Gemcitabine plus Vinorelbine as First-Line Chemotherapy in Advanced Nonsmall Cell Lung Carcinoma A Phase II Trial

Emilio Bajetta, M.D.
Simonetta Chiara Stani, M.D.
Daniela De Candis, M.D.
Paolo Bidoli, M.D.
Luigi Mariani, Ph.D.
Nicoletta Zilembo, M.D.
Paola Pozzi, M.D.
Giuseppe Procopio, M.D.

Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy.

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Address for reprints: Emilio Bajetta, M.D., Unit of Medical Oncology B, Istituto Nazionale per lo Studio e la Cura dei Tumori, Via Venezian 1, 20133 Milan, Italy.

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BACKGROUND. Response and survival in patients with advanced or metastatic nonsmall cell lung carcinoma (NSCLC) remain poor. As single agents, the nucleoside analog gemcitabine, and the semisynthetic vinca alkaloid vinorelbine, have been shown to be effective in NSCLC and to have a low toxicity profile.

METHODS. Fifty-four chemotherapy-naive patients with NSCLC Stage IIIB (any TN3M0 or T4 any NM0) or IV (any T any NM1) were enrolled in this single-institution Phase II study. Gemcitabine 1250 mg/m^2 and vinorelbine 25 mg/m^2 were both administered on Days 1 and 8 every 3 weeks for up to 9 courses unless disease progression or severe toxicity required their discontinuation.

RESULTS. Partial tumor regression was observed in 16 patients, for an overall response rate of 30% (95% confidence interval, 18.4–46.7%) on an intent-to-treat basis. The median time to progression was 5 months (range, 3–20). The median survival was 12 months (range, 5–42+); 1-year and 2-year survival rates were 49.1% and 17%, respectively. Hematologic toxicity was mild with only 11% of the patients developing Grade 3 neutropenia. None of the patients developed any Grade 4 toxicity.

CONCLUSIONS. The combination of gemcitabine plus vinorelbine is feasible on an outpatient basis. The good activity and tolerability of the regimen make it a suitable candidate for further trials, using platinum-based regimens as comparators and possibly selecting elderly and less fit patients. ***Cancer*** **2000;89:763–8.**
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In Italy, lung carcinoma remains the leading cause of cancer-related death in men and the second in women after breast carcinoma. Although very good survival results can be surgically achieved in early stage non-small cell lung carcinoma (NSCLC), most patients present with advanced or metastatic disease at the time of the diagnosis. In these cases, palliation with radiotherapy and chemotherapy can be used to improve survival and relieve symptoms. The role of chemotherapy has been mainly emphasized over the last decade, ever since the publication of an extensive meta-analysis comparing surgery, radiotherapy, or best supportive care with the same treatment plus chemotherapy.[1] Cisplatin-based regimens had a favorable impact on prognosis in all settings, but particularly in the locally advanced and supportive care setting with a 10% survival benefit at 1 year.

New active agents such as the taxanes, the antimetabolite gemcitabine, the topoisomerase inhibitors, and the latest semisynthetic vinca alkaloid vinorelbine have been tested in NSCLC with very en-

couraging results with respect to response rates.[2] Almost all of these drugs have been combined with cisplatin or its analog carboplatin, but Phase III trials are needed to demonstrate a real survival advantage over single-agent chemotherapy, especially in the case of palliative treatment.

Among the new drugs, vinorelbine and gemcitabine are noteworthy because of their demonstrated activity against NSCLC and particularly their good toxicity profile.

Vinorelbine is a semisynthetic vinca alkaloid that is different from the other drugs in the same family (such as vincristine and vinblastine), because of its relative selectivity for mitotic tubules: the finding that has less toxic effects on axonal microtubules leads to a reduction of vinorelbine-related neurotoxicity.[3] Both in vivo and in vitro studies have demonstrated that vinorelbine is active against many human tumors including NSCLC; this activity seems to be related to its lipophilicity, which ensures a high level of drug distribution inside the cells. Phase II and III trials of vinorelbine as a single agent, usually given on a weekly basis at 25–30 mg/m^2, have shown objective response rates of 15–30% when it is used as first-line chemotherapy in patients with NSCLC.[4] Gemcitabine (2′,2′-difluorodeoxycytidine) is a novel antimetabolite that has a number of advantages over its analogs (such as cytosine arabinoside) with respect to intracellular uptake, prolonged intracellular retention, and antitumor effects in preclinical human cancer models.[5] Several Phase II trials have been performed using gemcitabine as a single agent in advanced NSCLC: at 1000 mg/m^2 weekly $\times$ 3 every 4 weeks, a response rate of 20–23% was obtained with minimal hematologic toxicity. Nonhematologic toxic effects, such as a transient increase in transaminases, mild proteinuria, nausea and vomiting, edema and flu-like syndrome, have been reported but have rarely been clinically significant. Allergic reactions, mostly represented by cutaneous rash of mild to moderate severity, have been reported in approximately 25% of patients.[6,7]

A former Phase I study of the combination of vinorelbine plus gemcitabine recommended a vinorelbine dose of 20–25 mg/m^2 and a gemcitabine dose of 1000–1200 mg/m^2, both administered on Days 1, 8, and 15, with careful monitoring of myelotoxicity.[8] However, using this regimen, the authors found a Grade 3–4 leucopenia in approximately 50% of patients.

In this Phase II trial, we decided to test the same combination of vinorelbine and gemcitabine, at a different schedule to find an active and well tolerated regimen, which could be easily administered on an outpatient basis, for the palliative treatment of NSCLC. Dose and schedule of administration of gemcitabine and vinorelbine were chosen on the basis of previous experience with single agents and with each drug in association to cisplatin.

PATIENTS AND METHODS

Between October 1996 and October 1998, a consecutive sample of 54 patients entered the study. All of them gave their informed consent, and the study was conducted according to the ethical principles laid down in the latest version of the Declaration of Helsinki and the guidelines for good clinical practice.

Eligibility Criteria

Before entering the study, all of the patients had to meet the following criteria: a histologic or cytologic diagnosis of NSCLC; clinical Stage IIIB or IV according to the American Joint Committee of Cancer; clinically documented measurable disease; no previous chemotherapy; no previous or concomitant radiotherapy unless the irradiated area was not the only source of measurable disease; an age of 18–75 years; no second malignancies (except adequately treated in situ cancer of the cervix or nonmelanomic skin carcinoma); an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 for patients younger than 70 years and 0–1 for 70–75 year olds; a life expectancy of greater than 3 months; the absence of cerebral metastasis at computed tomography (CT) scan or magnetic resonance imaging; adequate bone marrow function (leukocyte $\geq$ 4000/mm^3; platelets $\geq$ 100,000/mm^3; hemoglobin $>$ 100 g/L); adequate renal function; adequate liver function (without hepatic metastasis: bilirubin $\leq$ 1.25 times the normal value, transaminases $\leq$ 2.5 times the normal value, cholinesterase $>$ 1200 U/L, alkaline phosphatase $<$ 2.5 times the normal value; with hepatic metastasis: bilirubin $\leq$ 1.5 times the normal value, transaminases $\leq$ 5 times the normal value, cholinesterase $>$1200, alkaline phosphatase $<$ 2.5 times the normal value); a negative pregnancy test and adequate contraception for women of childbearing age; written informed consent; ability to comply with the protocol follow-up.

Therapy Schedule

Gemcitabine 1250 mg/m^2 intravenously (i.v.) over 30 minutes and vinorelbine 25 mg/m^2 i.v. bolus were both administered on Days 1 and 8. The cycles were repeated every 21 days. Premedication with metoclopramide was administered to prevent chemotherapy-related emesis; hydrocortisone 125 mg was administered before gemcitabine to prevent allergic reactions.

In the event of a response or stable disease, the chemotherapy could be administered for a total of

nine courses. Toxicity was assessed after each administration, and the chemotherapy had to be discontinued in the presence of any Grade 4 toxicity or 2 consecutive episodes of Grade 3 toxicity.

Baseline Data and Follow-Up Assessment

Before enrollment, the patients' history and the results of a physical examination, body weight, and the measurement of indicator lesions were recorded. In addition, the following assessments were required: blood chemistry and blood cell counts, chest X-rays and a chest CT scan, liver ultrasound or CT scan, bone scan, and brain CT scan. Magnetic resonance imaging was performed only if necessary for tumor measurement. The patients were considered to have measurable disease only if at least one lesion could be clearly delineated in two dimensions.

Response and Toxicity Criteria

Responses were evaluated according to World Health Organization criteria. A complete response (CR) required the disappearance of all known lesions observed on 2 different occasions separated by at least 4 weeks, and no appearance of new lesions. A partial response (PR) required a greater than 50% reduction in the sum of the products of the longest perpendicular dimensions of all measurable lesions. Regressions observed by serial evaluations needed to persist for at least 4 weeks to be classified as a PR.

All toxicities were evaluated according to the National Cancer Institute Common Toxicity Criteria.

Statistical Considerations

The primary objective of this study was to assess the probability of a response (CR or PR) to the gemcitabine plus vinorelbine combination. The study was planned according to Simon's optimal 2-stage design to compare a response probability of 20% under the null hypothesis and 40% under the alternative hypothesis, with a 5% alpha level and a power of 90%.[9] With this design, the treatment must be rejected if less than 5 responses are observed at the end of the first stage (19 patients) or less than 16 responses at the end of the second stage (54 patients overall). The 95% confidence interval for response probability was computed as proposed by Atkinson and Brown.[10]

The time to disease progression and time to death were calculated from the date of the start of the first cycle to the date of the event occurrence, or the date of the last visit in living progression free patients.

The progression free and overall survival curves were obtained using the Kaplan–Meier method.[11] All of the accrued patients were included in the analysis according to the intent-to-treat principle. Response probability also was estimated by excluding the patients who failed to complete at least three cycles of chemotherapy for reasons other than tumor progression (standard analysis).

TABLE 1
Main Characteristics of Entered Patients (n = 54)

Characteristic	No. of patients	%
Median age (range)	59 (39–75)	
ECOG (performance status)		
0	12	22
1	41	76
2	1	2
Gender		
Male	44	81
Female	10	19
Histology		
Epidermoid	16	30
Adenocarcinoma	28	52
Others	10	18
Stage		
IIIB	18	33
IV	36	67
No. of metastatic sites		
< 2	23	43
≥ 2	31	57

ECOG: Eastern Cooperative Oncology Group.

RESULTS

The main characteristics of the study patients are provided in Table 1. Fifty-four patients with advanced NSCLC were enrolled in the trial. Most patients (67%) had Stage IV disease with 2 or more disease sites (57%), mainly pulmonary and lymph node disease. All 54 patients were evaluable for toxicity; 51 were evaluable for response. Of the three patients unevaluable for response, two developed intercurrent disease unrelated to chemotherapy after the second course, and one refused chemotherapy after the first course; all of these events occurred before tumor reassessment.

None of the patients was lost to follow-up.

The median duration of follow-up was 11 months (range, 5–42+). The tumor responses calculated according to the intent-to-treat analysis and in the evaluable patient population are shown in Table 2. There were no CRs. Partial response was observed in 16 patients (according to intent-to-treat analysis: 30%; 95% confidence interval [CI], 18.4–46.7). The median duration of the PR was 14 months (range, 10–42+). Twelve responses were observed among the 36 patients with Stage IV disease (response rate, 33%); 4 responses were observed among the 18 remaining patients with Stage IIIB disease (response rate, 22%).

TABLE 2
Clinical Efficacy

Clinical result	No. of patients (n = 54)	%
Intent-to-treat analysis		
Complete response	0	—
Partial response	16	30
Stable disease	12	22
Progressive disease	26	48
Standard analysis		
Evaluable	51	
Not evaluable	3	6
Complete response	0	—
Partial response	16	31
Stable disease	12	24
Progressive disease	23	45

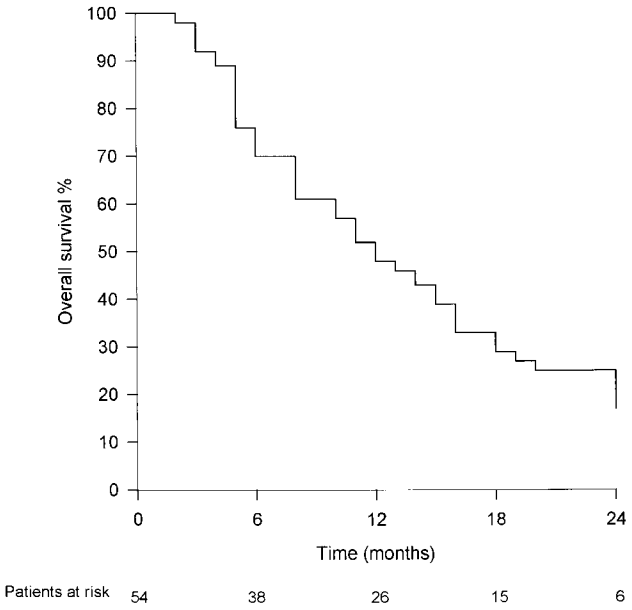

FIGURE 1. Kaplan–Meier survival curve is shown.

Stable disease occurred in 12 patients (24%) and lasted a median of 12.5 months (range, 5–28).

The overall survival and progression free survival curves are shown in Figures 1 and 2, respectively. Median survival was 12 months (range, 5–42+); 1- and 2-year survival rate were 49.1% and 17%, respectively.

The toxicity data are given in Table 3. Grade 3 neutropenia and thrombocytopenia were observed in 11% and 2%, respectively, of the patients. None of the patients experienced any Grade 4 toxicity.

The median number of administered courses was 6 (range, 1–9). From a total of 286 courses, 8 required a 25% dose reduction of both drugs because of hematologic toxicity. The nonhematologic toxicity was mild and consisted mainly of flu-like syndrome, constipation, and injection site reactions; all recovered without

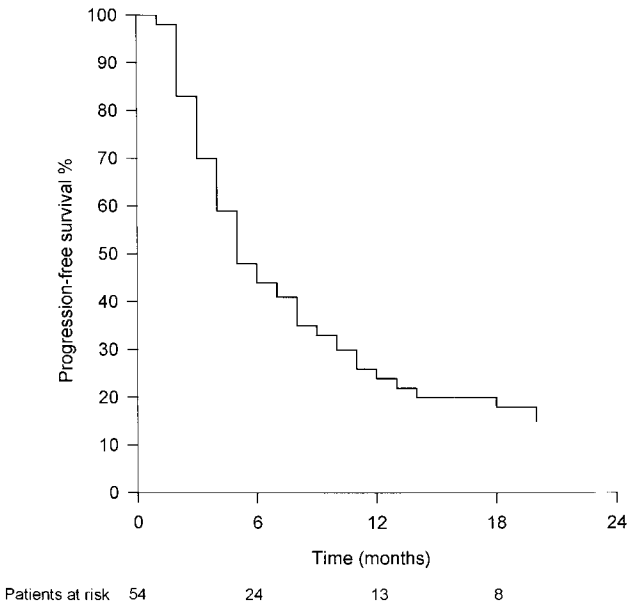

FIGURE 2. Kaplan–Meier progression free survival is shown.

TABLE 3
Toxicity Using National Cancer Institute Common Toxicity Criteria

	Grade 1–2		Grade 3	
Symptom	n	%	n	%
Nausea/vomiting	10	19	1	2
Alopecia	3	6	—	—
Mucositis	3	6	—	—
Neurotoxicity	5	9	—	—
Constipation	12	22	3	6
Fatigue	6	11	1	2
Liver toxicity	3	6	1	2
Phlebitis	7	13	—	—
Flu-like syndrome	10	19	5	9
Skin rashes	1	2	—	—
Anemia	5	9	1	2
Neutropenia	5	9	6	11
Leucopenia	2	4	2	4
Thrombocytopenia	2	4	1	2

requiring therapy. Vinorelbine-related neurotoxicity was observed in 5 of the 54 patients (9%), but its severity did not exceed Grade 2. There was an increase in platelet counts in 33 of the 54 patients (61%) with a median platelet count of $582 \times 10^3/mm^3$ (normal value, $140–440 \times 10^3/mm^3$) and a range of $469–1373 \times 10^3/mm^3$. The increase in platelet levels was observed after the first cycle of chemotherapy in all cases and lasted until the end of treatment. The median platelet count in all subjects was of $273 \times 10^3/mm^3$ at baseline, $549 \times 10^3/mm^3$ at the end of the first cycle (Day 21), and $268 \times 10^3/mm^3$ 1 month after the last cycle. The difference versus baseline was significant at

the end of the first cycle ($P = 0.0001$ at the signed rank Wilcoxon test) but not 1 month after the last cycle ($P = 0.3871$).

DISCUSSION

Most of newly diagnosed patients with NSCLC have inoperable disease at presentation, either because it is locally advanced or metastatic or because of coexistent medical conditions such as cardiac disease or chronic bronchopneumopathy. Over the last 2 decades, there have been many efforts to improve survival in patients with unresectable NSCLC. Although increased response rates have been achieved using polychemotherapy, the improvement was only modest in comparison with single-agent regimen.[12] A recent meta-analysis comparing the effects of single-agent versus combination chemotherapy on response rates, toxicity, and the survival of patients with advanced NSCLC considered data from 25 randomized trials. It was found that combination chemotherapy led to a 2-fold increase in the objective response rate, but also a 3.5-fold increase in the risk of treatment-related deaths. A significant increase in both hematologic and nonhematologic toxicity also was observed.[13]

Encouraging results have been obtained using new combinations such as cisplatin-gemcitabine and cisplatin-vinorelbine,[14,15] or carboplatin-paclitaxel,[16] with response rates of greater than 40% in previously untreated patients with advanced NSCLC. Unfortunately, these regimens are generally associated with considerable toxicity, which may not be completely justified in extensively diseased patients for whom the primary treatment goal is palliation. Recent attention to clinical benefit has led to the consideration of Phase II and III clinical trials endpoints, such as the careful assessment of toxic effects and the impact of quality of life on survival.[17]

In this Phase II study, we evaluated the activity and toxicity of the combination of two cytotoxic drugs that have been widely studied over the last decade as single agents or in association with cisplatin in the treatment of NSCLC. Our primary objective was to find a feasible and active regimen that could be easily administered as palliative treatment on an outpatient basis. Gemcitabine and vinorelbine represent an attractive combination for clinical evaluation, because each is directed against a different cell target: the inhibition of DNA synthesis for gemcitabine, and selective activity against mitotic tubules in the case of vinorelbine. When used as single agents, gemcitabine and vinorelbine have led to encouraging results and have the added benefit of mild toxicity profiles.[7,18]

The results with respect to response rate and survival were encouraging in our trial: the response rate (30%) was similar to that obtained using more aggressive cisplatin-containing regimens, and the overall 1-year survival was similar to that reported in other trials using cisplatin-based polychemotherapy. In a Phase I trial using gemcitabine combined with vinorelbine in untreated patients, Krajnik et al.[8] obtained a similar response rate in the higher dose levels (32%) but with a considerable hematological toxicity, probably related to the higher dose intensity. In fact, the Phase I trial used a Day 1, 8, 15, and 28 schedule of administration of both drugs in contrast to the Day 1, 8, and 21 schedule of our study.

In particular, in our experience the combination of gemcitabine and vinorelbine was very well tolerated because no Grade 4 toxicity was observed. Note that most of the patients had Stage IV disease (67%) and an ECOG performance status of 1 or 2 (77%): the activity and the tolerability of the chemotherapy in these patients overlapped those observed in the patients with less extensive disease (Stage IIIB) and a better performance status.

Note also that most of our patients experienced increased platelet counts from the first administration of gemcitabine and vinorelbine until the end of treatment. Such variation was significant at statistical analysis. This unexpected phenomenon, which to the best of our knowledge has not been reported in the literature concerning the single agents, could have been due to an interaction between the drugs. In any case, the abnormal increase in the number of platelets did not cause any vascular disease as appropriate prophylactic therapy with platelet aggregation inhibitors was applied.

In conclusion, combined chemotherapy with gemcitabine and vinorelbine is feasible and well tolerated in an outpatient setting. The proposed schedule and doses may be of interest for further trials, including a randomized study comparing it with cisplatin regimens in elderly or less fit patients.

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