First-Line Treatment of Advanced Nonsmall Cell Lung Carcinoma with Docetaxel and Vinorelbine

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BACKGROUND. Docetaxel and vinorelbine are active agents in the treatment of nonsmall cell lung carcinoma (NSCLC). The efficacy and toxicity of this combination was evaluated in a Phase II study in patients with advanced NSCLC.

METHODS. Forty-six chemotherapy-naive patients (44 men and 2 women with a median age of 64 years) with NSCLC (11 with Stage IIIB and 35 with Stage IV disease) were entered into the study; the World Health Organization (WHO) performance status was 0, 1, and 2 in 32, 11, and 3 patients, respectively. Patients received vinorelbine (25 mg/m^2) on Day 1 and docetaxel (100 mg/m^2) on Day 2 in cycles repeated every 3 weeks. Granulocyte-colony stimulating factor was given to all patients from Day 3 to Day 10.

RESULTS. One hundred and seventy-seven courses of chemotherapy were administered. Adverse events included WHO Grade 4 neutropenia (15 patients), Grade 3/4 thrombocytopenia (3 patients), Grade 3 anemia (2 patients), Grade 2 and 3 neurotoxicity (7 patients and 1 patient, respectively), and Grade 3 fatigue (2 patients). Twenty patients (43%) required hospitalization: 11 (24%) for neutropenic fever (2 deaths from sepsis), and 9 (20%) for nonneutropenic pulmonary infections (2 deaths from cardiopulmonary insufficiency). The median overall survival was 5 months and the 1-year survival was 24%. Four complete responses (9.8%) and 11 partial responses (26.8%) (overall response rate of 36.6%; 95% confidence interval, 21.8–51.3%) were documented in 41 evaluable patients (intent-to-treat: 32.6%). Stable and progressive disease occurred in 13 patients each (31.7%). The median duration of response was 5 months and the median time to progression was 3 months (6 months for the responders).

CONCLUSIONS. This schedule of docetaxel and vinorelbine combination is effective but its relatively high incidence of complicated neutropenia precludes its general use in patients with advanced NSCLC. ***Cancer* 1998;83:2083–90.**

KEYWORDS: docetaxel, vinorelbine, nonsmall cell lung carcinoma, chemotherapy.

Nonsmall cell lung carcinoma (NSCLC) is the leading cause of death after cardiovascular diseases in men. Unfortunately, at the time of diagnosis the majority of patients with NSCLC present with locally advanced or generalized disease. The median survival of patients with Stage IIIB and IV NSCLC ranges from 6–8 months and only 10–20% survive for 1 year.[1]

Single agent chemotherapy with cisplatin, ifosfamide, mitomycin C, or vinca alkaloids in previously untreated patients with NSCLC results in objective responses ranging from 8–22%.[2,3] Combination therapy with these agents in patients with advanced disease has been reported to achieve higher response rates (30–51%).[4] Phase III studies comparing platinum-based chemotherapy[4,5] with best supportive care, along with meta-analysis studies,[6] have shown that chemother-

apy may confer a marginal, but statistically significant, survival benefit in patients with advanced NSCLC.

Recently, several new active agents against NSCLC have been developed. For docetaxel, response rates of 23–33% [7–10] with 40% 1-year survival rates have been reported in Phase II studies. In addition, docetaxel has shown activity in pretreated patients (19% objective responses).[11] Vinorelbine, a semisynthetic vinca alkaloid, also is an active agent in patients with advanced NSCLC, with responses ranging from 20–32% and lasting 15–44 weeks.[12–13]

Docetaxel and vinorelbine induce cell cycle arrest in metaphase by using different mechanisms. Docetaxel promotes tubulin assembly into microtubules and inhibits depolymerization to free tubulin[14,15]; conversely, vinorelbine causes disruption of microtubule formation by binding reversibly to tubulin, resulting in dissolution of the mitotic spindle.[16]

Because of the reported single agent activity of docetaxel and vinorelbine in chemotherapy-naive patients with NSCLC, the evaluation of the tolerance and efficacy of a combination of these two agents in a Phase II study was considered to be of interest. To avoid a possible drug antagonism due to their opposite mechanism of action as well as any pharmakokinetic drug interactions, we decided to administer the drugs on 2 consecutive days.

In a pilot study including seven patients with NSCLC treated with a combination of docetaxel and vinorelbine without growth factor support, five patients developed Grade 4 neutropenia on Days 5–8 after treatment. Therefore, recombinant human granulocyte-colony stimulating factor (rhG-CSF) was given prophylactically to all patients.

PATIENTS AND METHODS

Patients and Staging

Chemotherapy-naive patients with histologically or cytologically confirmed Stage IIIB or IV NSCLC who were ages 18–75 years and who had bidimensionally measurable disease were included in the study. Prior radiotherapy, either in the adjuvant setting or for the treatment of bone metastases, was allowed provided that the measurable lesions were located outside the radiation fields. Patients with irradiated brain metastases could be enrolled if the brain lesions were radiographically stable or improved and clinical manifestations also were improved. Other inclusion criteria were a World Health Organization (WHO) performance status of 0–2, a life expectancy of $\geq$ 3 months, adequate hematologic parameters including an absolute granulocyte count (AGC) $>$ 1500/dL and a platelet count $>$ 120,000/dL, adequate renal (creatinine $<$ 1.5 mg/dL) and hepatic function (bilirubin concentration $<$ 2 mg/dL), and normal cardiac function. Patients were considered ineligible if they had a history of other malignancy (except nonmelanomatous skin cancer or cervical carcinoma in situ), severe infection, or malnutrition. Informed consent was obtained from all patients for participation in the study.

Patients' Evaluation

Pretreatment evaluation included a complete medical history and a physical examination; a complete blood count (CBC) with differential and platelet count; a standard biochemical profile; an electrocardiogram (ECG); chest X-rays; computed tomography (CT) scans of the chest, abdomen and brain; and a whole bone scan. Magnetic resonance imaging was performed if indicated.

During treatment, CBC with differential and platelet counts were performed weekly; in patients with Grade 3/4 neutropenia and thrombocytopenia, CBC with differential and platelets counts were performed daily until the AGC was $>$ 1200/dL and the platelet count was $>$ 45,000/dL on 2 successive measurements after the nadir. A detailed medical history was taken and a physical examination was performed before each course of treatment to document symptoms of disease and toxicities of treatment. Biochemical tests, ECG, and chest X-rays were performed every 3 weeks. A neurologic evaluation was performed by clinical examination every 3 weeks. Motor and sensory conduction velocity measurements and vibration tests were performed in patients with $>$ Grade 2 neurotoxicity. Lesions were measured after each cycle by physical examination or chest X-rays, and by ultrasound and/or CT scans after every three courses of treatment.

Treatment

Vinorelbine (Navelbine; Pierre Fabre Oncologie, Boulogne, France) was administered on Day 1 at a dose of 25 mg/m^2 diluted in 50 mL of normal saline by intravenous (i.v.) infusion over 15 minutes, with appropriate flushing of the vein with 500 mL of normal saline. Docetaxel (Rhone-Poulenc Rorer Pharmaceuticals Inc., Collegeville, PA) was administered on Day 2 at a dose of 100 mg/m^2 as a 1-hour infusion. All patients received premedication comprised of dexamethasone, 16 mg orally 14 hours and 7 hours before treatment, and 16 mg twice daily orally for 3 days after the treatment. In addition, ondansetron (16 mg i.v. before treatment followed by 8 mg twice daily given orally for 3 days after treatment) was given to all patients. rhG-CSF (Granocyte; Rhone-Poulenc Rorer) was administered prophylactically to all patients at the dose of 150 μg/m^2 subcutaneously from Day 3 to Day 10 after

treatment if the nadir of neutrophils was not reached, or until the AGC was at least 1200/dL on 2 consecutive occasions after the nadir. Treatment was repeated every 3 weeks and was continued until there was evidence of disease progression or if intolerable (Grade 4) toxicity, excluding neutropenia, precluded further treatment. Disease progression after two chemotherapy courses as well as radiologically confirmed stable disease after three chemotherapy courses required treatment discontinuation; patients with radiologically stable disease who presented with an improvement in performance status and/or of disease-related symptoms were allowed to receive up to six chemotherapy courses.

Dose Modification

Doses of both drugs were reduced by 25% when Grade 4 neutropenia or a sustained platelet count of $<$ 25,000/dL lasting for $>$ 5 days or febrile neutropenia occurred. In the absence of fever, all drugs were reduced by 15% if the AGC was $<$ 500/dL and the platelet count was $<$ 75,000/dL. A 25% dose reduction of both drugs as well as a 1-week treatment delay was implemented for patients with Grade 2/3 neurotoxicity. In patients with symptomatic arrhythmias or atrioventricular block (except first-degree), administration of docetaxel was discontinued and the patient was withdrawn from the study. Toxicity criteria were those adopted by the WHO.[17]

Criteria for Response

Complete response (CR) was defined as the disappearance of all clinical evidence of active tumor, with complete reossification of bone lesions and absence of disease-related symptoms for a minimum of 4 weeks. Partial response (PR) was defined as a $>$ 50% reduction in the sum of the products of the greatest perpendicular dimensions of the measurable lesions, in the absence of any new or progressive tumor lesion for a minimum of 4 weeks. Stable disease (SD) was defined as an objective response not satisfying the criteria of a PR, or an increase of $<$ 25% in the tumor measurements in the absence of any new lesion. Progressive disease (PD) was an increase by $>$ 25% in the above measurements, or the appearance of a new lesion.[17]

Statistical Methods

All patients who received two or more courses of chemotherapy were evaluated for response to the treatment; all patients who received at least one course were evaluated for toxicity and survival. The duration of response was calculated as the time that the PR or CR criteria were first met until the first documentation of clinical progression. The time to tumor progression (TTP) and overall survival were calculated from initiation of chemotherapy using the method of Kaplan and Meier.[18] Confidence limits of response rates were the usual large sample estimates based on the binomial distribution. Comparison of values was performed using the chi-square test.

TABLE 1
Patient Characteristics

	No.	%
No. of patients at entry to study	46	
No. assessable for response	41	
No. assessable for toxicity	46	
Median age (yrs) (range)	64 (43–78)	
Gender		
Male	44	96
Female	2	4
WHO performance status (%)		
0	32	70
1	11	24
2	3	6
Histology type		
Squamous cell carcinoma	22	48
Adenocarcinoma	20	43
Large cell carcinoma	4	9
Stage		
IIIB	11	24
IV	35	76
Prior treatment		
None	39	85
Surgery	7	15
Radiotherapy	5	11

WHO: World Health Organization.

RESULTS

Demographic Data

From July 1995 to February 1996, 46 chemotherapy-naive patients (2 women and 44 men with a median age of 64 years) with NSCLC entered the study. Thirty-two patients had a performance status of 0, 11 had performance status of 1, and 3 had a performance status of 2. Twenty-two patients (48%) had squamous cell carcinoma, 20 patients (43%) had adenocarcinoma, and 4 patients (9%) had large-cell carcinoma. Seven of the 46 patients had undergone previous curative surgery; 5 patients had received radiotherapy either for metastases in the central nervous system or for palliation of painful bone metastatic lesions. Eleven patients (24%) had Stage IIIB disease and 35 patients (76%) had Stage IV disease. Thirty-seven of the patients (80%) had involvement of $>$ 2 organs. Characteristics of the patients are shown in Table 1.

Therapeutic Response and Survival

Forty-one patients were evaluable for response to therapy. Five patients were not evaluable (one due misdiagnosis, two due to active and clinically progressive central nervous system metastatic disease, one due to active pulmonary infection, and one due to a second primary urothelial carcinoma). CR was observed in 4 patients (9.8%) and PR in 11 patients (26.8%). The overall response rate (ORR) (CR + PR) was 36.6% (95% confidence interval, 21.8–51.3%; intent-to-treat: 32.6%). SD was observed in 13 patients (31.7%) and PD in 13 patients (31.7%). Three out of four complete responders had Stage IIIB disease and 2 patients had disease recurrence 4 and 5 months later, respectively.

An objective response was achieved in 12 of 32 patients (38%) and 3 of 9 patients (33%) with a PS of 0 and a PS of 1 + 2, respectively; in addition, 3 (30%) and 12 (39%) responses were documented in 10 and 31 patients with Stage IIIB and IV disease, respectively. Moreover, objective responses were documented in 9 patients (45%) with squamous cell carcinoma, 4 patients (25%) with adenocarcinoma, and 2 patients (67%) with large cell carcinoma. However, these differences were not statistically significant. Responses were documented at all sites of tumor involvement including the liver (3 responses in 8 patients; 38%), lymph nodes (12 responses in 33 patients; 36%), lung (12 responses in 37 patients; 32%), and adrenals (1 response in 4 patients; 25%).

The median duration of response was 5 months (range, 1.5–14 months); the median TTP was 3 months (for patients with CR, PR, and SD) whereas the median TTP for the responders (CR + PR) and those who completed 6 courses of chemotherapy (n = 10) was 6 months (range, 2–16 months) and 9 months (range, 5–10 months), respectively. At the time of analysis, two complete responders (1 with Stage IIIB disease and 1 with Stage IV disease [a lung adenocarcinoma with multiple pulmonary nodules and mediastinal lymphadenopathy]) remained progression-free at 8+ and 10+ months, respectively. After a median follow-up period of 5 months (range, 1–8 months), 9 patients (22%) remained alive, whereas 32 patients had died (28 from disease progression, 2 from nonneutropenic pulmonary infection and cardiopulmonary insufficiency, and 2 from neutropenic sepsis). The median overall survival was 5 months (range, 1–18 months) and it was significantly longer (log rank test: $P = 0.073$) in patients with a performance status of 0 (median, 7 months) than in patients with a performance status of 1 + 2 (median, 3.4 months). The projected 1-year survival was 24% (Fig. 1).

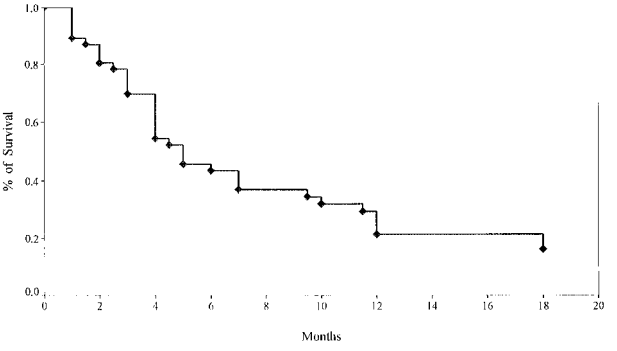

FIGURE 1. Overall survival of patients treated with docetaxel and vinorelbine by Kaplan-Meier analysis.

Compliance with Treatment

A total of 177 treatment courses were administered. The median number of courses per patient was 3 (range, 1–13 courses). The median interval between courses was 21 days (range, 21–31 days); treatment was delayed in 21 courses (12%) for the following reasons: hemoptysis due to pulmonary bleeding (1 course), neutropenic fever (2 courses), thrombocytopenia (1 course), fatigue (2 courses), and personal reasons (at the patients' request, 15 courses). Two patients refused to continue treatment for reasons directly related to the treatment (one patient for Grade 3 fatigue and one patient for hypotension and first-degree atrioventricular block during docetaxel administration).

The main reason for dose reduction was neutropenia; 37% of patients received reduced doses because they developed, at least once, an AGC < 500/dL during the first 6 courses. The median dose intensity was 29 mg/m^2/week for docetaxel and 7 mg/m^2/week for vinorelbine, accounting for 88% and 87% of the planned doses, respectively.

At the time of the analysis, all 15 responders had been withdrawn from treatment for the following reasons: disease progression (7 patients), Grade 3 fatigue (1 patient), hemoptysis and pulmonary bleeding (1 patient), declining performance status due to cardiopulmonary insufficiency (2 patients), and treatment completion (4 patients; 2 patients with CR and 2 patients with PR after they had received 6–13 courses of chemotherapy). Treatment characteristics, available from all patients and from all treatment courses, are shown in Table 2.

Toxicity

Drug toxicity was evaluated for all patients. Myelosuppression was the main toxicity observed with the combination of docetaxel and vinorelbine (Table 3). Grade

TABLE 2
Treatment Characteristics

Total no. of cycles	177
No. of administered cycles	No. of patients
1	8
2	13
3	9
4	5
5	2
>6	9
Median no. of cycles/patient (range)	3 (3–13)
Median interval between cycles (days) (range)	21 (21–31)
Median dose intensity (mg/m^2/week) (range)	
Docetaxel	29 (15–33)
Vinorelbine	7 (4–11)
Median % of protocol dose (range)	
Docetaxel	88 (45–100)
Vinorelbine	87 (52–100)

TABLE 3
Toxicity of the Docetaxel and Vinorelbine Combination

	Grade (WHO)			
	1	2	3	4
Toxicity	No. of patients (%)			
Hemoglobin	29 (63)	10 (22)	2 (4)	—
Neutrophils	4 (9)	1 (2)	6 (13)	15 (33)
Platelets	6 (13)	—	2 (4)	1 (2)
Nausea/emesis	12 (26)	10 (22)	—	—
Mucositis	6 (13)	2 (4)	1 (2)	—
Diarrhea	11 (24)	4 (9)	1 (2)	—
Constipation	2 (4)	3 (7)	—	—
Neurotoxicity	18 (39)	7 (15)	1 (2)	—
Fatigue	15 (33)	2 (4)	2 (4)	
Alopecia	10 (22)	36 (78)		

WHO: World Health Organization.

3/4 neutropenia occurred in 21 patients (46%) and 76% of the neutropenic episodes were observed from Day 5 to Day 8 after treatment with a median duration of 3 days (range, 2–5 days). Neutropenia was not cumulative. The median AGC nadir was 750 cells/dL (range, 20–2370 cells/dL). Grade 3/4 thrombocytopenia was infrequent, occurring in three patients (7%), one of whom required hospitalization for platelet transfusions. Severe anemia also was infrequent; Grade 2 and 3 anemia was reported in 10 (22%) and 2 (4%) patients, respectively. Anemia appeared to be cumulative because all episodes occurred in patients who had received more than four treatment courses. Two patients required packed red blood cell transfusions (a total of 9 units), whereas all patients with an hemoglobin level $<$ 10 g/dL received recombinant human erythropoietin (rhEPO) (200 U/kg subcutaneously twice weekly for 4–6 weeks). Four patients required rhEPO administration more than once during treatment.

Nonhematologic toxicity also is presented in Table 3. Grade 2 neurotoxicity occurred in 7 patients (15%) and Grade 3 neurotoxicity in 1 patient (2%). None of the patients refused treatment, but a reduction in dose was made in six patients because of neurotoxicity. Grade 3 fatigue was reported in 2 patients (4%), leading to treatment delay for up to 12 days in 1 patient and treatment refusal in the other patient; 2 other patients developed Grade 2 fatigue. Grade 2 nausea/emesis was observed in 10 patients (22%) but it was controlled easily with antiemetics. Grade 3 and 2 mucositis occurred in 1 patient (2%) and 2 patients (4%), respectively. Grade 3 diarrhea was reported in one patient and Grade 1/2 alopecia was observed in all patients. Mild allergic reactions were observed in 7 patients (15%), nail changes in 8 patients (17%), and phlebitis at the site of vinorelbine administration in 3 patients (7%). In addition, 4 patients (9%) experienced pain at the site of the primary tumor during or within a few hours after the administration of vinorelbine, which was treated with opioids in 2 patients. No edema or fluid retention syndrome were reported.

A 73-year-old patient developed acute myocardial ischemia 8 days after the first treatment course, requiring hospitalization in the coronary care unit for 10 days. Another patient developed a first-degree atrioventricular heart block and hypotension during docetaxel administration. The latter patient subsequently again developed first-degree atrioventricular block after receiving etoposide in combination with cisplatin, but ultimately tolerated a lower docetaxel dose (30 mg/m^2) with radiotherapy without overt toxicity. Both patients were withdrawn from the study.

Twenty-four patients required hospitalization during the study. Eleven patients (24%) were hospitalized for neutropenic fever, with a median duration of hospitalization of 5 days (range, 3–10 days). Two patients died from sepsis despite the prophylactic use of rhG-CSF. The first patient, aged 56 years with a PS of 2, was admitted for further treatment of an operated brain metastasis from a lung adenocarcinoma. Grade 4 neutropenia with fever occurred 3 days after the administration of the first chemotherapy course; blood cultures were negative. Despite rhG-CSF support (300 μg/m^2 subcutaneously) and broad-spectrum antibiotics the patient became hemodynamically unstable, developed septic shock, and died 24 hours later. The second patient, aged 74 years and with a PS of 2, received docetaxel and vinorelbine for a Stage IV, poorly differentiated squamous cell carcinoma; on postchemotherapy Day 5, he developed Grade 4 neutropenia and Grade 1 thrombocytopenia, fever (38.7

°C), and septic shock without any evidence of localized infection. Despite the administration of broad-spectrum antibiotics and rhG-CSF (300 $\mu g/m^2$, subcutaneously), the patient died the same day. Nine additional patients (20%) were hospitalized for deterioration of their respiratory function, which was attributed to pulmonary infection without neutropenia. The median duration of hospitalization was 7 days (range, 5–17 days). Two of these patients died of severe cardiopulmonary insufficiency. Another patient presented with acute abdominal pain and rebound tenderness that was attributed to acute diverticulitis according to radiologic and colonoscopic findings; he recovered with conservative treatment. Finally, a diabetic patient was hospitalized for an hyperosmotic coma attributed to the administration of corticosteroids during premedication, Grade 3 diarrhea, and his decision to discontinue antidiabetic treatment.

DISCUSSION

The combination of docetaxel and vinorelbine is an effective regimen in chemotherapy-naive patients with advanced NSCLC; the ORR of 36.6% with 9.7% CRs is comparable to that obtained using other regimens in advanced NSCLC.[4,19] In addition, responses were observed at all sites of tumor localization.

Both docetaxel and vinorelbine have shown significant single agent activity in advanced NSCLC with an ORR range of 23–33% for docetaxel[7–9] and 20–33% for vinorelbine.[12,13] However to the authors' knowledge only a few studies combining these agents with other active drugs have been reported to date. A European randomized study compared the efficacy of the weekly administration of vinorelbine (30 mg/m^2/weekly) with that of vinorelbine plus cisplatin and vindesine plus cisplatin (120 mg/m^2); the ORR was 14%, 30%, and 19%, respectively, and a statistically significant advantage in terms of overall survival for the vinorelbine plus cisplatin arm was observed.[20] The comparison of weekly administration of vinorelbine versus vinorelbine (weekly) plus cisplatin combination, demonstrated an ORR of 16% and 43%, respectively, without any survival difference.[21] Moreover, the efficacy and toxicity of single agent cisplatin (100 mg/m^2) versus cisplatin every 4 weeks and vinorelbine (25 mg/m^2) weekly was studied in 412 patients with advanced NSCLC; the ORR was 10% and 25% (with 2% CR), respectively,[22] whereas the progression free and overall survival were significantly higher in the cisplatin and vinorelbine arm. In a Phase II study, the combination of cisplatin (100 mg/m^2), 5-fluorouracil (600 mg/m^2 continuous infusion for 4 consecutive days), leucovorin (600 mg/m^2 every 6 hours for 4 days), and vinorelbine (20 mg/m^2 on Days 1 and 8) resulted in a high response rate (ORR = 65%) but with severe toxicity and several treatment-related deaths.[23] Similarly, the combination of vinorelbine (25 mg/m^2 on Days 1 and 8) plus ifosfamide and cisplatin resulted in an ORR of 60% with a median overall survival of 12 months.[24] In the aforementioned trials, vinorelbine was given for > 2 weeks per course and at a higher weekly dose than that used in our study, thus explaining, at least in part, the observed higher response rates. Recently, Monnier et al.[25] reported the preliminary results of a docetaxel (75 mg/m^2) and vinorelbine (20 mg/m^2 on Days 1 and 5) combination, with an ORR of 23%; unfortunately, no more information regarding the efficacy data was presented in this report,[25] making any comparison with the current study difficult.

Despite the relatively high response rate of the combination of docetaxel and vinorelbine and the observed CRs in Stage IIIB patients, the cumulative 1-year survival was lower than that observed for each single agent in Phase II studies[7–9,12,13] indicating that improvement of response does not necessary translate into improved survival. This low 1-year survival should be attributed to several factors such as: 1) the early deaths from both neutropenic and nonneutropenic infections; 2) the treatment delays perhaps leading to tumor progression; and 3) the low total vinorelbine dose administered because the drug could not be given on Day 8 due to the granulocytopenia nadir occurring at that time. A similar observation recently was reported for the vinorelbine and paclitaxel combination in pretreated breast carcinoma and lung carcinoma patients; in that study vinorelbine (25 mg/m^2 i.v. on Days 1 and 8) was combined with 2 different doses of paclitaxel (90 mg/m^2 and 175 mg/m^2 over 3 hours with rhG-CSF support), but severe granulocytopenia precluded the easy administration of the second vinorelbine dose.[26] Therefore, the need for additional studies is obvious. In a different approach, Vialet et al.[27] administered docetaxel (100 mg/m^2), alternating every other cycle with cisplatin (100 mg/m^2) plus weekly vinorelbine (30 mg/m^2) in a 6-week course; the ORR was 44% with a projected median survival of 39 weeks. In that schedule, the planned mean dose intensity of docetaxel was lower (16.5 mg/m^2/week) whereas the planned mean dose intensity of vinorelbine was higher (15 mg/m^2/week) than in our study. These observations appear to indicate that the dose intensity for vinorelbine could be a more important parameter than dose intensity for docetaxel with regard to response rate and the patients' overall survival, as previously suggested.[28]

Eleven patients who failed to respond to the docetaxel and vinorelbine regimen subsequently were

treated with docetaxel and cisplatin. It is interesting to note that five responses were observed after the patients received two to four courses, suggesting that there is no complete cross-resistance between vinorelbine and cisplatin (data not shown).

Myelosuppression was the reason for dose reduction in 10 patients (37% of the chemotherapy cycles). However, the compliance with the regimen was relatively good because 88% of the docetaxel planned doses and 87% of the vinorelbine planned doses could be administered. The most severe toxicity was neutropenia, which required hospitalization for neutropenic fever in 24% of the patients whereas 2 patients died of sepsis; in addition, approximately 50% of the patients developed Grade 3/4 neutropenia at least once during the treatment. This high incidence of febrile neutropenia should be considered excessive for patients with an incurable and fatal disease. Similarly, Monnier et al.[25] reported Grade 3/4 neutropenia and febrile neutropenic episodes in 77% and 42% of the patients, respectively; the incidence of these adverse events was higher than the incidence observed in our trial. This should be attributed to the lower dose of vinorelbine and the prophylactic use of rhG-CSF which appear mainly to decrease the degree of neutropenia.[29] Conversely, the alternate schedule of Vialet et al.[27] was complicated by febrile neutropenia in only 15% of the administered cycles, indicating that this schedule is better tolerated than the schedule described in the current study.

Nonneutropenic pulmonary infections requiring hospitalization were relatively frequent (20% of patients) and severe enough to result in 2 deaths from cardiopulmonary insufficiency. The tumor-related bronchial obstruction as well as the use of corticosteroids may account for this high incidence of nonneutropenic infections.

The acute myocardial ischemia we observed in one patient cannot be attributed directly to the treatment regimen because the patient had several other predisposing factors (advanced age, hypertension, and hypoxia due to respiratory insufficiency). Another patient developed first-degree atrioventricular block and hypotension during the administration of either docetaxel or etoposide; because this patient tolerated lower doses of docetaxel very well, it appears reasonable to hypothesize that he had an intrinsic sensitivity to these agents that was dose-dependent.

Neurotoxicity and fatigue were mild and well tolerated as previously reported.[30] Only one patient developed Grade 3 neurotoxicity whereas another patient refused to continue treatment because of fatigue.

Our findings indicate that the docetaxel and vinorelbine combination is effective in patients with advanced NSCLC; however, the excessive toxicity of this regimen, in terms of febrile neutropenia, limits its general use in the schedule and dosages studied.

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