Flexible Chemotherapy Regimen with Gemcitabine and Vinorelbine for Metastatic Nonsmall Cell Lung Carcinoma

A Phase II Multicenter Trial

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BACKGROUND. This Phase II study evaluated a flexible 3- or 4-week dosing schedule of gemcitabine and vinorelbine to determine its effect on response rate and survival of patients with metastatic nonsmall cell lung carcinoma (NSCLC).

METHODS. Thirty-four response-evaluable patients, 24 with performance status (PS) 0–1 and 10 with a PS of 2, 30 with Stage IV, and 4 with Stage IIIB NSCLC were treated with gemcitabine 1000 mg/m^2 intravenously and vinorelbine 25 mg/m^2 intravenously (first 15 patients) or 30 mg/m^2 intravenously (next 19 patients) on Days 1, 8, and 15 of a 4-week cycle, if on Day 15 neutrophils were $\geq$ 1500/uL and platelets $\geq$ 100,000/uL. If chemotherapy could not be administered on Day 15, then Day 22 became Day 1 of the next cycle.

RESULTS. When vinorelbine 25 mg/m^2 was given with gemcitabine 1000 mg/m^2, 11 patients received 4-week cycles, 3 patients 3-week cycles, and 1 patient both 3- and 4-week cycles. With vinorelbine 30 mg/m^2 and gemcitabine 1000 mg/m^2, 7 patients received 4-week cycles, 2 patients 3-week cycles, and 10 patients both 3- and 4-week cycles. The partial response rate for 34 patients was 53% (18 patients). Median survival (MS) was 11.1 months, and 1-year survival 50% (17 patients). Patients with PS 0+1 had a MS of 17.5 months compared with patients with PS 2, who had MS of 3.3 months. Patients $<$ 70 years of age had a MS of 18 months, and those $\geq$ 70 years had a MS of 5.5 months.

CONCLUSION. This flexible schedule with gemcitabine and vinorelbine enabled optimal dose delivery and suggested excellent efficacy but less toxicity than treatment with platinum regimens. ***Cancer* 2001;92:830–5.**

KEYWORDS: gemcitabine, vinorelbine, nonsmall cell lung carcinoma, Phase II study.

The incidence of lung carcinoma has grown during the last 20 years. More than 170,000 new cases were diagnosed in the U.S.A. last year. Of these, 80% were of nonsmall cell type. An estimated 156,900 men and women died of lung carcinoma in 2000, accounting for 28% of all cancer deaths according to estimates by the American Cancer Society. The majority of patients with nonsmall cell lung carcinoma (NSCLC) present, at the time of diagnosis, with locally advanced (International Union Against Cancer Stage IIIB) or metastatic (Stage IV) disease.[1] Metaanalysis of clinical trials comparing cisplatin regimens with the best supportive care demonstrated a modest benefit in survival.[2,3] Chemotherapy has also reduced costs for hospitalization and subsequent palliative care.[4] This benefit must be balanced with treatment-related toxicity and quality of life (QOL). New chemother-

apy agents such as gemcitabine and vinorelbine have more activity than older agents for treating NSCLC and are less toxic.[5] Each one has a different mechanism of action. Gemcitabine is an analogue of the pyrimidine antimetabolite cytarabine, and vinorelbine is a new semisynthetic vinca alkaloid. They have at least partially nonoverlapping toxicity. Vinorelbine can cause peripheral neuropathy and phlebitis, and gemcitabine can cause a flu-like syndrome, fever, rash, and elevation of liver enzymes. Both can cause myelosuppression, which usually does not require the use of growth factors or a significant reduction of dose, which can compromise efficacy. Both are administered very easily on an outpatient basis in less than an hour, vinorelbine over 8–10 minutes and gemcitabine over 30 minutes intravenously. Premedication, such as required for taxanes, or hydration, as required for cisplatin, are unnecessary, thus reducing the stay of patients in the clinic, which improves not only the efficiency of the clinic function but also the patients' QOL.[6–8] Administering these two chemotherapy agents weekly allows frequent exposure of tumor cells and multiple targeting of clones with different growth kinetics. It permits dose intensification over the course of 3- or 4-week cycles without increase in hematologic toxicity.

Reports of results with gemcitabine plus vinorelbine have all been for treatments in rigid nonflexible 3- or 4-week cycles.[9] Lorusso[10] reported on 52 evaluable patients who received 3-week cycle treatments. Only 24 patients had Stage IV NSCLC, and 28 had Stage IIIB disease but in the lung and mediastinum only. These Stage IIIB patients are eligible in most North American institutions for protocols with curative intent, usually including both chemotherapy and radiotherapy. In his report, 57% of Stage IIIB patients indeed received radiotherapy, and 86% also received a platinum regimen. It is not surprising that these patients had better survival rates than the usually included Stage IIIB patients with supraclavicular nodes or pleural effusion. In our trial, only 4 patients had Stage IIIB NSCLC, 2 with pleural effusion, 1 with a supraclavicular node, and 1 had superior vena caval (SVC) syndrome and died of progressive disease early after entry into our study. Our report thus reflects not only the results of using a flexible chemotherapy regimen but also the impact of optimal patient-specific drug delivery on response and survival rates in patients with metastatic Stage IV disease.

MATERIALS AND METHODS

Patient Eligibility

Patients, previously untreated with chemotherapy, were eligible for this study if they had histologically or cytologically proven locally advanced Stage IIIB (i.e., pleural effusion or supraclavicular nodes) or metastatic NSCLC (Stage IV). They had to have bidimensionally measurable or unidimensionally evaluable lesions for response. They had to be $\geq$ 18 years old, with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of $\leq$ 2. All patients had to have adequate bone marrow, hepatic, and renal function. Patients with known brain metastases were not eligible for this study. Patients with a history of other malignancies were allowed to enroll if their histology of lung carcinoma was different from their prior cancer and if these patients had been treated curatively and had had no evidence of disease for at least 5 years. Only patients who were accessible for treatment and willing to be followed at a participating center were eligible. A written informed consent, signed by each patient, was obtained. The study's safety parameters included a medical history update and a physical examination, to assess adverse events and toxicity symptoms, and laboratory tests, to assess myelosuppressive, renal, and hepatic toxicity, which were performed before initiating treatment and also before each subsequent treatment. The efficacy parameters were to assess measurable lesions every cycle by physical examination and routine chest X-ray. All other lesions, whether measurable or not, were assessed every 2 cycles by scans or other special procedures. The primary objective of the study was to determine the efficacy of gemcitabine and vinorelbine as a first-line chemotherapy in this group of patients by determining their objective response rate, duration of response, time to disease progression, and survival time on the treatment with the 3- or 4-week flexible cycle. The secondary objectives were to characterize further the toxicity of the gemcitabine and vinorelbine combination in this flexible schedule and to examine our dose modifications for hematologic toxicity for the purpose of optimizing the dosage delivery for each patient.

Treatment

Treatment consisted of gemcitabine 1000 mg/m^2 intravenously administered over a 30 minute intravenous infusion before administration of vinorelbine at 25 mg/m^2 intravenously for 8–10 minutes to the first 15 patients. Then the dose of vinorelbine was increased to 30 mg/m^2 for the next 19 patients. The chemotherapy was administered on Days 1, 8, and 15 of each 4-week cycle. If the Day 15 treatment was omitted because of protocol-defined hematologic toxicity and Day 22 blood counts were acceptable, then Day 22 became Day 1 of the next cycle.[11] Patients with partial response (PR) were treated for 2 cycles after

best response and only 4 cycles were given for stable disease (SD). Therapy was stopped if there was progressive disease or unacceptable toxicity. Toxicities were evaluated according to a graded scale of 1 to 4 using the National Cancer Institute (NCI) Common Toxicity Criteria. Maintenance or second-line chemotherapy was not specified by the protocol; the decision was left to the treating physician.

Response Criteria and Statistical Analysis

Partial response was defined as a $\geq$ 50% decrease in the sum of the products of the diameters of measurable indicator lesions sustained for a minimum of 4 weeks. No simultaneous increase in the size of any lesion or the appearance of a new lesion was permitted to occur. Progressive disease meant a $\geq$ 25% increase in the size of a measurable indicator lesion or the appearance of an unequivocal new lesion. Stable disease (SD) was defined as a $<$ 50% decrease or $<$ 25% increase in the sum of the diameters of indicator lesions sustained for at least 4 weeks. The survival time was defined as the interval between the date of initial dose of chemotherapy and the date of the last follow-up examination for censored observations, or date of death for uncensored observations. Survival distribution curves were computed by the Kaplan–Meier method,[12] and were compared statistically by the log-rank test.[13] The QOL was assessed by the European Organization for Research on the Treatment of Cancer (EORTC) QOL-C30.

RESULTS

Patient Characteristics

The first 15 of the 35 planned response-evaluable patients were entered between March and May 1998, and the next 20 patients were entered between November 1998 and March 1999. Of these, only 19 of the entered patients were evaluable according to preset eligibility criteria, as 1 patient was not response-evaluable. Follow-up, including X-rays and CT scans were refused by this patient after initiation of treatment in spite of the absence of clinical evidence of treatment-related toxicity or progressive disease. Of the 34 response-evaluable patients, 30 had Stage IV and 4 had Stage IIIB disease — 2 with pleural effusion, 1 with supraclavicular nodes, and 1 with rapidly advancing SVC syndrome who died of progressive disease shortly after entering this study. The characteristics of the 34 patients are shown in Table 1. Their median age was 64 years for the 17 men and the 17 women (all between ages 38–74 years), and their median ECOG PS was 1 (range, 0–2); 25 patients had adenocarcinoma, 6 had large cell anaplastic carcinoma, and 3 had squamous cell carcinoma. Sites of the metastatic disease included contralateral lung, pleura, pericardium, bones, adrenal gland, liver, spleen, and other than mediastinal or supraclavicular nodes (Table 2).

TABLE 1
Patient Demographics

Characteristics	No. of patients
Gender	
Males	17
Females	17
Performance status	
0	6
1	18
2	10
Median age (yrs)	64
Range	(38–77)
Stage at diagnosis	
IIIB	4
IV	30
Histology	
Adenocarcinoma	25
Squamous cell carcinoma	3
Large cell anaplastic	6

TABLE 2
Sites of Disease

Lung primary plus other	No. of patients
Lymphadenopathy (supraclavicular, axillary, abdominal)	6
Pleura (effusion ± pleural masses)	17
Bilateral lung masses	11
Pericardium	3
Adrenal	6
Liver	2
Ascites	1
Spleen	1
Bones	9

Toxicity

One hundred thirty-four cycles of chemotherapy were administered to all 34 patients. The hematologic toxicities were mild. There were no Grades 3 or 4 thrombocytopenia; 12 patients had Grade 3 and 1 had Grade 4 neutropenia. No bleeding or febrile neutropenia occurred. Nine patients were transfused with a total of 28 units of packed red cells. Platelet transfusions were not given. Growth factor support was neither given nor needed.

Nonhematologic toxicity was also mild (Table 3). There was only 1 Grade 4 toxicity, an allergic reaction postchemotherapy treatment, with the patient requiring intubation and high-dose intravenous corticosteroids for severe dyspnea secondary to pulmonary infiltrates, which cleared up with the treatment; subsequent treatments for this patient were with vi-

TABLE 3
Hematologic Toxicity and Non-Hematologic Toxicity

	No. of patients		
Toxicity	**Grade 2**	**Grade 3**	**Grade 4**
Hematologic			
Anemia	16	3	0
Neutropenia	6	12	1
Thrombocytopenia	3	0	0
Non-Hematologic			
Asthenia	6	1	0
Peripheral neuropathy	3	1	0
Gastrointestinal symptoms (constipation, diarrhea, nausea)	8	1	0
Phlebitis (superficial)	6	2	0
Leg edema	3	2	0
Infection (pulmonary)	1	2	0
Dyspnea during treatment	3	1	0
Hematuria	0	1	0
Increased liver function tests	2	3	0
Allergic reaction (pulmonary infiltrates)	0	0	1

norelbine only. Infections, unrelated to neutropenia, leg edema, or superficial phlebitis, were easily treated by the usual means (Table 3). Of the first 15 patients on vinorelbine 25 mg/m^2, 11 were able to receive the 4-week cycles, 3 received the 3-week cycles only, and 1 received both the 3-week and 4-week cycles. One patient's doses were reduced by 20% according to the protocol. Fourteen patients received 100% of both drugs. Of the next 19 evaluable patients on vinorelbine 30 mg/m^2, 10 had both 3-week and 4-week cycles; 7 received 4-week cycles only, 5 of whom had only 2 cycles of chemotherapy with gemcitabine and vinorelbine. Two patients received the 3-week cycles. One patient in this group required a 20% dose reduction according to protocol-specified dose modifications on Days 1, 8, and 15 of the treatment. Eighteen patients received 100% of both drugs. A 100% dose of both chemotherapy agents could be delivered if on Days 1 and 15 neutrophils were $\geq 1.5 \times 10^9$/L and platelets were $\geq 100 \times 10^9$/L, and if on Day 8 neutrophils were $\geq 1.0 \times 10^9$/L and platelets were $> 75 \times 10^9$/L, respectively. If no treatment could be given on Day 15, then Day 22 became Day 1 of the next cycle. When the dose of vinorelbine was increased to 30 mg/m^2, 12 of 19 patients could not receive the 4-week cycle only, and there was a trend to the 3-week cycle after the first 2 cycles were administered to a given patient. There was no difference in the administered number of 3-week vs. 4-week cycles of chemotherapy, according to the patient's age or PS.

Response and Survival

Of the 34 patients, 18 (53%) achieved a PR, 6 (17.6%) remained in SD, and 10 (29.4%) progressed while on treatment (Table 4). Patients who received vinorelbine 25 mg/m^2 had a 40% (6 out of 15) PR rate, and for those on 30 mg/m^2, PR was 63.2% (12 out of 19). The difference in PR rate was not statistically significant ($P = 0.179$); however, this may be because of the low number of patients enrolled in the current study. Three patients with PR died in PR at an early stage of their disease. One refused transfusion and died of heart failure, one died of diabetic complications, and another developed a lung abscess (unrelated to neutropenia). The median time to disease progression of the 34 patients was 4.5 months; for the partial responders, it was 6.75 months, and for partial responders and patients with SD, 7 months. The median duration of PR was 5.5 months. The median survival time and 1-year survival rate were 11.1 months and 50% (17 patients), respectively.

TABLE 4
Response and Survival (34 Evaluable Patients)

	No. of patients	%	Months
Partial response	18	53	
Stable disease	6	17.6	
Progressive disease	10	29.4	
1-year survival	17	50	
Median survival	34	100	11.1
Median survival			
Age < 70	23		18
Age ≥ 70	11		5.5
Median survival			
PS 0 + 1	24		17.5
PS 2	10		3.3

PS: Performance status

For the whole cohort, the median survival time was 11.1 months, and the 1-year survival rate was 50% (17 out of 34 patients) (Fig. 1). The 18-month survival, as estimated by the Kaplan–Meier method,[12] was 35%.

The analysis of patients younger than 70 years vs. those 70 years or older confirmed the observation of Lorusso's study.[10] Of the 34 patients, 11 patients ≥ 70 years had a median survival of 5.5 months, whereas younger patients had a median survival of 18 months. There was a significant difference in patient survival distribution by age ($P = 0.0003$) (Fig. 1). Patients ≥ 70 years averaged 2–3 cycles of treatment and often died of complications related to other concomitant morbidities (e.g., diabetes, heart disease, etc.), in spite of achieving PR. Their PR rate was 54.5% (6 patients), similar to the one observed in the younger population (52.2%, 12 out of 23 patients). The survival analysis, according to PS, confirmed the findings of Lilenbaum et al.[14] The 10 patients with a PS of 2 had a median survival of only 3.3 months, in contrast to 17.5 months

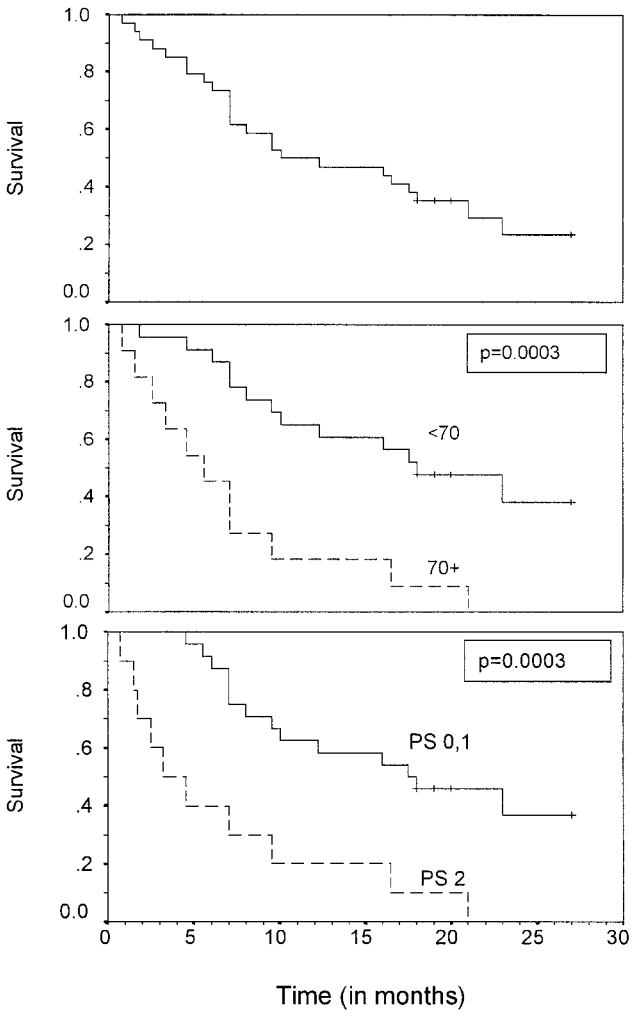

FIGURE 1. Survival distribution curves for all patients (top graph), according to age group (middle graph), and performance status (bottom graph).

for the 24 patients with a PS of 0+1. The difference in survival distribution curves was also highly significant ($P = 0.003$) (Fig. 1).

Further chemotherapy after the prescribed protocol cycles was administered to 17 (50%) patients. At the time of additional treatment, 9 had SD, and 8 had progressive disease. The 9 SD patients (some in PR) received only vinorelbine 30 mgm^2 intravenously on Days 1 and 8, every 3 weeks, immediately after discontinuation of protocol treatment. One patient switched to gemcitabine 1000 mg/m^2 intravenously. on Day 1 and 8, every 3 weeks, after 4 months of treatment with vinorelbine, for an additional 10 months. For these 9 SD patients, the survival, in months, as of November 5, 2000 was 31^+, 31^+, 27^+, 24^+, 23, 21 1/2, 21, 20^+, and 17 $1/2^+$. Of the 8 PD patients, 4 received low-dose cisplatin and vinorelbine, and 3 responded again, 1 stabilized clinically but did not return for evaluation by X-ray or scan; 4 PD patients received vinorelbine single-agent and palliative radiotherapy to brain or bone lesions. The survival, in months, of 8 PD patients as of November 5, 2000 was 24^+, 24^+, 18^+, 17 1/2, 12 1/4, 10, 9 1/2, and 7. The three shortest survivals corresponded to patients progressing on the initial treatment, who did not obtain response or stabilization of their disease and who refused platinum or taxane treatment (as secondary chemotherapy) because of toxicity concerns.

DISCUSSION

Combination chemotherapy for patients with metastatic NSCLC plays an important role, both in extending survival and improving quality of life, especially in patients with a PS of 0+1 and $<$ 70 years of age. The treatment-related toxicity with the newer agents, such as vinorelbine and gemcitabine, is very mild, even when both agents are combined in full doses. Both can be administered to outpatients in less than an hour, thus shortening patients' stay in the clinic because they do not require the premedications, antiemetics, or hydration that are needed when platinum or taxane regimens are given. From our study, we conclude that an optimal drug dose delivery for each patient is important. The flexible 3-week or 4-week schedule with dose modification for hematologic toxicity, which makes drug delivery on Day 8 more feasible, may result in a higher response rate. We have shown that our patients $\geq$ 70 years of age, especially those with a PS of 2, do not benefit from this regimen and most likely would be better treated by a single agent only. Conversely, patients $<$ 70 years of age who have a PS of 0 or 1 should be evaluated in a Phase III trial that compares this regimen to platinum regimens, including carboplatin-containing ones, for differences in both survival and QOL.

Most of the trials, particularly Phase III, demand treatments of up to 6 cycles and do not specify maintenance or second-line treatments. With more active and less toxic agents, which could be administered for 1–2 years or longer, as in our trial, maintenance or second-line chemotherapy may now be an important factor in assessing the 1-year and even 2-year survival for this group of metastatic NSCLC patients.[15] This question should also be answered in Phase III trials that compare maintenance chemotherapy of stable patients (with or without response) to second-line treatment given to patients who responded to first-line chemotherapy but who were given second-line treatment only at the time of disease progression or relapse because many centers now use second-line therapy. Time to disease progression probably represents the best and cleanest parameter to evaluate the efficacy of a given chemotherapy regimen, as further chemotherapy, radiotherapy, or different degrees of palliative treatments given to patients

with metastatic NSCLC after the protocol recommended treatment confound the overall results, especially in what concerns survival.

The flexible schedule of gemcitabine and vinorelbine enables optimal dose delivery to each patient. The results suggest as good a response rate and survival as with cisplatin and gemcitabine or vinorelbine regimens or with carboplatin and paclitaxel regimens but with less toxicity and shorter and easier administration on an outpatient basis.[16–20] Results of randomized Phase III trials are needed to evaluate the advantage of gemcitabine and vinorelbine regimens when compared with cisplatin-based chemotherapy. The National Cancer Institute of Canada trial, conducted with the Italian Group, has finished accrual to such a study. A primary endpoint of this trial will be a QOL analysis. The combination of carboplatin and paclitaxel is being compared to the combination of gemcitabine and vinorelbine in a randomized U.S. trial. A primary endpoint will be QOL as in the Canadian and Italian study. Patients $>$ 70 years should be eligible for trials with combination chemotherapy if their PS is 0 or 1 and if they have no significant comorbidities. The Italian randomized MILES trial of elderly patients compared single-agent gemcitabine or vinorelbine to the combination of gemcitabine and vinorelbine. The results will be reported soon. Finally, it is possible that survival may be prolonged by the administration of a platinum regimen after a nonplatinum regimen, as a good response rate was seen in this group of patients both in the current study and the Lorusso study.[10] Chemotherapy modestly improves survival and QOL of patients with advanced NSCLC. With triplet chemotherapy combinations, as well as in conjunction with novel agents, including antiangiogenesis factors, monoclonal antibodies against epidermoid growth factor receptors, epidermal growth factor vaccines, farnesyltransferase inhibitors, and signal-transduction inhibitors, the overall survival may be improved further. Studies of therapies for patients with metastatic NSCLC are presently being conducted on these biologic modifiers combined with chemotherapy compared with chemotherapy alone.

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