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 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/m² and 500 mg/m², 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/m² vinorelbine and 1000 mg/m² 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
**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 pre-existing 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, 2×10³ 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 mm³ 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 mm³. Each treatment group consisted of five animals, and each experiment was repeated three times. Tumor growth delay were defined as the mean ± SE days to reach a size of