response rate 39.6%; 95% C.I. 25.8% – 53.4%). Results were similar in the second-line (40.6%; 95% C.I. 23.6% – 57.6%) and in the first-line setting (37.5%; 95% C.I. 13.8% – 61.2%). Fifteen patients (31.2%) had disease stabilization and 7 (14.5%) progressive disease. Among patients pretreated for advanced disease, 11 (42.3%) responded to the second-line regimen (5 were responders to the first-line regimen, 3 had stable-disease and 3 had disease progression). Among 15 patients with stable or progressive disease at the first-line regimen, 6 (40.0%) had a response to the second-line treatment. At least partial improvement of disease-related symptoms was recorded in 25 patients (52.0%) and in 11 of these, symptomatic relief was not associated with an objective response. At a median follow-up of 23 months, median progression-free survival was 6.1 months, median survival 8.0 months and the 1-year survival rate 39.5% (95% C.I. 25.4% – 53.6%). Data were not different in the two groups.

Discussion

Carboplatin and weekly Paclitaxel have been shown to be a safe and active combination in untreated patients with NSCLC (13). Our trial suggests that this combination is also feasible and active in pretreated or unfit patients: 39.6% achieved an objective response and 52.0% had symptomatic relief. While the response rate observed is predictable in the first-line setting when a two-drug, platinum-based regimen is given, this is not true for second-line chemotherapy: when active single agents are used, only 1 out of 10 patients achieves an objective response (1, 2) and re-treatment with platinum is not considered an option. Two factors may account for the results observed: i) using the weekly schedule of Paclitaxel administration, a higher dose is given (7, 15) and other mechanisms of action (anti-angiogenesis and promotion of apoptosis) seem to be exploited (16); ii) the use of a two-drug regimen including Carboplatin. Other phase II trials, investigating multi-drug regimens in the second-line setting, showed high response rates (17, 18). This observation is well known in oncology and can be justified on the basis of the Goldie and Coldman model of clonal selection: the concomitant use of drugs with different mechanisms of action rather than single agents may be able to overcome resistance. Our findings also suggest that, when one of the two drugs is a platinum compound, the results are better than those obtained with a single-agent. Whether this is due to pharmacodynamic interactions between drugs or merely to a higher level of activity of platinum agents is difficult to establish. Re-challenge with Carboplatin resulted in objective responses, not only in responders to previous lines but also in patients progressing during previous treatment. Single-agent Paclitaxel, given as second-line chemotherapy, has produced conflicting results, with some studies suggesting no activity (19, 20) and others showing high response rates. In the study reported by Juan *et al.*, in which Paclitaxel was administered weekly at the dose of 80 mg/m^2 to 40 patients with disease progression after Cisplatin-based treatment, a response rate of 37.5% was obtained with no grade 3-4 hematological toxicity and little neurological toxicity (15). Koumakis *et al.* reported a response rate of 29% in 24 pretreated patients (21). However, when a similar schedule was applied to 45 patients with disease progression after Carboplatin-Paclitaxel, a response rate of only 7% was obtained (22).

In our trial, treatment was feasible and approximately 50% of the patients were able to receive 4 courses. The lower number of courses received by unfit patients (median 2.5) compared with the overall population is an indirect measure of higher toxicity in this setting. In 20% of the courses, Paclitaxel could not be administered on day 15, generally because of neutropenia: this is a common finding with regimens including three weekly administrations and could probably be overcome with a 1,8,21 regimen. Peripheral sensory neuropathy occurred in 73% of patients, a figure comparable to the 50% – 76% range reported in trials using high-dose, weekly Paclitaxel (7, 15, 23). Grade 3-4 neutropenia occurred in 33% of the patients and was complicated by fever in only 8%. Omission of Paclitaxel administration on days 8 or 15 in case of a neutrophil count below 1,000/μL prevented, in our opinion, serious infective complications and should be considered mandatory in further trials exploring this regimen. The use of a complete, standard-dose pre-medication scheme at every Paclitaxel administration resulted in an unacceptable rate of hyperglycemia in the Cancer and Leukemia Group B trial (7). The use of a lower Dexamethasone dose accounted for the complete avoidance of hyperglycemia and an incidence of HSR reactions not higher than expected (24).

Conclusion

The regimen employed in this trial showed activity both in second-line and in first-line, unfit patients. The results of the study justify further assessment of this schedule, at least in the second-line setting where a randomized trial comparing this strategy to single-agent chemotherapy should be considered. In unfit patients, however, toxicity may be a concern: either a reduced Paclitaxel dose (80 mg/m^2) or a 1,8,21 regimen may improve tolerability and compliance.

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