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ORIGINAL ARTICLE

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Biweekly regimen of cisplatin, gemcitabine and vinorelbine for advanced non-small-cell lung cancer

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Abstract *Purpose*: Improving chemotherapeutic efficacy in non-small cell lung cancer (NSCLC) will require the development of new strategies to better use currently available agents. To assess the efficacy and safety of a biweekly regimen of cisplatin, gemcitabine and vinorelbine for advanced non-small-cell lung cancer. *Methods*: Patients with selected stage IIIb (pleural effusion)/stage IV NSCLC, performance status of 0–2 and normal organ function were eligible. Treatment consisted of cisplatin 100 mg/m^2 on day 1 plus gemcitabine, 1,000 mg/m^2 and vinorelbine 25 mg/m^2 on days 1 and 15 every 28 days. *Results*: Of the 40 patients enrolled and assessable for response, there were five (12.5%) with confirmed complete response and 14 (35%) with a confirmed partial response for an overall response rate of 47.5%. Nine patients had stable disease while 12 (30%) progressed. Median progression-free survival and overall survival for all patients were 6.3 and 11.1 months, respectively. Toxicity was principally hematologic, with grade 3–4 neutropenia in 30%, and grade 3–4 nausea/vomiting in 22.5%. There were no treatment-related deaths. *Conclusions*: The biweekly regimen of cisplatin, gemcitabine and vinorelbine is associated with a high rate of response, lesser toxicity than other three-drug regimens and no benefit of survival. Therefore, the regimen under study may be an appealing alternative when considering other treatment modalities for advanced lung cancer, such as neoadjuvant therapy.

Keywords Non-small-cell lung carcinoma · Gemcitabine · Cisplatin · Chemotherapy · Vinorelbine · Triplets

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Introduction

Non-small-cell lung cancer (NSCLC) accounts for approximately 75% of lung cancers, and is worldwide the leading cause of cancer-related deaths. The prognosis for patients with advanced NSCLC is disappointing. While chemotherapy has been demonstrated to be slightly but significantly superior to the best supportive care [1], chemotherapy efficacy in NSCLC remains modest. The standard treatment consists of a combination of a platinum agent (cisplatin o carboplatin) and gemcitabine [2], vinorelbine [3], or taxane (paclitaxel [4] or docetaxel [5]). All these two-drug regimens have been shown to be equally efficient, with an objective response rate of 30%, median survival rate of 9 months and 30–35% of patients surviving one year [6], though different schemes differ as regards safety and financial cost.

The aim of three-drug regimens is to enhance treatment activity. Thus, numerous three-drug schemes with a platinum agent, gemtabicine, vinorelbine or taxane

have been attempted. While these chemotherapeutic regimens have resulted in higher response rates, they are associated with a significant increment of attendant toxicity. Because of severe toxicity and the absence of a significantly improved survival rate in the majority of clinical trials, most authors currently advocate two-drug regimens [7]. Nevertheless, it should be borne in mind that many of these three-drug schemes have been developed based uniquely on the mere sum of dosage schedules of the different drugs as single drugs or as individual components of two-drug regimens, which could account for the significant increment of toxicity, which has resulted in the lack of adherence to the intended schedule, which, in turn, may have given rise to the absence of benefit to survival. In order to overcome this drawback, alternative schemes, such as weekly, biweekly or sequential administration, have been developed.

A scheme combining cisplatin and biweekly administration of gemcitabine and vinorelbine (CGV) has now been developed. Preliminary results showed that biweekly administration of these three drugs may result in a high response rate with a reduced toxicity rate [8]. It was the aim of the present study to assess the chemotherapeutic activity and toxicity of the above scheme involving cisplatin, and biweekly gemcitabine and vinorelbine in chemo-naive patients with advanced NSCLC.

Patients and method

Eligibility criteria

To be included in the study, patients were required to have histologically or cytologically confirmed NSCLC (squamous cell carcinoma, adenocarcinoma or large-cell carcinoma), and stage IIIB (pleural effusion or not amenable to radiation therapy) and IV disease according to the International Staging System for lung cancer proposed by Mountain [9]. Also, patients were required to have at least one measurable or assessable lesion in accordance with World Health Organization (WHO) guidelines [10] and no prior therapy for NSCLC. Pleural effusion, ascites, osteoblastic lesions or previously irradiated lesions were not accepted as measurable disease.

Evaluation was performed within three weeks prior to treatment initiation, and included history and physical examination; complete blood count and serum chemistry (lactate dehydrogenase, alkaline phosphatase, AST or ALT, bilirubin, albumin, and calcium); chest radiograph; chest, liver and adrenal computed tomography (CT); and radionuclide bone scan. Brain CT was carried out in the presence of symptoms suggestive of brain metastases. ECOG performance status and body weight were recorded.

Eligible patients were to meet the following inclusion criteria: (1) aged ≥18–75; (2) performance status ≤ 2, according to the Eastern Cooperative Oncology Group (ECOG) scale; (3) life expectancy of at least 3 months; (4) adequate bone marrow function (i.e., WBC 4,000/ml, platelets $>100\times10^9$/l); (5) adequate liver function (i.e., serum bilirubin <1.25 times the upper normal limit, glutamic oxaloacetic transaminase values [SGOT] and glutamic pyruvic transaminases [SGPT] <3 times the upper normal limit in the absence of hepatic metastases); and (6) adequate renal function (i.e., serum creatinine less than 150 μmol/l, or creatinine clearance of at least 60 ml/min).

Previous radiotherapy was allowed if $<25\%$ of bone marrow was involved, there was at least one measurable lesion outside the radiation field and radiation treatment was completed at least 4 weeks before enrolment. Patients with brain metastases were eligible if they had no neurological deficits and were off steroids after definitive holocranial radiotherapy. The presence of significant heart disease (congestive heart failure or unstable angina) and neuropathy greater than grade 2 was considered as an exclusion criteria. Patients with tumors others than lung cancer were also excluded, with the exception of radically-resected non-melanoma skin cancer or in situ cervical carcinoma. All patients were informed of the investigational nature of the study and signed a written informed consent in accordance with the local institutional review board guidelines.

Study design

The study regimen consisted of cisplatin 100 mg/m^2 on day 1 plus gemcitabine, 1,000 mg/m^2 and vinorelbine 25 mg/m^2 on days 1 and 15 every 28 days. This scheme was repeated every 28 days for a minimum of three courses per patient unless disease progression was detected. Hydration was performed by administering 2 l of physiological saline for 4 h before cisplatin administration. All patients received antiemetic prophylaxis with either ondansetron or granisetron plus dexamethasone. Treatment was administered on an outpatient basis. The patients participating in the study may have received a maximum of six cycles.

Toxicity, dose adjustment and evaluation during treatment

During the study, clinical examinations, complete blood counts and biochemistry blood tests were performed before each administration of chemotherapy. Toxicities were graded according to the NCI Common Toxicity Criteria, version 2.0. Toxicity for each course was recorded before the next treatment course and graded according to WHO scales.

Full doses of the drugs were given if neutrophil and platelet counts on the day of treatment were at least 1.5×10^9/l and 100×10^9/l, respectively. If WHO grade ≥2 neutropenia or grade ≥1 thrombopenia was found on the day of cisplatin, gemcitabine and vinorelbine administration, chemotherapy was delayed for 1 week. If grade

2 neutropenia or grade 1 thrombopenia persisted 1 week later, cisplatin, gemcitabine and vinorelbine doses were reduced by 25%, but if greater degree of toxicity persisted 2 weeks after the scheduled time of recycling, chemotherapy was definitively discontinued. Gemcitabine or vinorelbine dose was also reduced up to 25% if grade 2 neutropenia or grade ≥1 thrombopenia had been seen on day 14 of the CGV scheme. The dose of each drug was reduced by 25% if WHO grade 4 neutropenia/thrombopenia or grade 3–4 non-hematologic toxicity had occurred in the previous course. Cisplatin and vinorelbine dose was reduced by 25% when grade 2 neurotoxicity had occurred. Cisplatin dose was lowered by 50% when creatinine level was seen to be at 141–148 μmol/l, and the drug was withheld if the level was above 141–148 μmol/l. Patients were allowed to receive granulocyte colony-stimulating factor (G-CSF) when there was grade 4 neutropenia lasting longer than 7 days, neutropenic fever o grade ≥2 neutropenia persisting for more than 2 weeks. However, G-CSF was not used routinely.

Study evaluation and statistical methods

Response determination

Patients who had received one cycle of therapy were assessable for response. All patients who received treatment were assessable for toxicity and survival. Tumor response was assessed every three cycles by standard WHO criteria [11,12] The responses were to be confirmed at least 4 weeks later. Patients participating in the study may have received a maximum of six cycles.

Subsequently, follow-up posttreatment evaluation was performed every 3 months until death. Patients were removed from the protocol for disease progression because of unacceptable toxicity as assessed by the investigator, development of recurrent non-cancer-related illnesses precluding continued treatment, or on patient's request.

Statistics

Data statistical analysis was performed using SPSS software (version 9.0; SPSS software, Inc., Chicago, IL,USA) for all patients who had received at least one infusion. All parameters were calculated with a 95% confidence interval (CI), using appropriate methods [13]. The sample size was calculated to reject a response rate less than 20%. According to the Fleming method, 19 patients were first included. Because the observed response rate was greater than 21% in these first 19 patients, the sample was increased to 35 plus 10% to allow for losses, which resulted in a total of 38 patients evaluable for tumor response. Dose intensity was calculated by dividing the total amount of the drug given in the first two courses (mg/m^2) by the number of weeks between the first dosing and the beginning of the third course. Overall response rate was defined as complete plus partial responses. Time to disease progression was defined as the interval from the first day of treatment to the time when disease progression was first documented. Response duration was measured from the first documented response to disease progression. Survival was defined as the time between the first day of treatment and the date of death or last known follow-up visit. Overall survival and response duration were determined by the Kaplan and Meier method [14].

Results

Clinical outcomes

A total of 40 patients were enrolled between September 2000 and January 2002. Patient characteristics are summarized in Table 1. The median age was 61 years (range, 40–73 years). Eighty percent of the patients had stage IV and 57.5% had a performance status of 0–1. The majority of patients were male. The most frequent histological subtype was squamous cell carcinoma. Thirty per cent of the patients presented more than one metastatic site, the most frequent metastatic site being the lung.

The median number of cycles was four (range 1–6), with 14 (35%) patients completing all six cycles. The primary reason for discontinuation of treatment was disease progression. The median dose intensity were 23, 475 and 12.5 mg/m^2/week for cisplatin, gemcitabine and vinorelbine, respectively. Thirty-six patients (90%) received at least 90% of the scheduled doses.

Table 1 Patients' clinical and demographic characteristics ($N = 40$)

	No of patients (%)
Age (years)	
Median age	61
Range	(40–73)
Sex	
Male	31 (77.5%)
Female	9 (22.5 %)
Performance status (ECOG)	
0	3 (7.5%)
1	20 (50%)
2	17 (42.5%)
Stage	
IIIB	8 (20%)
IV	32 (80%)
Histology	
Squamous cell carcinoma	18 (45%)
Adenocarcinoma	12 (30%)
Large cell carcinoma	10 (25%)
No. of involved sites	
1	28 (70%)
2	10 (25%)
3	2 (5%)

ECOG Eastern Cooperative Oncology Group

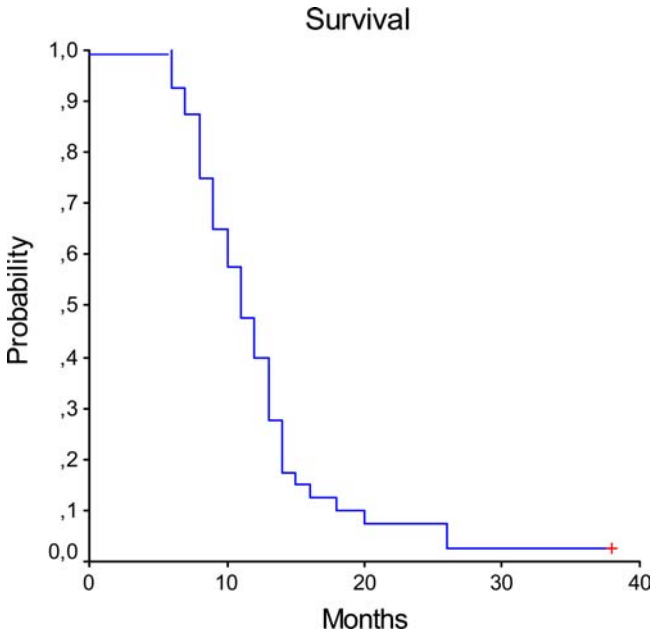

Fig. 1 Overall survival

Five (12.5%) patients had a complete response and 14 (35%) had a partial response, which represents an overall response rate of 47.5% (95% CI: 32.8–62.6). In addition, 9 (22.5%) patients achieved stabilization of their disease and 12 (30%) presented disease progression. By stages, the response rate was 50% for stage IIIB patients and 46% for stage IV patients.

After a median follow-up of 24 months, median survival rate was 11.1 months (95% CI: 9.4–13.2) (Fig. 1). Median time to progression was 6.3 months (95% CI: 5.2–7.4), and actuarial 1-year survival rate was 40%.

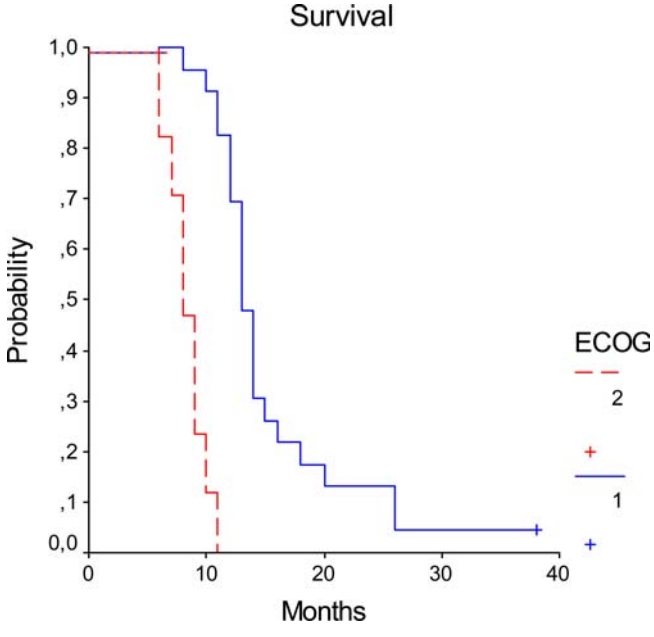

Fig. 2 Overall survival according to performance status (ECOG)

Table 2 Treatment toxicity per patient

WHO toxicity	1–2 no (%)	3–4 no (%)
Neutropenia	10 (25%)	12 (30%)
Anemia	6 (15%)	5 (12.5%)
Thrombopenia	3 (7.5%)	2 (4%)
Nausea/vomiting	12 (30%)	9 (22.5%)
Asthenia	7 (17.5%)	3 (7.5%)
Renal	4 (10%)	3 (7.5%)
Diarrhea	2 (4%)	
Alopecia	9 (22.5%)	7 (17.5%)
Peripheral neurotoxicity	9 (22.5%)	6 (15%)

WHO World Health Organization

By stages, median survival rate was 12.5 months for stage IIIB patients and 11.3 months for stage IV patients, with this difference not reaching statistical significance ($P = 0.08$). However, PS 2 patients have a significantly worse outcome. Thus, for PS 2 patients median survival rate was 8 months, while for PS 0–1 patients it was 13 months ($P = 0.0001$) (Fig. 2).

Toxicity

Toxicity was assessed at every cycle in all patients who received at least one cycle of treatment. There were no toxic deaths reported. Table 2 summarizes the most common toxic effects. Hematologic toxicity, specifically grade 3–4 neutropenia, was the most important side effect, and it was seen in 12 (30%) patients. There were no cases of neutropenic fever. Grade 3–4 anemia was noted in 5 (12.5%). The incidence of grade 3–4 thrombocytopenia was 4%. Non-hematologic toxicity was relatively manageable. Nausea/vomiting was seen in 42.5% of patients, but grade 3–4 nausea/vomiting was noted in only 6 (15%).

Poststudy treatment

Fifteen patients received second-line chemotherapy, this being weekly paclitaxel in seven cases and docetaxel either alone or combined with mitomycin in eight. Palliative radiotherapy was administered to eight patients.

Discussion

In the present study, an overall response rate of 47.5% has been achieved, which is within the range (33–65%) reported in earlier phase-I-II trials using the combination CGV [9, 15–21]. As expected, this response range was lower in subsequent phase-III trials [22–24], with response rates of 47, 41 and 28%. Our median survival rate and percentage of patients suviving one year after are similar to those reported in most phase-II trials.

Toxicity found in the present study should be emphasized. Of note, in our study toxicity was predominantly hematologic in nature, especially grade 3–4

Table 3 Treatment schedule

Study	Day 1	Day 8	Day 15
Present study	• Cisplatin 100 mg/m^2 • Gemcitabine 1,000 mg/m^2 • Vinorelbine 25 mg/m^2 (every 28 days)		• Gemcitabine 1,000 mg/m^2 • Vinorelbine 25 mg/m^2
Frasci, Comella	• Cisplatin 50 mg/m^2 • Gemcitabine 1,000 mg/m^2 • Vinorelbine 25 mg/m^2 (every 21 days)		• Cisplatin 50 mg/m^2 • Gemcitabine 1,000 mg/m^2 • Vinorelbine 25 mg/m^2
Ginopoulos	• Gemcitabine 1,000 mg/m^2 • Vinorelbine 25 mg/m^2 (every 21 days)	• Cisplatin 75 mg/m^2 • Gemcitabine 1,000 mg/m^2 • Vinorelbine 25 mg/m^2	
Hesketh	• Cisplatin 50 mg/m^2 • Gemcitabine 1,000 mg/m^2 • Vinorelbine 25 mg/m^2 (every 21 days)	• Cisplatin 50 mg/m^2 • Gemcitabine 1,000 mg/m^2 • Vinorelbine 25 mg/m^2	
Laack	• Cisplatin 75 mg/m^2 (day 2) • Gemcitabine 1,000 mg/m^2 • Vinorelbine 25 mg/m^2 (every 21 days)	• Gemcitabine 1,000 mg/m^2 • Vinorelbine 25 mg/m^2	
Esteban	• Cisplatin 50 mg/m^2 (day 2) • Gemcitabine 1,000 mg/m^2 • Vinorelbine 25 mg/m^2 (every 21 days)	• Cisplatin 50 mg/m^2 (day 9) • Gemcitabine 1,000 mg/m^2 • Vinorelbine 25 mg/m^2	

neutropenia (30% of patients). This figure differs from the very high hematologic toxicity rates reported by earlier authors. Thus, studies by the Italian group [22] report 46% of patients with G 3–4 neutropenia, while the Spanish group reports an incidence of severe neutropenia of 57%, with 19% of patients presenting neutropenic fever [23]. In the two studies by Laack et al.[20, 24], neutropenia incidence exceeded 40%. On the other hand, in the study by Ginopoulos et al. [18], 77% of their patients required administration of G-CSF from the third or fourth course on. Finally, in the phase-II trial by Hesketh et al. [19], there were 67% neutropenia, 21% neutropenic fever and 9% neutropenia-related deaths, thereby the authors conclude that there is no therapeutic benefit with the the three-drug regimen. Although in our study the other types of hematologic toxicity were less relevant, they differ from those reported by other authors as well. Thus, while in the present study only 7% of patients presented grade 3–4 thrombopenia, in earlier studies this rate ranges from 17 to 67%, the median rate being 31%. On the other hand, in the present study severe anemia rate was 10%, in contrast with almost 20% in earlier studies. On the contrary, the rates of other toxicities (mainly renal and neurorologic toxicity) we found are similar to those reported by other other authors.

Such important differences in hematologic toxicity between the present studies and earlier trials may be due to the combination schemes of cisplatin, gemcitabine and vinorelbine (Table 3). Thus, we used a biweekly scheme every 28 days, while in the other studies the three cytostatic drugs were given on days 1 and 8 every 21 days. Our preliminary studies showed that a scheme administered every 21 days resulted in greater hematologic toxicity than did the biweekly scheme [8, 17]. This greater toxicity obliged us to reduce ther schedules dose or to adjourn the treatment in many cases. Likewise, weekly administration of gemcitabine and vinolrebine was associated with a large number of cases in which treatment adjourment was required [25], and earlier authors have reported a potential dose increment with acceptable safety when the biweekly regimen [26] was adopted.

On the other hand, our results with regard to both clinical efficacy and safety are similar when using a biweekly sequential CGV scheme [27]. Although the intensity of such a scheme may have been less than in earlier studies, especially as far as gemcitabine and vinorelbine are concerned, the response rate we have achieved is as high as that in ealier studies, which might be due to a synergistic rather than additive effect exerted by the combination of the three drugs.

As in earlier studies with CGV, we noted a slightly higher response rate in stage IIIB patients relative to patients with disseminated disease [21, 24] (stage IV: 46%, stage IIIB: 50%), but this difference did not result in a benefit of survival for IIIB patients [20, 23]. In fact, IIIB patients had a median survival of 12 months, which, though 1 month longer than that of IV patients, was not statistically significant ($P = 0.08$). However, the patient's health status seems to be of great importance for response to chemotherapy, especially for overall

survival. Thus, patients with good health status (ECOG: 0–1) had a median survival of 13 months compared with 8 months for those with unsatisfactory health status ($P < 0.0001$).

In conclusion, biweekly sequential CGV combination for advanced NSCLC patients results in a high response rate with no benefit of survival and less toxicity than weekly CGV schemes. To our knowledge, this is the first study on biweekly CGV published in the literature. Therefore, clinical efficacy and slighlty higher survival rate in advanced NSCLC patients with good health status make biweekly sequential CGV combination advisable for selected patients. In fact, such combination may be of clinical benefit as a neoadjuvant treatment modality in stage III lung cancer patients when the aim is to provide therapy to patients with good health status resulting in a high response rate and moderate toxicity.

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