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ORIGINAL ARTICLE

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# Gemcitabine and vinorelbine in patients with advanced lung cancer: preclinical studies and report of a phase I trial

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**Abstract** *Purpose*: This study was designed to assess the efficacy of gemcitabine plus vinorelbine using the mouse Lewis lung carcinoma model and to translate this regimen to a phase I clinical study of these two agents in patients with advanced lung cancer. *Materials and methods*: Using the mouse Lewis lung cancer model, employing growth delay and isobologram analysis, we demonstrated that gemcitabine, in combination with vinorelbine, produced additive activity with little increased toxicity over a wide range of doses. At the highest dose level studied, antagonism was observed. Based on these results, we initiated a phase I study of this combination at the Dana Farber Cancer Institute (DFCI) in patients with untreated or once pretreated non-small-cell lung cancer (NSCLC) or once pretreated small-cell lung cancer (SCLC). Vinorelbine (given in an intravenous bolus) and gemcitabine (given in a 30-min infusion) were initially administered to patients at a dose of 15 mg/m$^2$ and 500 mg/m$^2$, respectively, on days 1, 8, and 15 of a 28-day cycle. Seven dose levels were subsequently explored over the course of the study. There was no intrapatient dose escalation. *Results*: From November 1996 to March 1998, 40 patients were enrolled: 32 had NSCLC, 5 had SCLC and 3 had mixed disease (both SCLC and NSCLC). The patients were evenly divided by gender, the median age was 58 years (range 38 to 73 years), and the median ECOG performance status was 1 (range 0 to 2). All patients had normal renal and hepatic function and none had previously received gemcitabine or vinorelbine. Toxic reactions included mild to moderate fatigue, nausea, constipation, and, most significantly, neutropenia and thrombocytopenia. Phlebitis was a major problem when central venous lines were not used with 15% grade 1/2 events. The day-15 dose was held in 43% of patients at the expanded dose. No true maximum tolerated dose was reached after completion of seven dose levels. Dose level 4 (22.5 mg/m$^2$ vinorelbine and 1000 mg/m$^2$ gemcitabine) was chosen for expansion and future study due to the potential increased ability of patients to receive the full doses on time. *Conclusions*: We conclude that this drug combination and dosage are feasible and have potential as either a front- or second-line chemotherapeutic regimen for advanced lung cancer, and phase II/III trials should be performed. However, hematologic toxicities, as found in this study, could probably be reduced with treatment on days 1 and 8 every 21 days, and current literature would suggest this to be the preferred schedule.

**Keywords** Gemcitabine · Vinorelbine · Non-small-cell lung cancer · Preclinical studies · Combination therapy

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## Introduction

Lung cancer is the leading cause of adult cancer deaths in the United States [18], with non-small-cell lung cancer (NSCLC) accounting for 80% of the cases. The majority of lung cancer patients present with advanced disease. Recent clinical guidelines support the role of systemic chemotherapy in selected patients [1]. A modest survival benefit has been demonstrated in multiple meta analyses for patients who receive cisplatin-based chemotherapy compared with best supportive care [20]. In small-cell lung cancer (SCLC), initial response rates to chemotherapy are better, but the majority of patients still relapse. More effective therapeutic drug combinations are therefore needed [6, 12, 14, 16, 19, 24, 28].

A number of new non-platinum agents (taxanes, irinotecan, gemcitabine, and vinorelbine) with improved activity in NSCLC and SCLC have become available [13, 26]. Randomized trials, comparing combinations of these new chemotherapy agents with cisplatin alone or cisplatin in more traditional combinations, have shown a modest therapeutic advantage to the new-agent-plus-platinum combinations in NSCLC [3, 5, 25, 30, 34]. No particular new-agent regimen, however, is clearly superior, which leaves the clinician with multiple therapeutic options [17]. The opportunity to explore the feasibility and efficacy of non-platinum-containing regimens now exists both in SCLC and NSCLC.

Gemcitabine (difluorodeoxycytidine) is a pyrimidine analog that was initially synthesized as a potential antiviral drug [22]. It is active against a variety of solid tumors in vitro and several human tumor xenografts [23]. Phase II studies in untreated NSCLC patients have demonstrated consistent response rates of approximately 20% with mild toxic reactions (myelosuppression, transient transaminase elevations, fever, dyspnea, 'flu-like symptoms) [31]. Phase III studies, comparing gemcitabine-cisplatin combinations with cisplatin alone or more traditional cisplatin-containing regimens, have demonstrated that the gemcitabine-cisplatin combinations are active regimens having response rates ranging from 31% to 41% [7, 9, 30].

Vinorelbine is a semisynthetic vinca alkaloid whose antitumor activity is related to its ability to depolymerize microtubules and disrupt the mitotic spindle apparatus [29]. It has a higher affinity for mitotic tubules than for axonal microtubules, which probably accounts for its better efficacy and improved toxicity profile [4]. A number of phase II trials in NSCLC have shown single-agent response rates of 8% to 37% [8, 11, 15, 27]. In a large pivotal European phase III trial, single-agent vinorelbine was compared with vinorelbine plus cisplatin and the European standard of vindesine plus cisplatin [25]. Vinorelbine plus cisplatin demonstrated significantly improved response rates compared with those of vindesine plus cisplatin and single-agent vinorelbine (30% vs 19% and 14%, respectively). The median survival duration was also significantly better in the vinorelbine-plus-cisplatin arm (40 weeks vs 32 weeks and 31 weeks, respectively). In a subsequent phase III trial in elderly patients with NSCLC, single-agent vinorelbine therapy was compared with best supportive care, and showed improvements in cancer-related symptoms as well as median survival duration with the vinorelbine arm [2].

To identify novel non-platinum-containing regimens, we explored the feasibility and efficacy of combining gemcitabine and vinorelbine for advanced lung cancer. While this phase I study was aimed mostly at NSCLC, we did include several patients with once pretreated SCLC given the limited treatment options for this population [6, 12, 14, 16, 19, 24, 28]. Cisplatin therapy may not be appropriate for patients with preexisting neuropathy, renal insufficiency, or congestive heart failure. Therefore, alternative non-platinum-containing chemotherapy regimens having comparable activity would be useful. If equally efficacious, it is possible that non-platinum combinations could replace platinum due to ease of administration and potentially fewer toxic reactions. Since gemcitabine and vinorelbine both have reasonable single-agent activity in NSCLC and SCLC and are given on a weekly schedule, they represent a novel non-platinum, non-taxane combination. We demonstrated a solid preclinical rationale using the mouse Lewis lung carcinoma model and, subsequently, demonstrated clinical tolerability as well as efficacy using this combination in our phase I clinical study.

## Materials and methods

### Preclinical studies

#### *Drugs*

For our preclinical studies, gemcitabine was provided by Lilly Oncology (Indianapolis, Ind.) and vinorelbine was obtained as a gift from Glaxo Wellcome (Research Triangle Park, N.C.). Clinical grade material was used for all animal studies.

#### *Tumor growth delay*

Lewis lung carcinoma was carried in male C57BL mice (Taconic, Germantown, N.Y.) [33]. For each experiment, $2\times10^6$ tumor cells prepared from a brei of several stock tumors were implanted subcutaneously into the legs of conventional 8- to 10-week-old mice on day 0. When the Lewis lung tumors were approximately 100 $mm^3$ in volume, which was on or about day 7 after tumor cell implantation, therapy was initiated. Gemcitabine (40, 60, or 80 mg/kg) was administered by intraperitoneal (i.p.) injection on days 7, 10, and 13 while vinorelbine was administered by i.p. injection on one of three schedules: (1) 10.0 mg/kg on day 7, (2) 10.0 mg/kg on day 7 and 5.0 mg/kg on day 13, and (3) 7.5 mg/kg on days 7, 10, and 13. The combination regimen included vinorelbine (10 mg/kg on day 7 and 5 mg/kg on day 13) administered along with gemcitabine (40, 60, or 80 mg/kg on days 7, 10, and 13).

The progress of each tumor was measured twice a week until it reached a volume of 500 $mm^3$. Each treatment group consisted of five animals, and each experiment was repeated three times. Tumor growth delay were defined as the mean $\pm$ SE days to reach a size of

500 $mm^3$ in the treatment group compared with that in the untreated controls.

*Assessment of lung metastases*

The external lung metastases in animals treated as described above were counted manually on day 20 after tumor implantation and scored if they were greater than or equal to 3 mm in diameter. The data are presented as the mean value from 6 to 12 pairs of lungs. Typically, untreated control animals died of lung metastases on day 21 to 25 after injection.

*Data analysis*

Using the method described by Deen and Williams [10], isobolograms were generated for the special case in which the dose of one agent is held constant (Fig. 1). This method produces envelopes of additive effect for different levels of the variable agent. Dose-response curves for each agent alone were first generated. The envelopes of additivity were then generated from a series of effective curves derived from the complete dose-response curves for each agent alone. Overall, combinations that produce the desired effect and are within the envelope boundaries are considered additive; those displaced to the left are supra-additive while those displaced to the right are subadditive. Statistical comparisons for the assays were carried out using Dunnett's multiple comparisons test after a significant effect was found by analysis of variance [32].

Phase I clinical study

*Eligibility*

Patients were required to have a confirmed diagnosis of stage IIIB or IV NSCLC (untreated or previously treated using one regimen) or SCLC (any stage, previously treated using one regimen). A minimum age of 18 years with an ECOG performance status of 0 to 2 was required. Patients over the age of 70 years were required to have a performance status of 0 to 1. A computed tomography scan of the head was required upon study entry to evaluate for brain metastasis. Patients having central nervous system metastases were allowed if the metastases had been previously treated using radiation therapy. Radiotherapy or chemotherapy was not allowed in the 3 weeks prior to study entry and prior therapy, using either vinorelbine or gemcitabine, was not allowed. A central line catheter was strongly encouraged for agent administration but not required. Written informed consent was obtained from all patients.

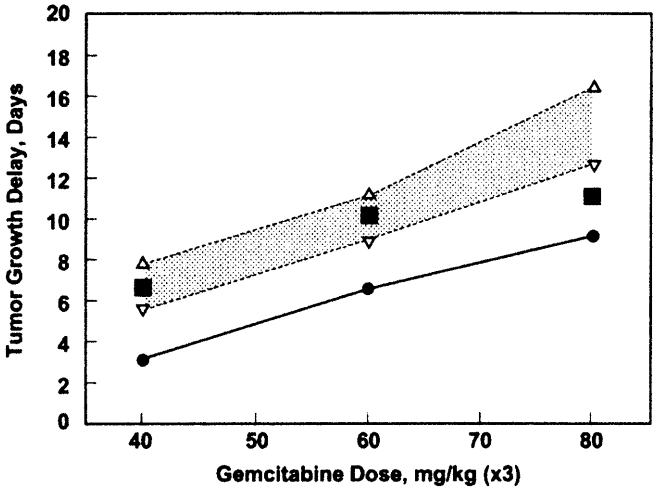


**Fig. 1** Growth delay of the Lewis lung carcinoma produced by a range of doses of gemcitabine alone (●) or in combination with vinorelbine (15 mg/kg total dose; ■). The shaded area marked by Δ and ∇ is the envelope of additivity determined by isobologram analysis

*Treatment plan*

Gemcitabine and vinorelbine were given on days 1, 8, and 15 of a 28-day schedule as they are most often administered as single agents. At the time of our study, data for days 1 and 8 administrations of a 21-day schedule were not available in the published literature. One cycle was defined as 28 days. The starting doses were 50% of each typical single-agent dose and the dose-escalation scheme is displayed in Table 1. Because of the vesicant properties of vinorelbine, it was given before gemcitabine since preclinical studies of drug sequence did not suggest any reason for the alternative. When given peripherally, vinorelbine was administered via intravenous (i.v.) push over 10 min with a nurse checking for blood return after every 1 ml administered as required by our institutional policy. Complaints of burning or discomfort by the patient or loss of blood return resulted in discontinuing the i.v. line and starting a new line to complete administration. Gemcitabine was administered as an i.v. bolus over 30 min.

Dose-limiting toxicity (DLT) was defined as any of the following reactions experienced during the first cycle of therapy: (1) grade 4 nonhematologic toxicity, (2) grade 4 hematologic toxicity (except neutropenia or thrombocytopenia), and (3) unacceptable neutropenia defined as an absolute neutrophil count (ANC) of less than 500/μl or a platelet count less than 20,000/$mm^3$ for more than 7 days. Doses on days 8 and 15 were modified as follows: for ANC 1–1.5×$10^3$/μl or platelet count 50–75×$10^3$/μl, each drug was reduced by 25%; for ANC $< 1\times10^3$/μl or platelet count $< 50\times10^3$/μl, both drugs were held. Three patients were studied at each level with expansion to six patients if one exhibited a DLT. Patients were considered evaluable for response if they completed at least 8 weeks on protocol although toxicity was evaluated in all patients receiving the drugs regardless of whether they completed even one dose. Doses held due to toxicity were not made up.

*Statistical methods*

Overall survival curves were estimated using the Kaplan-Meier method. Response was defined as a greater than 50% decrease in tumor volume as measured by the products of the two largest diameters of all measurable lesions. Progressive disease was defined as a greater than 25% increase in total tumor volume or the appearance of a new lesion. Stable disease was defined as those who did not fit either of those classifications.

## Results

### Preclinical combination of agents

The mouse Lewis lung carcinoma model was selected for the preclinical study of the combination of gemcitabine

**Table 1** Dose escalation scheme

| Dose level | Vinorelbine ($mg/m^2$/week) | Gemcitabine ($mg/m^2$/week) |
|---|---|---|
| 1 | 15.0 | 500 |
| 2 | 19.0 | 625 |
| 3 | 22.5 | 750 |
| 4 | 22.5 | 1000 |
| 5 | 25.0 | 1000 |
| 6 | 30.0 | 1000 |
| 7 | 30.0 | 1250 |

and vinorelbine because this tumor is a NSCLC that metastasizes avidly to the lungs from a subcutaneous (s.c.) implant of the tumor in the syngeneic host. Gemcitabine was active against Lewis lung carcinoma, having activity that increased as the dose of the drug increased (nontoxic doses only) (Table 2). Vinorelbine was administered via i.p. injection to animals bearing Lewis lung carcinoma using three different schedules: 10.0 mg/kg on day 7, 10.0 mg/kg on day 7 and 5.0 mg/kg on day 13, and 7.5 mg/kg combined with each of three dosage levels of gemcitabine administered on days 7, 10, and 13. Both gemcitabine and vinorelbine produced significant growth delay as single agents and decreased the number of lung metastases, with gemcitabine being the more active drug in this model. The combination of the two drugs was equally impressive and gemcitabine doses of 40 and 60 mg/kg resulted in additive tumor growth delay (Table 2). However, at the highest dose of gemcitabine (80 mg/kg), the combination resulted in less than additive tumor growth delay, suggesting antagonism or potential toxicity of this combination (Fig. 1) and the need for a phase I trial.

At each of the three doses tested, gemcitabine was highly effective in decreasing the number of lung metastases on day 20 after tumor cell implantation (Table 2). Specifically, the mean number of lung metastases in the gemcitabine-treated animals was 10 (range 1.0–1.5), while the mean number in the untreated control animals was 35. Vinorelbine was also effective against lung metastases on day 20. Importantly, the combination of gemcitabine and vinorelbine was most effective in decreasing the number of lung metastases in animals bearing Lewis lung carcinoma on day 20 after s.c. tumor cell implantation: animals receiving the combination regimen had a mean of less than one lung metastasis. Isobologram analysis, as described in the Materials and methods section, is shown in Fig. 1 and was used to determine the additivity synergy of the combination. The growth delay was plotted as a function of the gemcitabine dose using a fixed dose (15 mg/kg) of vinorelbine. Both the 40- and 60-mg/kg (×3) doses of gemcitabine fell within the envelope of additivity; however, the 80 mg dose was antagonistic. No effect of drug sequence was seen in this model. The main conclusion of these studies was the additive nature of this combination, and we elected to move immediately to a clinical trial.

**Table 2** Growth delay produced by gemcitabine/vinorelbine combinations and the number of lung metastases in the mouse Lewis lung carcinoma model described in Materials and methods. Control animals had, by definition, no growth delay and on average 35 lung metastases per animal. The results as shown represent ±1 standard deviation for gemcitabine at three doses, vinorelbine at three doses, and vinorelbine plus gemcitabine. For the combination, the dose of vinorelbine was held constant at 10 mg/kg on day 7 and 5 mg/kg on day 13 and was combined with three different doses of gemcitabine

| Treatment group | Growth delay (days) | No. of lung metastases |
|---|---|---|
| Control | – | 35.0 |
| Gemcitabine | | |
| 40.0 mg/kg (days 7, 10, 13) | 3.2 ± 0.3 | 1.5 |
| 60.0 mg/kg (days 7, 10, 13) | 6.6 ± 0.5 | 1.0 |
| 80.0 mg/kg (days 7, 10, 13) | 9.2 ± 0.7 | 1.0 |
| Vinorelbine | | |
| 10.0 mg/kg (day 7) | 1.5 ± 0.3 | 11.0 |
| 10.0 mg/kg (day 7) + 5 mg/kg (day 13) | 3.1 ± 0.3 | 10.5 |
| 7.5 mg/kg (days 7, 10, 13) | 4.9 ± 0.5 | 11.0 |
| Vinorelbine (10 mg/kg day 7 + 5 mg/kg day 13) + gemcitabine | | |
| 40.0 mg/kg (days 7, 10, 13) | 6.6 ± 0.6 | 0.8 |
| 60.0 mg/kg (days 7, 10, 13) | 10.2 ± 0.9 | 0.5 |
| 80.0 mg/kg (days 7, 10, 13) | 11.1 ± 1.2 | 0.0 |

## Patient characteristics

Table 3 shows the characteristics of 40 patients enrolled in this trial as described in the Materials and methods section. All 40 patients were entered onto this study at DFCI from November 1996 to March 1998.

According to the dosing schedule (Table 1), three patients received each dose level with increases based on the need to add or replace patients to a cohort due to toxicity or response inevaluability (inability to complete

**Table 3** Selected baseline patient characteristics (*NOS* not otherwise specified)

| | No. | % |
|---|---|---|
| Dose level | | |
| 1 | 5 | 12.5 |
| 2 | 3 | 7.5 |
| 3 | 3 | 7.5 |
| 4[a] | 14 | 35.0 |
| 5 | 4 | 10.0 |
| 6 | 8 | 20.0 |
| 7 | 3 | 7.5 |
| Sex | | |
| Male | 20 | 50.0 |
| Female | 20 | 50.0 |
| Performance status | | |
| 0 | 14 | 35.0 |
| 1 | 23 | 57.5 |
| 2 | 3 | 7.5 |
| Cancer stage | | |
| IIIb | 7 | 17.5 |
| IV | 33 | 82.5 |
| Disease type | | |
| NSCLC | 32 | 80.0 |
| SCLC | 5 | 12.5 |
| Mixed NSCLC and SCLC | 3 | 7.5 |
| Histology | | |
| Squamous | 4 | 10.0 |
| Adenocarcinoma | 20 | 50.0 |
| Large cell | 6 | 15.0 |
| Mixed NSCLC and SCLC | 3 | 7.5 |
| Bronchoalveolar | 1 | 2.5 |
| SCLC | 5 | 12.5 |
| Poorly differentiated, NOS | 1 | 2.5 |
| Prior chemotherapy | | |
| No | 14 | 35.0 |
| Yes | 26 | 65.0 |

[a]Dose level chosen for further study

cycle 1). Thus, 5 patients (12.5%) received dose level 1 (2 were inevaluable for response), 3 (7.5%) received dose level 2, 3 (7.5%) received dose level 3, 14 (35.0%) received dose level 4 (expanded for further study), 4 (10.0%) received dose level 5 (1 additional patient was added while the study team awaited Institutional Review Board amendment), 8 (20.0%) received dose level 6 (5 patients were added because of one DLT and one dropped out for non-compliance), and 3 (7.5%) received dose level 7.

Patients were divided equally by gender and had a median age of 58 years (range 38–73 years) and median performance status of 1 (range 0–2); only three patients (7.5%) presented with a performance status of 2. Distant metastases were evident in 82.5% of the patients, while locally advanced disease was present in 17.5%. Of the 40 patients, 32 (80%) presented with NSCLC, 5 (12.5%) had SCLC, and 3 (7.5%) had mixed disease, and 26 (65%) had received prior chemotherapy (including all those having SCLC or mixed disease) while 14 patients (35%) were chemotherapy-naive. This included two IIIb patients who were not felt to be primary radiation therapy patients. Among the NSCLC patients, the largest single disease type was adenocarcinoma (50%); other disease types are listed in Table 3.

## Treatment and toxicity

The primary endpoint of this study was assessment of the toxicity of this novel combination of gemcitabine and vinorelbine. Table 4 shows the frequency of moderately severe (grade 3), severe (grade 4), and fatal (grade 5) toxic reactions in the study by the number of patients. The most frequent toxic reaction was neutropenia, with ten patients (25%) experiencing grade 3 neutropenia and four patients (10%) experiencing grade 4 neutropenia. Seven patients (17.5%) experienced moderately severe grade 3 pain at the tumor site, shoulder, or back; six patients (15.0%) experienced grade 3 fatigue; and six patients (12.5%) experienced grade 3 dyspnea or shortness of breath. Grade 4 diarrhea (DLT) occurred in one patient (possibly related to viral enteritis since family members were also ill), requiring removal from the study and the addition of three patients to this dose level. One patient on dose level 4 was noncompliant with antiemetics and had grade 4 emesis requiring removal from the study and the addition of two patients. There were two (5%) fatal (grade 5) toxic reactions, both of which were pulmonary: one patient suffered a pulmonary embolism of uncertain etiology that was suspected to be related to malignant disease while the second patient suffered from acute respiratory distress syndrome that was felt to be possibly gemcitabine-related (see Discussion). The first patient died during cycle 3, week 3, and the second patient died during cycle 5, week 3. Toxicity by dose level is shown in Table 5.

**Table 4** Toxic reaction incidence by patient

| Reaction | Grade | | |
|---|---|---|---|
| | 3 | 4 | 5 |
| Neutropenia | 10 | 4 | 0 |
| Thrombocytopenia | 4 | 0 | 0 |
| Nausea | 2 | 0 | 0 |
| Vomiting | 2 | 1 | 0 |
| Diarrhea | 1 | 1 | 0 |
| Neurologic | 1 | 0 | 0 |
| Fever/neutropenia | 1 | 0 | 0 |
| Hypotension | 1 | 0 | 0 |
| Headache | 1 | 0 | 0 |
| Deep venous thrombosis | 2 | 0 | 0 |
| Fatigue | 6 | 0 | 0 |
| Pain[a] | 7 | 0 | 0 |
| Phlebitis | 2 | 0 | 0 |
| Hyperglycemia | 1 | 0 | 0 |
| Mental status change | 1 | 0 | 0 |
| Pulmonary/dyspnea | 6 | 0 | 0 |
| Pulmonary embolism | 0 | 0 | 1 |
| Adult respiratory distress syndrome (possibly drug-related) | 0 | 0 | 0 |
| Myalgia | 1 | 0 | 0 |
| Anemia | 2 | 0 | 0 |
| Gastrointestinal (other than N/V/D) | 1 | 0 | 0 |
| Infection | 1 | 0 | 0 |
| Dehydration | 1 | 0 | 1 |

[a]Includes pain at the tumor site, shoulder pain, and back pain

## Dose modifications

As reported above, the primary toxic reaction to the combination of gemcitabine and vinorelbine was hematologic when the regimen was administered on days 1, 8, and 15 of each cycle. The median number of cycles received was four (range one to six). As stated in the Materials and methods section, each cycle was composed of three doses of gemcitabine plus vinorelbine. In total, 30 patients (75%) received some type of dose modification while 10 patients (25%) did not. In the 10 patients (25%) who received all three doses per cycle, the median number of cycles received was three (range one to six). Six patients (15%) received fewer than three doses per cycle but no dose modifications. Eight patients (20%) received all three doses per cycle but required a dose modification at some time, 16 (40%) required both dose modification and received fewer than 3 weeks of treatment at some time. Ten patients (41.7%) received initial dose reductions on day 8, while the remaining 14 patients (58.3%) received initial dose reductions on day 15. Many of these initial reductions were required early in the therapy with 50% occurring during the first cycle and the remainder distributed among the other cycles. At least one dose of the drugs was missed by 22 patients (55%) in this study, and the median dose received was 83% (range 56–100%) of that attempted. As previously stated, for those patients who received a dose reduction, it occurred most often on day 15 during cycle 1 (58.3%).

**Table 5** Toxic reaction incidence (grade 3/4/5) by patient and dose level

| Reaction | Dose level | | | | | | |
|---|---|---|---|---|---|---|---|
| | 1 ($n=5$) | 2 ($n=3$) | 3 ($n=3$) | 4 ($n=14$) | 5 ($n=4$) | 6 ($n=8$) | 7 ($n=3$) |
| Neutropenia | | 1/0/0 | 1/0/0 | 7/0/0 | | 0/2/0 | 1/2/0 |
| Thrombocytopenia | | | | 1/0/0 | | 2/0/0 | 1/0/0 |
| Nausea | | | | | 1/0/0 | 1/0/0 | |
| Vomiting | | | | 1/1/0 | | 1/0/0 | |
| Diarrhea | | | | 1/0/0 | | 0/1/0 | |
| Neurologic | | | | | 1/0/0 | | |
| Fever/neutropenia | | | | | | 1/0/0 | |
| Hypotension | | | | 1/0/0 | | | |
| Headache | 1/0/0 | | | | | | |
| Deep vein thrombosis | | | | 2/0/0 | | | |
| Fatigue | 1/0/0 | 1/0/0 | | 2/0/0 | | 2/0/0 | |
| Pain | | | | 6/0/0 | | 1/0/0 | |
| Phlebitis | | 1/0/0 | | | | 1/0/0 | |
| Hyperglycemia | | | | | | | 1/0/0 |
| Mental status change | | | | 1/0/0 | | | |
| Pulmonary/dyspnea | | 1/0/0 | 2/0/0 | 2/0/0 | 1/0/0 | | |
| Pulmonary embolism | | | | 0/0/1 | | | |
| Adult respiratory distress syndrome (possibly drug related) | | | | 0/0/1 | | | |
| Myalgia | 1/0/0 | | | | | | |
| Anemia | | | | 1/0/0 | | | 1/0/0 |
| Gastrointestinal | | | | 1/0/0 | | | |
| Infection | | | | 1/0/0 | | | |
| Dehydration | | 1/0/0 | | | | | |
| Anorexia | | | | 1/0/0 | | | |

## Choice of maximum tolerated dose (MTD)

Using strict standards, no formal MTD was reached for this trial as dose level 7 was achieved with acceptable toxicity. However, a formal review was held after completion of the administration of dose level 7 by the study team in conjunction with members of the DFCI Institutional Review Board and level 4 was chosen (Table 1) for expansion based on the presumed ability to give a full dose. Interestingly, the greatest response was seen in level 6 (two of five) but the objective of this trial was dose and toxicity in this disease population. However, even at dose level 4, which was expanded to 14 patients, there were still frequent dose modifications. The median number of cycles at this level was four with a range of one to seven. In this group, six patients (43%) required a dose reduction and missed a dose. Two patients (14%) had no dose reduction but missed a dose and two patients (14%) received all three doses but required reduction. At the expanded level, only two patients (14%) received all three full doses/cycles on time. The toxicity profile for this level was similar to that of the full study considering that it had the most patients. At that time, there were no studies published to demonstrate the efficacy at day-1 and day-8 schedule. Of these 14 patients tested, seven had grade 3 neutropenia, and one had grade 3 thrombocytopenia. Both pulmonary complications previously described (grade 5) occurred in this group.

## Objective response

While response was not the primary endpoint of this study, it was evaluated and Table 6 shows the best response observed in this study for each of the 40 patients. No complete responses were seen, although we observed partial responses in 5 patients (12.5%), stable disease in 14 patients (32.5%), and progressive disease in 17 patients (42.5%). Four patients (10%) were considered unevaluable for response analysis because they did not complete the first cycle of therapy. Two of the five partial responses were treated at dose level 6, while the remaining three patients received dose levels 3, 4, and 7, respectively. Four of the five partial responses were seen in the NSCLC patients, while the fifth was seen in a patient who had mixed disease. Three of the five patients who had a partial response had received prior taxane chemotherapy (only one of these three patients had previously responded). The remaining two patients were chemotherapy-naive.

## Relapse and survival

Figure 2 shows the survival curves broken down by prior vs no prior chemotherapy. The median survival was 8.5 months for all patients, while it was 10 months for those who had not received prior therapy and 7.9 months for those had received prior therapy.

## Discussion

Treatment of metastatic lung cancer has improved significantly in recent years; however, it remains an incurable disease. There is a great need to continue searching for more active and better-tolerated therapeutic combinations. If platinum and its significant associated neurologic and renal toxic effects could be avoided in these combinations, there would be potential for developing a regimen having equal or greater potency with less toxicity. This type of regimen would greatly benefit patients in the palliative setting and, if more active, could then be moved up for the treatment of earlier stage disease.

In the development of new treatment combinations for malignant disease, it remains important to determine whether the activity of each drug in a multidrug combination provides additive or, perhaps, synergistic activity. This question can initially be addressed in preclinical studies in mice. When we combined gemcitabine with vinorelbine for the treatment of primary and metastatic Lewis lung carcinoma, it was clear that their combined activity was maintained over a wide dosage range. The additive efficacy of this regimen was evident in both the response of the primary s.c. tumor and decrease in the number of lung metastases seen on day 20. Based on these data, we proceeded with our phase I clinical trial.

In designing this trial, we chose to start at 50% of the standard single-agent dose of each drug for lung cancer (500 mg/m$^2$ gemcitabine and 15 mg/m$^2$ vinorelbine). We showed that the combination of gemcitabine and vinorelbine could be given safely at a number of dose levels. In fact, we set our maximum dose at 30 mg/m$^2$ vinorelbine with 1250 mg/m$^2$ gemcitabine and were successful in achieving the full dose. Consequently, a typical MTD was never reached; rather, we were concerned by frequent dose reductions and omissions due to neutropenia or thrombocytopenia, but they were never to an extent that led to defining a DLT. Thus, dose level 4 (1000 mg/m$^2$ gemcitabine and 22.5 mg/m$^2$ vinorelbine) given 3 out of 4 weeks was chosen by our team for patient expansion because it was initially felt that this level would allow us to deliver a full dose of both drugs. There were still considerable dose modifications at this level as described, but for the most part, it was better tolerated.

The main toxic reaction to this combination was non-life-threatening myelosuppression, which was dose-related; however, there were no severe consequences ascribed to this problem. Rather, this reaction was inconvenient for physicians and patients alike, as the most common dose modification was the need to hold the dose on day 15. Of note, however, is the absence of toxic reactions that are usually seen with platinum-based chemotherapy. Specifically, renal toxicity, neurotoxicity, nausea, and alopecia were rare, though still present. Significant fatigue did occur, although it is unclear whether this was due to the therapy or simply progression of disease. Many patients experienced burning at the i.v. site when a central line was not used, including grade 3 pain in seven patients. This was thought to be secondary to vinorelbine, but burning often occurred during gemcitabine infusion. It is possible that vinorelbine sensitized the vein to the 30-min gemcitabine infusion as well. Administration of the drugs through a central line avoided this problem.

Although measurement of response was not the primary objective of this study, 5 patients did show a response and 14 had stable disease. Importantly, of the patients who had a response, three had received prior therapy, all with carboplatinum and paclitaxel. Two of these patients had experienced disease progression through their prior regimen. This suggests potential further study of this regimen in both first and second NSCLC.

We conclude that gemcitabine plus vinorelbine is an active regimen for NSCLC, demonstrating efficacy as both first- and second-line therapy. The main drawback of the 28-day schedule is myelosuppression and day-15 dose omission and reduction. Importantly, Lilenbaum et al. [21] recently reported a front-line response rate of this regimen of 35% in an untreated patient group using a 21-day schedule with administration on days 1 and 8.

**Table 6** Best response to gemcitabine and vinorelbine

| Response | No. | % |
|---|---|---|
| Complete response | 0 | 0.0 |
| Partial response | 5 | 12.5 |
| Stable disease | 14 | 35.0 |
| Progressive disease | 17 | 42.5 |
| Unevaluable[a] | 4 | 10.0 |

[a]Treated for less than one cycle only and did not receive follow-up disease assessment

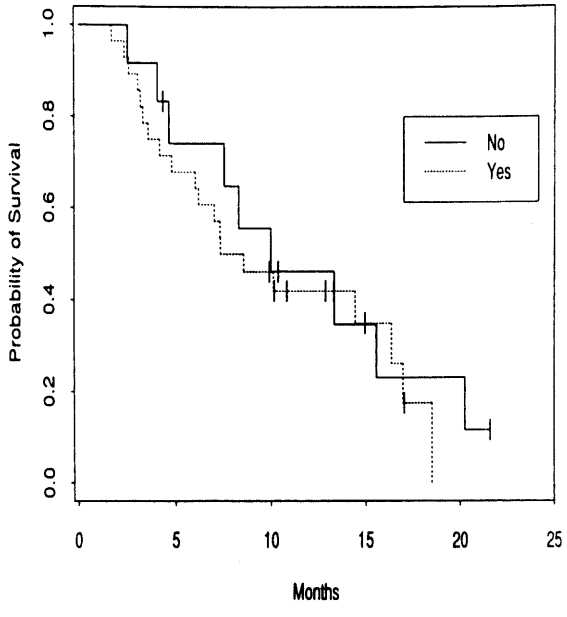


**Fig. 2** Kaplan-Meier survival curve for all 40 patients broken down by no prior therapy (*solid line*) vs prior chemotherapy (*dotted line*)

In their study, dose reduction was much less frequent on day 15. Therefore, it might be preferential to use this schedule to avoid expected dose reductions. Regardless of this fact, our data, demonstrate that gemcitabine plus vinorelbine is a reasonably well-tolerated drug combination suitable for future phase II and randomized phase III studies, some of which are already underway in Europe and North America.

## References


1. Anonymous (1997) Clinical practice guidelines for the treatment of unresectable non-small-cell lung cancer. Adopted on May 16, 1997 by the American Society of Clinical Oncology. J Clin Oncol 15:2996–3018
2. Anonymous (1999) Effects of vinorelbine on quality of life and survival of elderly patients with advanced non-small-cell lung cancer. The Elderly Lung Cancer Vinorelbine Italian Study Group. J Natl Cancer Inst 91:66–72
3. Belani CP, Natale RB, Lee JS, Socinski M, Robert F, Waterhouse D, Rowland K (1998) Randomized phase III trial comparing cisplatin/etoposide versus carboplatin/paclitaxel in advanced and metastatic non-small cell lung cancer. Proc Am Soc Clin Oncol 17:455a
4. Binet S, Fellous A, Lataste H, Krikorian A, Couzinier JP, Meininger V (1989) In situ analysis of the action of Navelbine on various types of microtubules using immunofluorescence. Semin Oncol 16 [2 Suppl 4]:5–8
5. Bonomi P, Kim K, Chang A, et al (1996) Phase III trial comparing etoposide-cisplatin versus taxol with cisplatin-G-CSF versus taxol-cisplatin in advanced non-small cell lung cancer. Proc Am Soc Clin Oncol 15:382a
6. Bunn PA Jr, Carney DN (1997) Overview of chemotherapy for small cell lung cancer. Semin Oncol 24 [2 Suppl 7]:69–74
7. Cardenal F, Lopez-Cabrerizo MP, Anton A, Alberola V, Massuti B, Carrato A, Barneto I, Lomas M, Garcia M, Lianes P, Montalar J, Vadell C, Gonzalez-Larriba JL, Nguyen B, Artal A, Rosell R (1999) Randomized phase III study of gemcitabine-cisplatin versus etoposide-cisplatin in the treatment of locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol 17:12–18
8. Carrato A, Rosell R, Camps C, Anton A, Garcia-Gomez R, Aranda E, Massuti B, Diaz-Fernandez N, Sanchez JJ, Garcia-Paredes ML (1997) Modified weekly regimen with vinorelbine as a single agent in unresectable non-small cell lung cancer. Lung Cancer 17:261–269
9. Crino L, Conte P, De Marinis F, Rinaldi M, Gridelli C, Ceribelli A, Matano E, Marangolo M, Bartolucci R, Oliva C, Tonato M (1998) A randomized trial of gemcitabine cisplatin versus mitomycin, ifosfamide and cisplatin in advanced non-small cell lung cancer. A multicenter phase III study. Proc Am Soc Clin Oncol 17:455a
10. Deen DF, Williams ME (1979) Isobologram analysis of X-ray–BCNU interactions in vitro. Radiat Res 79:483–491
11. Depierre A, Lemarie E, Dabouis G, Garnier G, Jacoulet P, Dalphin JC (1991) A phase II study of Navelbine (vinorelbine) in the treatment of non-small-cell lung cancer. Am J Clin Oncol 14:115–119
12. Earle CC, Stewart DJ, Cormier Y, Evans WK, Gertler SZ, Mihalcioiu C, Walde PD (1998) A phase I study of gemcitabine/cisplatin/etoposide in the treatment of small-cell lung cancer. Lung Cancer 22:235–241
13. Edelman MJ, Gandara DR (1996) Promising new agents in the treatment of non-small cell lung cancer. Cancer Chemother Pharmacol 37:385–393
14. Ettinger DS (1995) New drugs for treating small cell lung cancer. Lung Cancer 12:S53–61
15. Furuse K, Kubota K, Kawahara M, Ogawara M, Kinuwaki E, Motomiya M, Nishiwaki Y, Niitani H, Sakuma A (1994) A phase II study of vinorelbine, a new derivative of vinca alkaloid, for previously untreated advanced non-small cell lung cancer. Japan Vinorelbine Lung Cancer Study Group. Lung Cancer 11:385–391
16. Furuse K, Kubota K, Kawahara M, Takada M, Kimura I, Fujii M, Ohta M, Hasegawa K, Yoshida K, Nakajima S, Ogura T, Niitani H (1996) Phase II study of vinorelbine in heavily previously treated small cell lung cancer. Japan Lung Cancer Vinorelbine Study Group. Oncology 53:169–172
17. Gandara D, Edelman M, Lara P, et al (1999) Current status and novel therapeutic approaches in advanced non-small cell lung cancer. ASCO Educational Book, pp 362–369
18. Greenlee RT, Murray T, Bolden S, Wingo PA (2000) Cancer statistics, 2000. CA Cancer J Clin 50:7–33
19. Gridelli C, Perrone F, Ianniello GP, Brancaccio L, Iaffaioli RV, Curcio C, D'Aprile M, Cioffi R, Cigolari S, Rossi A, Palazzolo G, Veltri E, Pergola M, De Placido S, Gallo C, Monfardini S, Bianco AR (1998) Carboplatin plus vinorelbine, a new well-tolerated and active regimen for the treatment of extensive-stage small-cell lung cancer: a phase II study. Gruppo Oncologico Centro-Sud-Isole. J Clin Oncol 16:1414–1419
20. Group NC (1995) Chemotherapy of advanced non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomized clinical trials. BMJ 311:899–909
21. Lilenbaum R, Cano R, Schwartz M, Siegel L, Lutzky J, Lewis M, Krill E, Barreras L, Danila E (2000) Gemcitabine and vinorelbine in advanced non-small cell lung carcinoma: a phase II study. Cancer 88:557–562
22. Hertel L, Kroin J, Misner J, et al (1988) Synthesis of 2-deoxy-2′,2′-difluoro-D-ribose and 2-deoxy-2′,2′-difluoro-D-ribofuranosyl nucleosides. J Organic Chem 53:2406–2409
23. Hertel LW, Boder GB, Kroin JS, Rinzel SM, Poore GA, Todd GC, Grindey GB (1990) Evaluation of the antitumor activity of gemcitabine (2′,2′-difluoro-2′-deoxycytidine). Cancer Res 50:4417–4422
24. Iaffaioli RV, Facchini G, Tortoriello A, Caponigro F, Illiano A, Gentile M, Gravina A, Muto P (1997) Phase I study of vinorelbine and paclitaxel in small-cell lung cancer. Cancer Chemother Pharmacol 41:86–90
25. Le Chevalier T, Brisgand D, Douillard JY, Pujol JL, Alberola V, Monnier A, Riviere A, Lianes P, Chomy P, Cigolari S, et al (1994) Randomized study of vinorelbine and cisplatin versus vindesine and cisplatin versus vinorelbine alone in advanced non-small-cell lung cancer: results of a European multicenter trial including 612 patients [see comments]. J Clin Oncol 12, 360–367
26. Lilenbaum RC, Green MR (1993) Novel chemotherapeutic agents in the treatment of non-small-cell lung cancer. J Clin Oncol 11:1391–1402
27. Lonardi F, Pavanoto G, et al (1994) Vinorelbine as single-agent chemotherapy in advanced non-small cell lung cancer. Proc Am Soc Clin Oncol 13:1123a
28. Postmus PE, Schramel FM, Smit EF (1998) Evaluation of new drugs in small cell lung cancer: the activity of gemcitabine. Semin Oncol 25:79–82
29. Potier P (1989) The synthesis of Navelbine prototype of a new series of vinblastine derivatives. Semin Oncol 16:2–4
30. Sandler A, Nemuniatis J, Dehnam C, Cormier Y, von Pawel J, Niyikiza C, Nguyen B, Einhorn L (1998) Phase III study of cisplatin with or without gemcitabine in patients with advanced non-small cell lung cancer. Proc Am Soc Clin Oncol 17:47
31. Shepherd FA (1995) Phase II trials of single-agent activity of gemcitabine in patients with advanced non-small cell lung cancer: an overview. Anticancer Drugs 6:19–25
32. Teicher BA, Herman TS, Eder JP (1991) Chemotherapeutic potentiation through interaction at the level of DNA. In: Chou

T-C, Rideout DC (eds) Synergism and antagonism in chemotherapy. Academic Press, New York, pp 541–576
33. Teicher BA, Holden SA, Ara G, Sotomayor EA, Huang ZD, Chen YN, Brem H (1994) Potentiation of cytotoxic cancer therapies by TNP-470 alone and with other anti-angiogenic agents. Int J Cancer 57:920–925
34. Wozniak AJ, Crowley JJ, Balcerzak SP, Weiss GR, Spiridonidis CH, Baker LH, Albain KS, Kelly K, Taylor SA, Gandara DR, Livingston RB (1998) Randomized trial comparing cisplatin with cisplatin plus vinorelbine in the treatment of advanced non-small-cell lung cancer: a Southwest Oncology Group study [see comments]. J Clin Oncol 16:2459–2465