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CLINICAL TRIAL REPORT

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Carboplatin and vinorelbine in advanced non-small-cell lung cancer

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Abstract A total of 32 patients with advanced non-small-cell lung cancer were treated with carboplatin (350 mg/m^2, day 1) and vinorelbine (days 1 and 8) every 28 days. A response rate of 28% (95% confidence limits 12.5–43.7%) was observed. The activity of this combination was demonstrated in an outpatient setting with acceptable toxicity.

Key words Carboplatin · Vinorelbine · Non-small-cell lung cancer

Introduction

Inoperable locally advanced or metastatic non-small-cell lung cancer (NSCLC) represents an incurable disease and the patients are candidates for palliative treatment. A recent metaanalysis has shown that chemotherapy improves only slightly the survival of advanced NSCLC patients such that improvement of the quality of life becomes a major end point [11]. Therefore, the development of chemotherapy programs both effective in inducing tumor regression and devoid of important toxicities has become an outstanding issue. For many years, combinations of cisplatin and one or more of the few other drugs displaying some activity in NSCLC have represented the standard chemotherapy. In recent years the pharmaceutical arsenal has been enriched with some new compounds, including carboplatin and vinorelbine.

On the basis of the positive results obtained in favor of the combination of cisplatin and vinorelbine in a randomized trial [7], we carried out a phase II trial in a group of chemotherapy-untreated NSCLC patients with stage IIIB-IV disease so as to assess the activity and toxicity of this outpatient chemotherapy regimen.

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Patients and methods

To be eligibile for the trial patients were required to fulfil the following criteria: histologically documented NSCLC of stage IIIB (invasion of mediastinal structures or metastases to controlateral mediastinal or hilar lymph nodes) or IV (distant metastases); no previous chemotherapy; the presence of measurable nonirradiated lesions; an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2; normal renal and hepatic function as documented by pretreatment serum creatinine (≤ 1.2 mg/dl) and bilirubin (≤ 1.2 mg/dl) values. Informed consent for participation in the trial was obtained from all patients.

Chemotherapy was given on an outpatient basis for a maximum of six cycles, with courses being repeated every 4 weeks. Carboplatin was given on day 1 of each cycle at the dose of 350 mg/m^2 diluted in 250 ml of normal saline and was infused intravenously in 30–60 min. Vinorelbine was given on days 1 and 8 of each cycle at the dose of 25 mg/m^2 diluted in 100 ml of normal saline and was infused intravenously in 20 min. A cycle was delayed until marrow recovery if the WBC count was $<3{,}000/\text{mm}^3$ and the platelet count was $<100{,}000/\text{mm}^3$. It was planned that the dose of carboplatin be reduced by 50% if the serum creatinine level increased to between 1.5 and 2 mg/dl, and the treatment was discontinued for values of >2 mg/dl. Hemograms and blood chemistry were planned at the beginning of each cycle. In the case of grade III–IV leukopenia, granulocyte colony-stimulating factor (G-CSF, Filgrastim) at the dose 300 μg was given prophylactically from day 15 to day 25 of the subsequent cycles. Granisetron and dexamethasone were employed as antiemetics in all cases.

Patients were evaluated for response after the third and sixth cycles, provided that progression had not become evident. Lesions in the lungs, the mediastinum, and the thoracic wall were evaluated by chest computed tomography (CT); lesions in the liver and the abdomen were evaluated by means of CT or echography. A complete response was defined as a the complete disappearance of all objective lesions. A partial response was defined as a decrease of 50% or more in the sum of the products of the two longest diameters of all measurable lesions. Stable disease was defined as a decrease of $<50\%$ or an increase of $<25\%$.

All patients entered into the study were considered evaluable for response and toxicity assessment. The time to disease progression was measured in all patients from the date of entry into the study to the date of progression of disease, and overall survival was measured from the date of entry to the date of death or of the last visit.

Table 1 Patients' characteristics

Number of patients	32	
Median age (years)	63	(range 46–74)
Median performance status (ECOG scale)	1	(range 0–2)
Sex:		
M	20	
F	12	
Pathologic type:		
Squamous-cell	19	
Adenocarcinoma	10	
Large-cell	3	
Stage and site of metastases:		
IIIB (nodes)	6	
IIIB (mediastinum)	3	
IV (lung)	6	
IV (distant nodes)	5	
IV (lung, nodes)	4	
IV (bone)	3	
IV (bone, liver)	1	
IV (bone, soft tissue)	3	
IV (lung, liver)	1	
Previous treatment		
Surgery	7	
Surgery + radiotherapy	3	
Radiotherapy	2	

Results

A total of 32 patients entered the study and 121 cycles were given. The main characteristics of the patients are shown in Table 1. A median of 3 cycles (range 1–6) of chemotherapy were given. The planned dose intensity of the drugs was actually delivered in 9 patients among the 25 who received 3 cycles or more. The cycles were delayed due to incomplete marrow recovery (neutropenia and/or thrombocytopenia) in 29 courses (for 16 patients). Two patients died before the second cycle was applied, apparently of neoplastic progression. One patient refused chemothepy after the first cycle, having experienced severe emesis.

Two patients had a complete response; complete responders included a 66-year-old woman with a relapse from resected squamous-cell carcinoma involving bone and soft tissue of the thoracic wall and a 67-year-old woman with pulmonary metastases from previously resected contralateral squamous-cell carcinoma. In all, 7 patients had a partial response, the disease remained stable in 12 patients, and treatment failure (including the early deaths and the progression observed after one or two cycles) was observed in the remaining 11 patients. The overall objective response (complete and partial) rate was 9/32 (28%; 95% confidence limits 12.5–43.7%). The duration of response was 6 (range 3–12+) months, and the median overall survival was 10 (range 1–18+) months.

Altogether, 14 patients were aged 65 years or more; they did not show a toxicity pattern different from that displayed by the younger patients. All the patients were symptomatic at the beginning of the trial, and 20 patients experienced symptomatic relief. A formal study of quality-of-life parameters was not planned in this study. No patient had to be hospitalized because of the administration of chemotherapy or the toxic effects. The toxicities observed are listed in Table 2.

Table 2 Toxicity encountered according to the ECOG scale

	Patients (*n*) with toxicity of grade		
	I–II	III	IV
Neutropenia	9	–	2
Thrombocytopenia	11	–	1
Anemia	12	10	
Constipation	10[a]	5[b]	
Renal toxicity	3	–	–
Nausea/vomiting	18	1	–
Local reactions	15[c]	1[d]	

[a] Mild
[b] Moderate
[c] Phlebitis and pain
[d] Necrosis

Discussion

Chemotherapy has been found to increase slightly the survival of patients with stage IIIB–IV NSCLC, and cisplatin-based combinations are considered to yield the best results in terms of tumor regression. Carboplatin is a platinum analog with a toxicity profile more favorable than that of the parent compound cisplatin; indeed, it is less likely to induce nephrotoxicity and neurotoxicity or to produce gastrointestinal symptoms (i.e., nausea and vomiting). Furthermore, a shorter infusion period with no need for pre- or posthydration renders carboplatin more suitable for outpatient-based regimens.

Many phase II studies have been performed using carboplatin alone or in combination in NSCLC patients. As a single agent the drug has achieved a 17% response rate in chemotherapy-untreated patients [2]. Combinations with etoposide [6, 8], ifosfamide [5], and vinblastine [4] have been extensively tested. A randomized study has compared the combination of cisplatin and etoposide with the combination of carboplatin and etoposide, showing a higher response rate for the former (27% versus 16%) but a superimposable overall survival. The patients treated with carboplatin had less toxicity and required less hospitalization [6].

Vinorelbine is the most recent vinca alkaloid introduced in cancer chemotherapy. Its interest lies also in the possible circumvention of multiple-drug-resistance mechanisms [1]. In chemotherapy-naive patients, vinorelbine can induce response as high as 40% [12], although the pattern of toxicity includes frequent myelosuppression [9, 12].

Le Chevalier et al. [7] carried out a multicenter study in which 612 patients with metastatic or locally advanced NSCLC were randomized to cisplatin plus vinorelbine versus cisplatin plus vindesine versus vinorelbine alone. An objective response was observed in 30% of patients treated with the vinorelbine combination and in 19% of

patients treated with the vindesine combination; patients treated with vinorelbine alone experienced an objective response in 14% of cases. In this study a statistically significant survival advantage for the combination of cisplatin and vinorelbine emerged, but the high dose of cisplatin used requires a 12-h period of hydration.

On the basis of these results we tried to develop a combination of vinorelbine with carboplatin instead of cisplatin so as to take advantage of the ability of the new platinum compound to be given without prolonged hydration in an outpatient setting and to avoid some of the unpleasant side effects of cisplatin, such as neurotoxicity and emesis. Our schedule consisted of a conventional dose of carboplatin (350 mg/m^2) given on day 1 and of two doses of 25 mg/m^2 of vinorelbine given on days 1 and 8. In the study by Le Chevalier et al. [7] administration of the vinca alkaloid was planned weekly, but the dose actually given was only 71% of the planned dose, and we thought it would be unlikely to maintain the administration of a higher dose of vinorelbine in combination with carboplatin, which is more myelotoxic than cisplatin.

A response rate of about 30% compares favorably with the reported results of chemotherapy in advanced NSCLC, even taking into account that our study population was not particularly prone to respond on the basis of known prognostic factors: 71% of the patients had stage IV disease, and the performance status was 2 (ECOG scale) in a third of the patients. A response rate of 36% has been reported in an abstract by another group using same schedule [10].

The toxicity observed was generally mild to moderate, but grade IV marrow toxicity was observed in three cases (thrombocytopenia in one case and leukopenia in two cases). Since patients who had experienced a grade III–IV toxicity were treated in subsequent cycles with prophylactic G-CSF, the myelotoxicity could have been higher in the absence of hemopoietins. Moreover, in this study we adopted as the initial dose of carboplatin the empirical level of 350 mg/m^2, with a reduction being planned in the case of increasing creatinine levels. Although very easy from a practical point of view, this type of dose calculation may show lack of accuracy in comparison with the method developed by Calvert [3], which is based on the glomerular filtration rate and the level of drug to be reached in the plasma. Theoretically, this approach may further ameliorate the activity and toxic effects of the carboplatin combination.

In conclusion, in patients with locally advanced or metastatic NSCLC the major aim of treatment is the achievement of the best possible quality of life, and the development of combinations that are effective in the control of disease-related symptoms and free of important toxic effects is needed. We have shown that carboplatin and vinorelbine is an active combination with acceptable toxicity; it may be given on an outpatient basis, and hospitalization is usually not required.

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