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ORIGINAL ARTICLE

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Second-line chemotherapy with weekly paclitaxel and gemcitabine in patients with small-cell lung cancer pretreated with platinum and etoposide: a single institution phase II trial

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Abstract *Purpose*: The safety and efficacy of a combined regimen of weekly paclitaxel and gemcitabine was tested in patients with refractory and sensitive small-cell lung cancer (SCLC). *Methods*: Treatment consisted of paclitaxel 80 mg/m^2 on days 1, 8, 15 and gemcitabine 1,000 mg/m^2 on days 1 and 8 every 3 weeks. Of the 31 patients enrolled, 10 had refractory and 21 had sensitive disease. Objective responses occurred in 8 patients (26%), including 2 out of 10 patients with refractory- and 6 out of 21 patients with sensitive SCLC. Median time to progression and median survival were 9.4 and 32 weeks, respectively. *Results*: The schedule was very well tolerated, with grade 3–4 thrombocytopenia in 26% of the patients, grade 3 neutropenia in 26%, grade 3–4 asthenia in 13% and grade 1–2 sensory neuropathy in 32%. *Conclusion*: To conclude, this weekly schedule of paclitaxel and gemcitabine was found to have moderate activity in platinum-etoposide pretreated SCLC patients and a favorable toxicity profile.

Keywords Small-cell lung cancer · Second-line chemotherapy · Gemcitabine · Weekly paclitaxel

Introduction

Smallcell lung cancer (SCLC) is an aggressive tumor that is highly sensitive to chemotherapy. A wide range of chemotherapeutic agents have proven to be effective in treating SCLC, including carboplatin, cisplatin, cyclophosphamide, etoposide, doxorubicin, epirubicin, ifosfamide, vincristine and vindesine [1]. Polychemotherapy (multi-agent therapy either doublets or triplets) in SCLC appears superior to single-agent treatment in first-line therapy [2]. Cisplatin (or carboplatin) plus etoposide is the widely preferred combination regimen in the first-line setting, leading to response rates between 61% and 80% [3, 4]. Compared with the combination of cisplatin and etoposide, no other combination has so clearly shown improved results in large phase III randomized trials [5].

Only a minority of SCLC patients are curable with chemotherapy. Despite a dramatic initial response, most patients are destined to relapse within a few months. The median survival is 10–16 months in patients with limited disease at diagnosis and 6–12 months in those with extensive disease; the corresponding 5-year survival rate is 18 and 1–2%, respectively [6, 7]. Results of second-line chemotherapy are usually poor. Moreover, there is no generally accepted approach for second-line treatment of SCLC. In patients with relapsed disease or failure to first-line platinum–etoposide, the widely used cyclophosphamide-doxorubicin-vincristine regimens have a response rate of around 10% [8, 9]. Responses are usually brief, with median survival rarely exceeding 6 months [10].

It has been recently demonstrated that the activity of second-line treatments depends on tumor responsiveness to first-line treatment and on the treatment-free interval between the last course of first-line chemotherapy and the appearance of progressive disease [9]. Patients who did not respond to first-line chemotherapy or who have responded but progressed within 3 months from the end of induction treatment are generally refractory to further chemotherapy treatments and may only respond to true non-cross-resistant combination chemotherapy. In contrast, patients who have responded to first-line chemotherapy and relapsed after a treatment-free interval ≥3 months have a reasonable chance of responding to

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second-line chemotherapy or even to first-line chemotherapy re-challenge [11].

Among the active new agents in the second-line approach to treat SCLC patients, taxanes have emerged as promising ones. In a phase II study, paclitaxel demonstrated a 38% response rate in patients with sensitive disease and 29% in those with refractory disease [12]. An important clinical issue regarding paclitaxel is the optimal schedule. Preclinical evaluation showed that frequent administration of paclitaxel provided better therapeutic effects than delayed schedules [13, 14]. This dose-dense approach may inhibit tumor re-growth between cycles and enhance the apoptotic and antiangiogenetic effects of the drug [15, 16]. In patients with breast cancer, weekly paclitaxel was reported to be more effective than every 21 days administration regimen, although the neurotoxicity was doubled [17]. Preliminary experiences with weekly paclitaxel administered to NSCLC patients confirmed that this schedule is well tolerated, permits maintenance of the planned dose intensity, and is potentially effective [18].

In SCLC patients single agent weekly paclitaxel (dose-dense) has been evaluated in chemonaïve disease and weekly paclitaxel was tested in combination with topotecan as second-line treatment. Both trials showed interesting results, response rate in 28 and 30% of the patients respectively [19, 20].

Gemcitabine, a novel third-generation chemotherapy agent, has been demonstrated to be active against SCLC in xenograft models [21]. Conflicting results have been reported in clinical trials, however. In two studies, the drug produced a response rate of 27% in untreated SCLC patients [22] and a response rate of 13% in resistant patients [23]. More recently, monotherapy gemcitabine failed to obtain responses in patients with sensitive or refractory disease [24].

When administered in combination the systemic clearance and volume of distribution of gemcitabine decreased to about 30% in the presence of paclitaxel [25]. However, this doublet is known to be a well-tolerated regimen [26, 27] and may be more active than either agent administered alone in patients with non-small cell lung cancer. In our study, we tested the combination of weekly paclitaxel plus gemcitabine in SCLC patients homogeneously pretreated with platinum and etoposide.

Patients and methods

To be eligible for the study, patients had to fulfill the following inclusion criteria: histologically or cytologically proven diagnosis of SCLC; limited or extensive disease with relapsed or progressing lesions after or during first-line treatment with cisplatin/carboplatin and etoposide chemotherapy and thoracic/brain radiation therapy; presence of at least one bidimensionally measurable tumor site (target lesions) outside a previously irradiated field, unless there was definite evidence of disease progression at this site; age greater than 18 and less than 75 years; an ECOG Performance Status (PS) from 0 to 2; adequate bone marrow reserves, defined as absolute neutrophil count (ANC) $\geq 2000/mm^3$, platelet count (PLTS) $\geq 100{,}000/mm^3$ and hemoglobin level ≥ 10.0 mg/dl); adequate renal and hepatic function (serum creatinine ≤ 1.5 mg/dl, serum bilirubin, AST and ALT ≤ 1.5 times the upper normal limit (UNL), alkaline phosphatase ≤ 2 times [UNL], except in case of bone metastases).

Exclusion criteria were: previous treatment with paclitaxel and/or gemcitabine; previous exposure to more than one chemotherapy line; presence of prior malignancies (except for basal cell carcinoma of the skin or carcinoma in situ of the cervix); a pre-existing sensory neuropathy greater than World Health Organization (WHO) grade 1, a history of recent (6 months) myocardial infarction, congestive heart failure or atrial or ventricular arrhythmia requiring medical treatment; an active infection. Prior radiotherapy was allowed as long as the therapy was completed at least 3 weeks before enrollment in the study. Brain or leptomeningeal involvement was not considered a criterion for an exclusion if the patient presented with another metastatic target lesion. The study was approved by our Institutional Review Board. Written informed consent was obtained from all patients.

Assessment of response and toxicity

Baseline evaluation included medical history, physical examination, ECOG-PS assessment, electrocardiogram, chest X-ray, thoracic and abdominal computed tomography (CT) scan. CT scan of the brain and radionuclide bone scanning were performed only if appropriate to define the extent of metastatic disease. Restaging and tumor measurement were performed no more than 4 weeks before registration. Laboratory studies at presentation included complete blood cell count, serum chemistries and liver function tests. Clinical monitoring and full blood count were planned to be performed every week; serum electrolytes, renal, and liver function tests were performed every 3 weeks. Tumor response was classified according to WHO criteria [28] and documented by two investigations at least 4 weeks apart. A complete response (CR) was defined as the complete disappearance of all clinically detectable malignant lesions for at least 4 weeks. A partial response (PR) required a 50% or greater reduction in the sum of the cross-sectional areas of all target lesions and no concomitant growth of new lesions for at least 4 weeks. Stable disease (SD) was defined as a less than 50% decrease or an increase of less than 25% in the product of the longest perpendicular diameters of target lesions lasting 2 months. Progressive disease (PD) was defined as the appearance of new lesions or an increase of more than 25% in the sum of the cross-sectional areas of all target lesions as compared with the lowest value re-

corded. Antitumor activity was evaluated every 6 weeks (two cycles). Response evaluation could be anticipated with respect to planned time points for clinically evident or suspected disease progression. Patients who received at least two chemotherapy cycles were eligible for tumor response assessment. Toxicity was evaluated according to the WHO criteria [24].

Time to progression (TTP) was measured from the beginning of second-line chemotherapy until the date of objective evidence of progressive disease or death, progression-free survival (PFS) was defined as the time elapsing from first response assessment and disease progression, time to treatment failure (TTF) was the time elapsing from the treatment start to disease pregression or treatment discontinuation whatever events occurred. Overall survival (OS) was calculated from the first day of treatment to the date of death or was censored on the date of the last follow-up appointment. Deaths and treatment discontinuations (due to toxicity or patient refusal) were considered to be treatment failures.

Treatment plan

Patients received paclitaxel at a dose of 80 mg/m^2 in 250 ml NaCl 0.9% via 1-hour intravenous infusion on days 1, 8, 15 and gemcitabine at 1,000 mg/m^2 diluted in 250 ml NaCl 0.9% intravenously over 30 min on days 1 and 8 of each 21-day cycle for up to six cycles. Thirty minutes before paclitaxel infusion, patients received 12 mg dexamethasone, 40 mg orphenadrine, and 50 mg ranitidine. Due to previous steroid treatment, no other prophylactic antiemetics were routinely provided.

Doses were modified as follows: on day 1 of each new cycle the drugs were administered at the full dose if the ANC was $\geq$1,500/mm^3 and the PLTS $\geq$100,000/mm^3; otherwise, the cycle was delayed until recovery or for a maximum of 3 weeks. Patients went off study if the delay exceeded 4 weeks.

On days 8 and 15, administration of paclitaxel and gemcitabine was omitted if the ANC was $<$1,000/mm^3 and/or if the PLTS was $<$75,000/mm^3; the dose of both drugs was reduced to 75% for an ANC count between 1,000 and 1,500/mm^3 and/or for a PLTS count between 75,000 and 100,000/mm^3. Whenever febrile neutropenia, grade 4 neutropenia lasting more than 5 days or grade 4 thrombocytopenia occurred, the dose of both drugs was reduced to 75% in the subsequent cycles. No dose adjustments were performed in case of grade 1 neurotoxicity. In case of grade 2 neurotoxicity, paclitaxel was administered at 50% of the planned dose. In case of grade 3 neurotoxicity or worse, patients were withdrawn from the study. Prophylactic use of G-CSF to maintain dose intensity was not permitted. Relative dose intensity was defined as the actual weekly dose of each drug at the end of the treatment divided by the planned weekly dose. Subsequent chemotherapy in case of progression during or after second-line treatment was left to the discretion of the physician in charge of the patient.

Statistical analysis

The primary study end point was the assessment of the response rate (intent to treat analysis). According to the optimal two-stage phase II study design of Simon [29], the sample size was assessed in order to refuse response rates $\leq$ 5% (p0) and to provide a statistical power of 80% in assessing the activity of the regimen as a 20% response rate. The upper limit for first-stage drug rejection was no responses out of the first 10 consecutive patients, the upper limit of second-stage rejection was three responses out of 29 consecutively enrolled patients. Response duration and survival were assessed using Kaplan–Meier survival curves. A two-sided significance of the 5% level was applied to all tests. All statistical analyses were performed using the Statistica for Windows software program.

Results

From July 1999 to February 2003, 31 patients were enrolled at our institution. The baseline characteristics are presented in Table 1. All patients had received a first-line regimen containing cisplatin or carboplatin and etoposide. At relapse, extensive disease was present in 84% of the patients. Brain and liver metastases were present in 16 and 48% of the patients, respectively. Eight patients (26%) had PS 2. Response rate to first-line chemotherapy was 81% (CR 16% and PR 65%). Median time from the last first-line chemotherapy cycle to the initiation of salvage treatment was 19.4 weeks (range, 3.3–61.6 weeks). Time to progression after the end of prior regimen was $\leq$ 3 months in 10 patients (median 5.7 weeks) and $>$3 months in 21 (median 28.1 weeks). All patients received at least one cycle of paclitaxel and gemcitabine and were therefore assessable for toxicity; 27 patients (87%) received at least two treatment cycles and were assessable for response.

Response to treatment and survival

All patients entering the study were included in the intention-to-treat analysis (Table 2). Eight patients (26%) achieved a partial response, five (16%) had stable disease and 18 progressed (58%). No complete responses were observed. The response rate was 20% (two out of ten patients) in patients with refractory disease and 29% (6 out of 21 patients) in those with sensitive disease. The median duration of response was 20.6 weeks (range, 12.1–39.1 weeks). Median PFS was 11.6 weeks. Median time to progression was 9.4 weeks. Median TTF was 7.4 weeks. Median survival time in the overall popula-

Table 1 Patient characteristics

Number of patients	31	
Median age: years (range)	64 (48–78)	
Men	24	(77%)
Women	7	(23%)
ECOG performance status		
0	3	(10%)
1	20	(64%)
2	8	(26%)
Stage at relapse		
Limited disease	5	(16%)
Extensive disease	26	(84%)
Prior chemotherapy		
Cisplatin/etoposide	20	(65%)
Carboplatin/etoposide	11	(35%)
Prior radiotherapy	21	(70%)
Thoracic	17	(55%)
Brain	5	(16%)
Palliative	2	(6%)
Response to first-line treatment		
Objective response	25	(81%)
Stable disease	4	(13%)
Progression	2	(6%)
Chemotherapy-free interval		
≤ 3 months	10	(32%)
> 3 months	21	(68%)
Metastatic sites		
Liver	15	(48%)
Lymph nodes	9	(29%)
Bone	8	(26%)
Lung	6	(19%)
Brain	5	(16%)
Adrenal	5	(16%)
Others	3	(9%)

tion was 32 weeks (10.6 weeks in refractory and 35.6 weeks in sensitive patients); the 1-year survival rate was 20% in the overall sample (10% in refractory and 25% in sensitive patients).

Treatment administered and toxicity

A total of 106 chemotherapy courses were given with a median number of three cycles per patient (range, 1–6). The median dose intensity was 58 mg/m^2/week (72% of planned dose) for paclitaxel and 553 mg/m^2/week (83% of planned dose) for gemcitabine. Fourteen cycles (13%) (in a total of 14 patients [45%]) were delayed for a maximum of 2 weeks because of toxicity, non-neutropenic infections, or other reasons unrelated to treatment. Dose reductions were required at days 8 and 15 in ten cycles (9%) (4 patients [13%]). Gemcitabine and paclitaxel were omitted on day 8 in 19 cycles (18%) in 14 patients (45%) and paclitaxel was omitted on day 15 in 43 cycles (40%) in 22 patients (71%) mainly because of hematological toxicity.

The worst toxicities per patient are shown in Table 3. The most frequent toxicity was hematological. Grade 3 thrombocytopenia occurred in seven patients and Grade 4 in one patient (22 and 3%), respectively. Grade 3 neutropenia occurred in eight patients (26%). Neither neutropenia G4 nor febrile neutropenia were recorded. Significant non-hematological toxicity was uncommon

Table 2 Response to second-line treatment

	Sensitive patients (n = 21)		Refractory patients (n = 10)		Total (n = 31)	
	No.	%	No.	%	No.	%
PR	6	29	2	20	8	26
SD	4	19	1	10	5	16
PD	11	52	7	70	18	58
TTP (weeks) median (range)	11.1 (3.3–91.4)		6.9 (1.9–31)		9.4 (1.9–91.4)	
OS (weeks) median (range)	35.6 (18.6–102)		10.6 (5–97.3)		32 (5–102)	

PR partial response; *SD* stable disease; *PD* progressive disease; *TTP* time to progression; *OS* overall survival

Table 3 Toxicity (WHO criteria)

	No. of patients (%)			
	G1	G2	G3	G4
Hemoglobin	9 (29%)	10 (32%)	–	1 (3%)
Neutrophils	13 (42%)	7 (23%)	8 (26%)	–
Platelets	7 (23%)	6 (19%)	7 (23%)	1 (3%)
Nausea/vomiting	6 (19%)	3 (10%)	–	–
Diarrhea	3 (10%)	2 (6%)	–	–
Mucositis	5 (16%)	2 (6%)	1 (3%)	-
Asthenia	4 (13%)	7 (23%)	1 (3%)	3 (10%)
Skin	3 (10%)	–	–	–
Hepatic	1 (3%)	–	–	–
Alopecia	–	1 (3%)	–	1 (3%)
Myalgia	3 (10%)	3 (10%)	–	–
Peripheral neuropathy	5 (16%)	5 (16%)	–	–

The most severe instance of toxicity was taken into account for each patient

with this regimen. Grade 3–4 asthenia was observed in four patients (13%) and grade 1–2 sensory neuropathy in ten (32%).

Discussion

Cisplatin (or carboplatin) plus etoposide is currently the mainstay of the first-line approach to treating SCLC. Second-line treatment should be considered in good performance status patients with relapsed disease or failure to first-line chemotherapy; however, no standard drug or combination exists. While relatively new agents, such as taxanes, vinorelbine, irinotecan, and topotecan have produced promising results in phase II investigations [22, 30, 31, 32, 33, 34, 35], it is difficult to appraise whether these drugs are really non-cross-resistant with respect to the standard cisplatin and etoposide regimen, since all published trials included both sensitive and refractory patients and many also enrolled patients previously submitted to non-platinum schemes.

Our study reports on the activity of a combination of weekly paclitaxel plus gemcitabine administered as a second-line approach in SCLC patients homogeneously pretreated with cisplatin or carboplatin in combination with etoposide. The response rate of 26% suggests that this chemotherapy regimen is moderately active. Interestingly, the treatment activity was only slightly higher in patients with sensitive disease than in those with refractory disease, indicating that the regimen may be more useful in the latter patient subgroup.

Table 4 summarizes the results of second-line approaches in SCLC patients with progressive disease to cisplatin/carboplatin and etoposide. Trials that enrolled patients receiving non-platinum-containing schemes as a first-line approach were excluded. The activity of the proposed drugs or regimens ranged from 0% to 73%, the greatest response rate being obtained when cisplatin or carboplatin was included in the rescue schemes. Despite the wide difference in treatment activity, the overall survival did not differ consistently. These data support the notion that second-line chemotherapy in SCLC has no impact on survival [9]. Since second-line treatments in SCLC patients are only palliative, the search for schedules with good compliance is mandatory.

The association of paclitaxel and gemcitabine at the schedule employed in our study was quite well tolerated. In our patients, the dose-limiting toxicity was neutropenia. The acceptable tolerance may be at least partly attributed to the weekly administration scheme that permitted frequent dose adjustment and treatment delay or omission if necessary. However four patients suffered of severe (grade 3–4) asthenia: all of them had PS 2 at baseline condition and had progressive disease at first evaluation making difficult to state whether this side-effect is attributable to treatment toxicity or tumor progression. The dose intensity of this regimen was relatively low, which may have influenced its overall activity. Paclitaxel and gemcitabine at the same schedule

Table 4 Second-line chemotherapy trials in platinum–etoposide pretreated patients

Author (year of study)	First-line CT agents	RR to first-line CT	No. of patients with refractory/sensitive disease	Second-line CT agents	RR to second-line CT	Overall survival (months)	Toxicity (% of patients)
von Pawel [27] (2000)	DDP(JM8)/VP16	100%	0/107; 0/104	TPT; CAV	TPT 24%; CAV 18%	5.8; 5.7	Neutropenia G4 70%–72% thrombocytopenia G4 29%–5%
Sonpavde [28](2001)	DDP/VP16	85%	14/32	Adm/Pac	41%	5.8	Neutropenia G4 63%
Kosmas [29](2003)	JM8/VP16	76%	20/13	DDP/Pac/Ifo	73%	6.4	Neutropenia G4 73%
Hainsworth [30] (2003)	DDP(JM8)/VP16	NR	17/12	VNR/Gem	10%	5	
Hirose[31] (2004)	DDP(JM8)/VP16	88%	9/15	JM8/CPT11	68%	6.4	Neutropenia G3–4 63% thrombocytopenia G3–4 58% diarrhea G3 21%1 toxic death
Hoang [22] (2003)	DDP(JM8)/VP16	NR	12/15	Gem	0%	6.4	1 treatment-related death
Joos [32] (2003)	JM8/VP16	NR	44/0	Pac	20%	4	Neuropathy G3 8% Febrile neutropenia 23%
Present study	DDP(JM8)/VP16	81%	10/21	Weekly Pac/Gem	26%	7.4	Neutropenia G4 0%

Adm adryamicin; *CAV* cyclophosphamide, adryamicin, vincristine; *CPT-11* irinotecan; *CT* chemotherapy; *DDP* cisplatin; *Gem* gemcitabine; Ifo, ifosfamide; *JM8* carboplatin; *NR* not reported; *Pac* paclitaxel; *RR* response rate; *TPT* topotecan; *VNR* vinorelbine; *VP16* etoposide

was employed by our group as a second-line approach in patients with NSCLC, but the dose intensity was consistently higher [24]. More than half of our patients received thoracic radiotherapy, which might have reduced tolerability of the chemotherapeutic regimen.

In conclusion, a weekly schedule of paclitaxel and gemcitabine was found to be moderately active as a second-line approach in treating SCLC and was found to have an acceptable toxicity profile. The apparent non-cross-resistance with a combination of cisplatin or carboplatin and etoposide needs further investigation in refractory patients. The addition of gemcitabine to paclitaxel seems to be not associated to improved activity compared to the published phase II trials with paclitaxel alone [12, 22, 32]. Hence, it is questionable whether the addition of gemcitabine could lead to further activity to that obtainable with paclitaxel alone. This issue, however, needs randomized comparisons. The weekly schedule of paclitaxel instead of the 3 weeks administration could have contributed to the good tolerability of the regimen.

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