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CLINICAL TRIAL REPORT

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Phase I study of vinorelbine and paclitaxel in small-cell lung cancer

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Abstract *Background*: Vinorelbine and paclitaxel interfere with mitotic spindle function through different mechanisms of action. Both of the drugs show antitumor activity in small-cell lung cancer when used as single agents; furthermore, in vitro and in vivo studies have shown a synergistic activity between the two drugs. *Patients and methods*: Patients with small-cell lung cancer no longer amenable to conventional treatment were entered into a phase I study in which vinorelbine was given at a fixed dose of 30 mg/m^2 by 15-min intravenous infusion, whereas paclitaxel was given by 3-h infusion starting 1 h after vinorelbine at an initial dose of 90 mg/m^2, which was subsequently escalated by 30-mg/m^2 steps. Cycles were repeated every 21 days. *Results*: Grade 3 neutropenia was observed only in three patients treated at the fifty dose level. Thrombocytopenia never reached grade 3. Neurotoxicity was considered dose-limiting, since grade 3 peripheral neuropathy occurred in three of five patients treated at the fifth dose level (paclitaxel 210 mg/m^2). Other side effects were generally mild. The overall response rate in 22 evaluable patients was 32% (95% CI 13–51%); in particular, 1 complete response (4.5%) and 6 partial responses (27.3%) were observed. The maximally tolerated doses recommended for phase II studies are 180 mg/m^2 for paclitaxel and 30 mg/m^2 for vinorelbine. The observed myelosuppression was less severe than anticipated on the basis of the effects of each drug alone. *Conclusions*: The promising activity of this drug combination warrants a phase II study in untreated patients with extensive-stage small-cell lung cancer.

Key words Paclitaxel · Small-cell lung cancer · Vinorelbine

Abbreviations *CI* Confidence intervals · *SCLC* small-cell lung cancer · *VRL* vinorelbine · *ECOG* Eastern Cooperative Oncology Group · *ECG* electrocardiogram · *CR* complete response · *PR* partial response · *SD* stable disease · *PD* progressive disease · *NIH* National Institutes of Health · *NCI* National Cancer Institute · *DLT* dose-limiting toxicity · *MTD* maximally tolerated dose · *CAV* cyclophosphamide, doxorubicin, vincristine · *CAE* cyclophosphamide, doxorubicin, etoposide · *G-CSF* granulocyte-colony-stimulating factor

Introduction

In spite of the availability of a number of active agents for the treatment of small-cell lung cancer (SCLC) [6], the majority of patients, although initially responding to chemotherapy, almost invariably die of the disease. The identification of new drugs with significant antitumor activity in this disease is therefore clearly needed.

Vinorelbine (VRL, Navelbine; Pierre Fabre Medicament, Boulogne, France) is a semisynthetic vinca

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alkaloid that differs from the others by a substitution that affects the catharantine moiety and not the vindoline moiety of the molecule [15]; furthermore, VRL is substantially less neurotoxic than other vinca alkaloids, probably due to its selective affinity for mitotic tubulin and tubulin-associated proteins [15], with relative sparing of axonal microtubules [7]. Paclitaxel (Taxol; Bristol-Meyer, Squibb, Princeton, N.J.) is a novel diterpene plant product isolated from the western yew *Taxus brevifolia*, which exerts its cytotoxic effect by interfering with the microtubule structure and function [9]; it has generated considerable enthusiasm because of its significant activity in patients with ovarian and breast cancer. When used as single agents, both vinorelbine [11] and paclitaxel [5, 13] show antitumor activity in SCLC.

The concept of combining vinorelbine and paclitaxel is intriguing because both agents target microtubules and interfere with mitotic spindle function. However, the two drugs bind to distinct sites on tubulin and have different mechanisms of action. Indeed, whereas vinorelbine inhibits the polymerization of tubulin, thus preventing the formation of microtubules [7], paclitaxel acts to stabilize polymerized tubulin into nonfunctional microtubule bundles [16]. The activity of both agents produces inhibition of cell mitosis. However, potential problems with this drug combination could arise due to their overlapping myelotoxicity and potential neurotoxicity.

Both in vitro and in vivo studies provide a rationale for the clinical evaluation of concurrent combination chemotherapy with vinorelbine and paclitaxel. Indeed, at clinically achievable concentrations (50% inhibitory concentration 1–10 nmol/l), synergistic activity was observed against two human breast cancer cell lines, MCF-7 and MDA-MB-231, when the two drugs were given concurrently [1]. However, the combination was antagonistic when cells were exposed to paclitaxel for 24 h prior to the addition of vinorelbine. On the other hand, synergistic activity with intraperitoneal administration of the two drugs was observed in vivo against intraperitoneally implanted P388 leukemia cells in mice when vinorelbine was given 30–60 min before paclitaxel. As single agents, neither vinorelbine nor paclitaxel generated meaningful numbers of 60-day cures, whereas optimal combination regimens induced 60-day cures in over 80% of the mice [14]. On the basis of the above-mentioned preclinical observations, we started a phase I pilot study of vinorelbine and paclitaxel in patients with SCLC.

Patients and methods

Patients' selection

Eligibility criteria for study entry included histologically or cytologically confirmed SCLC considered no longer amenable to conventional treatment; an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; adequate baseline organ function, defined as a WBC of $>3{,}000/\mu l$, a platelet count of $>100{,}000/\mu l$, a bilirubin level of <1.5 mg/dl, serum transaminase levels of <2 times the upper limit of normal, and a creatinine value of <1.4 mg/dl; as well as a life expectancy of at least 12 weeks. A minimum of 4 weeks was required since prior chemo- or radiotherapy; written informed consent was required from each patient.

Table 1 Paclitaxel dose escalation

Level	Dose/course (mg/m^2)	Number of patients
1	90	3
2	120	3
3	150	5
4	180	6
5	210	5

Treatment plan

Patients were given vinorelbine by 15-min intravenous infusion in 125 ml of normal saline solution and paclitaxel by 3-h infusion starting 1 h after vinorelbine administration. All patients were premedicated with 4 mg dexamethasone and 50 mg prometazine given intramuscularly 18 and 6 h before paclitaxel, respectively; 50 mg ranitidine was given intravenously 30 min before treatment. The vinorelbine dose was fixed at 30 mg/m^2 for all patients; paclitaxel was started at a dose of 90 mg/m^2, which was then escalated according to the scheme shown in Table 1. Doses were assigned at registration, and no dose escalation was permitted in individual patients. Cohorts of three to six patients were treated at each dose level. Prophylactic use of antiemetics was not routine. Courses were repeated every 21 days. Treatment was withheld for 1 week (until day 28) if the WBC was $<2{,}500/\mu l$ or the platelet count was $<75{,}000/\mu l$ on day 21.

Patients' evaluation

A complete history, physical examination, determination of performance status, complete blood cell count with differentials, serum biochemistry, urinanalysis, and electrocardiogram (ECG) were obtained at baseline for each patient. Patients were monitored weekly throughout treatment by physical examination, recording of toxic effects, complete blood cell count with differential; serum chemistry and ECG were repeated at the beginning of each cycle. Evaluation of the tumor response was performed every two cycles with repetition of all tests that had been abnormal at baseline. A complete response (CR) was defined as the complete disappearance of all symptoms and signs of disease. A partial response (PR) was defined as a reduction of $>50\%$ in the sum of the products of the perpendicular diameters of all measurable lesions; both CRs and PRs were required to persist for at least 4 weeks. Stable disease (SD) was defined as a reduction of $<50\%$ and an increase of $<25\%$ in the sum of the products of two perpendicular diameters of all measured lesions. Progressive disease (PD) was defined as an increase in the product of two perpendicular diameters of any measured lesion by more than 25% or the appearance of new lesions. Patients with stable or responsive disease after two courses of chemotherapy received at least two additional cycles up to a maximum of six courses; patients with progressive disease were withdrawn from the study.

Toxicity

Toxicity was assessed according to the NIH-NCI common toxicity criteria. Dose-limiting toxicity (DLT) was defined as grade 4 neutropenia or thrombocytopenia that lasted more than 7 days or any grade 3 or 4 nonhematologic toxicity other than nausea, vomiting, and anorexia. The maximally tolerated dose (MTD) was defined as

the dose level immediately below that causing DLT in a third or more of the patients in any cohort.

Results

Patients' characteristics

From June 1994 to October 1995, 22 patients with SCLC were enrolled in the study. Their median age was 58 (range 43–69) years; the ECOG performance status was 0 in 9 patients, 1 in 11 patients, and 2 in 2 patients. All of the patients had received first-line chemotherapy with cyclophosphamide, doxorubicin, and vincristine (CAV) or cyclophosphamide, doxorubicin, and etoposide (CAE); 11 patients had previously undergone thoracic radiation therapy. The patients' characteristics are detailed in Table 2. A total of 82 courses of treatment were given for a median of 2 (range 2–6) courses/patient.

Hematologic toxicity

Neutropenia was not observed in the patients treated at the first two dose levels; it was recorded in all patients thereafter but reached grade 3 in only three patients treated at the fifth dose level. Severe febrile infections never occurred; indeed, only two patients developed fever during treatment; these patients received intravenous antibiotics as outpatients and recovered rapidly. Thrombocytopenia was frequently observed in patients treated at the third, fourth, and fifth dose levels. However, it never reached grade 3, nor did it cause clinical problems. No patient required transfusion of blood cells.

Nonhematologic toxicity

Neurotoxicity was considered the DLT since grade 3 peripheral neuropathy occurred in three of five patients treated at the fifth dose level. In all these patients, loss of deep tendon reflexes was observed along with severe objective sensory loss and/or paresthesias interfering with normal function. In two of these patients, lower-extremity weakness was recorded as well. Other side effects were generally mild. Alopecia was universal; nausea and vomiting occurred frequently but reached grade 3 in only three cases. Cardiac dysrhythmias were frequently recorded during routine ECG evaluation. However, they were always benign, asymptomatic, and transient and never required treatment. No anaphylactoid reaction occurred. All toxic effects except neurotoxicity were reversible and vanished rapidly after therapy had been stopped. Recovery from neurotoxicity took an average of 3 months after the cessation of therapy. However, recovery was complete in all cases. Details on the toxic effects are shown in Tables 3–5.

Table 2 Patients' characteristics[a]

Age (years):	
Median	58
Range	43–69
Sex:	
M	16
F	6
Performance status:	
0	9
1	11
2	2

[a] $n = 22$ patients

Table 3 Hematologic toxicity[a]

Dose level	Number of patients	Neutropenia			Thrombocytopenia		
		1–2	3	4	1–2	3	4
1	3	–	–	–	–	–	–
2	3	–	–	–	–	–	–
3	5	5	–	–	3	–	–
4	6	6	–	–	5	–	–
5	5	2	3	–	5	–	–

[a] $n = 22$ patients

Table 4 Neurotoxicity[a]

Dose level	Number of patients	Peripheral neuropathy	
		Grade 1–2	Grade 3
1	3	2	–
2	3	3	–
3	5	5	–
4	6	6	–
5	5	2	3

[a] $n = 22$ patients

Table 5 Nonhematologic, non-dose-limiting toxicities[a]

Side effect	WHO grade	
	Any	3
Alopecia	22	–
Nausea & vomiting	17	3
Skin toxicity	10	–
Liver enzyme derangement	3	–
Mucositis	2	–
Cardiac arrhythmia	10	–
Lung toxicity	1	–

[a] $n = 22$ patients

Treatment delays

Treatment delays were recorded in only six courses (three patients) at the fifth dose level because of leukopenia and/or thrombocytopenia. In three courses (two patients) at the fifth dose level, both paclitaxel and vinorelbine doses were reduced by 25% due to grade 3 peripheral neuropathy.

Table 6 Response by dose level

Dose level	Number of patients	CR	PR	SD	PD
1	3	–	–	1	2
2	3	–	1	–	2
3	5	–	2	1	2
4	6	1	1	–	4
5	5	–	2	1	2

Response evaluation

Our combination showed a significant degree of antitumor activity. The overall response rate was 32% (95% CI 13–51%). In particular, one CR (4.5%) was observed at the fourth dose level in a patient with a primary lung lesion and multiple liver metastases, and six partial responses (27.3%) were observed; in two responding patients the disease was confined to the lung, whereas in the other four patients it had spread outside, involving the mediastinal lymph nodes (two cases), the liver (two cases), bones (two cases), and the surrenal gland (one case). Details on the response by dose level are provided in Table 6.

Recommended dose for phase II trials

The recommended doses for phase II studies are 180 mg/m^2 for paclitaxel +30 mg/m^2 for vinorelbine given according to the previously indicated schedule. Treatment should be repeated at 21- to 28-day intervals according to the observed toxicity.

Discussion

Paclitaxel has recently been evaluated in two phase II studies in patients with untreated extensive-stage SCLC receiving a dose of 250 mg/m^2 over 24 h every 3 weeks. In the first of these studies [5], 11 of 32 evaluable patients (34%) obtained a PR to treatment. The subsequent North Central Cancer Treatment Group study [13], in which granulocyte-colony-stimulating factor (G-CSF) support was added to paclitaxel, has obtained fairly similar preliminary results, including no CR and a PR rate of 15/37 (40.5%). These two studies confirm the activity of paclitaxel in the treatment of SCLC and demand the assessment of paclitaxel's efficacy in combination with other active agents. The University of Colorado Cancer Center has also obtained very promising preliminary results in a phase I study of paclitaxel combined with cisplatin and etoposide in untreated patients with SCLC, including an overall response rate of 100% in nine evaluable patients, although the MTDs have not yet been defined [2].

We decided to investigate the toxicity and activity of vinorelbine in combination with paclitaxel on the basis of both the preclinical evidence of synergistic activity between the two drugs [1, 14] and the results of a clinical study in which a fair degree of antitumor activity in pretreated SCLC was reported for vinorelbine (16% PR rate) [11]. We chose the 3-h administration schedule for paclitaxel, which, besides being more convenient and less costly, is associated with less myelotoxicity than the initially recommended 24-h schedule as shown by a randomized study that compared 2 doses of paclitaxel (135 versus 175 mg/m^2) and 2 infusion schedules (3 versus 24 h) in 407 patients with advanced ovarian cancer [4]. This observation is compatible with the hypothesis that neutropenia is likely to be related to the interval during which the plasma paclitaxel concentrations remain at or above a "threshold" level [12].

The combination of vinorelbine and paclitaxel is under evaluation in another phase I study in refractory breast cancer and lung cancer. In this trial the vinorelbine dose was fixed at 25 mg/m^2 on days 1 and 8 and the paclitaxel dose was 90 mg/m^2 for the first cohort of patients and 175 mg/m^2 for the second cohort. G-CSF support was provided from day 3 to day 17. The preliminary results of this study indicate that myelosuppression remains a major problem despite the use of G-CSF, and peripheral neuropathy is a significant toxic effect as well [3]. Ibrahim et al. [10] have recently presented the preliminary results of their phase I study of vinorelbine and paclitaxel given by simultaneous 3-h infusion to patients with untreated metastatic breast cancer. Myelosuppression and peripheral neuropathy were also the DLTs in that study, in which the MTD was 25 mg/m^2 for vinorelbine and 150 mg/m^2 for paclitaxel; one CR (4%) and eight PRs (32%) have thus far been observed.

In our trial we gave both drugs on day 1, introducing a 1-h interval between vinorelbine and paclitaxel infusions in agreement with preclinical findings [1, 14], which support this drug sequence. Since we felt that paclitaxel was the most active drug of the combination, we preferred both to use its common frequency of administration (every 21 days) and to escalate its dose, keeping the vinorelbine dose fixed at 30 mg/m^2 every 21 days; as a consequence, the weekly vinorelbine dose intensity was substantially lower than that commonly achieved in combination studies. In our trial we achieved clinically relevant doses of paclitaxel in combination with another myelosuppressive agent, vinorelbine. The myelosuppression caused by this regimen was substantially less severe than anticipated on the basis of the effects of each drug alone; dose escalation beyond the MTD was prevented by the development of grade 3 peripheral neuropathy as the DLT. Our combination looks fairly promising in terms of activity, especially considering that the study targeted only pretreated patients and that even the most active drugs in SCLC usually achieve quite poor results when used as second-line treatment [8].

We conclude that a phase II study of this combination in untreated patients with extensive-stage SCLC is warranted to provide a more proper definition of the

activity of the regimen and clarify if it is substantially better than the full-dose administration of each of the single agents. Furthermore, since paclitaxel is known to cause radiosensitization [17], studies evaluating this combination regimen with concurrent radiotherapy in the treatment of limited-stage SCLC are well worth conducting.

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