Historical Review of Trials With Vinorelbine in Non-Small-Cell Lung Cancer

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Two large-scale, randomized, phase III trials have offered new information on the response rates, survival benefits, and safety profile of vinorelbine (Navelbine) in non-small-cell lung cancer (NSCLC). In a multicenter, European trial, the response rate was significantly higher with vinorelbine/cisplatin (Platinol) than with vindesine (Eldisine)/cisplatin (P).

Introduction

The results of clinical trials have provided insights into the potential survival benefits to be gained with vinorelbine (Navelbine) in patients with non-small-cell lung cancer. These studies have also contributed important information on the safety profile of this agent.

Multicenter European Trial

Phase II studies in non-small-cell lung cancer were performed in France in the mid-1980s using vinorelbine as both a single agent and in combination with cisplatin (Platinol). As a single agent, vinorelbine produced a response rate of 33% in patients with advanced non-small-cell lung cancer. When vinorelbine was used in combination with cisplatin, the response rate was 37%, with acceptable toxicity.

The response rate observed in this preliminary work provided justification for Le Chevalier et al to undertake a phase III, multicenter, European study comparing the combination of vinorelbine and cisplatin to the combination of vindesine (Eldisine) and cisplatin.[1] The latter combination had shown a superior response rate and survival rate when compared with best supportive care in a randomized trial conducted by the National Cancer Institute of Canada.[2] Because vinorelbine alone had shown efficacy with low toxicity in phase II trials, it was included as a third arm in the study by Le Chevalier et al.

Materials and Methods

The eligibility criteria for this trial included inoperable non-small-cell lung cancer (stage III or IV), age ≤ 75 years, World Health Organization performance status ≤ 2, no prior malignancy, no prior chemotherapy, no symptomatic central nervous system metastases, and at least one measurable lesion.

Eligible patients were randomized to receive: vinorelbine alone at a dose of 30 mg/m^2 every week; vinorelbine at the same dosage plus cisplatin (120 mg/m^2 on day 1 and day 29, then every 6 weeks); or vindesine (3 mg/m^2 every week for 6 weeks, then every 2 weeks), plus cisplatin at the same dosage as in the previous group. This regimen was identical to that used in the National Cancer Institute of Canada trial.[2]

Vinorelbine was diluted in saline and administered as a 20-minute intravenous (IV) infusion. Vindesine was administered as an IV push, with a running 5% dextrose or normal saline infusion. Cisplatin was diluted in saline and infused over 1 hour. Treatment was continued until either disease progression or toxicity necessitated its termination.

For grade 2 neutropenia, the doses of vinorelbine and vindesine were reduced by 50%. For grade 3 or 4 neutropenia, the dose of vinorelbine or vindesine was withheld. Grade 3 or 4 neurologic, hepatic, or renal toxicity resulted in discontinuation of therapy. Treatment was also discontinued in cases of severe hearing loss.

The baseline assessment included a physical examination, complete blood count and blood chemistry, chest x-ray, fiberoptic bronchoscopy, and abdominal ultrasound. Optional studies included CT of the chest, abdomen, or brain, as well as bone scans. Patients were evaluated prior to treatment, after 10 weeks, and after 18 weeks to assess response rates. Objective responses required confirmation after an additional 4 weeks by a panel of at least
three experts, who blindly reviewed all documents for the response assessments. Survival was analyzed approximately 16 months after the close of the trial.

To demonstrate a difference of 12 weeks in median survival and a difference of 15% in response rates with a type I error of 5% and a power of 80%, 190 patients were needed in each arm of the study. Randomization was stratified by center and by stage. Response rates and survival rates in the three treatment arms were compared using the chi-square test and log-rank test adjusted for prognostic factors.

Because of a concern that efficacy might be lower in the vinorelbine-alone arm than in the two cisplatin arms, an unplanned interim analysis was performed after accrual of 323 patients. At that point, the P value for a survival difference was .15, and the study was continued.

Results

Patient Accounting and Characteristics

Between 1989 and 1991, 612 patients were enrolled at 45 European centers. A total of 206 patients were randomized to vinorelbine alone, 206 to vinorelbine/cisplatin, and 200 to vindesine/cisplatin. Three patients randomized to the vindesine/cisplatin arm received vinorelbine/cisplatin instead. These patients were included in the vindesine/cisplatin group in the survival analysis. Eight patients received no treatment (two in the vinorelbine-alone group, two in the vinorelbine/cisplatin group, and four in the vindesine/cisplatin group).

Of the 612 patients randomized, 24 (4%) were deemed ineligible for inclusion in the analysis. The reasons for ineligibility were brain metastases in 5 patients, prior malignancy in 2, diagnostic errors in 2, low performance status in 5, and a lack of measurable disease in 10. The numbers of ineligible patients were 4 in the vinorelbine-alone group, 9 in the vinorelbine/cisplatin group, and 11 in the vindesine/cisplatin group.

The median age of the 612 randomized patients was 60 years; 80% were men, and 80% had a performance status of 0 or 1. More than half of the patients had squamous-cell non-small-cell lung cancer, which is the most common histologic subtype in Europe. Approximately 60% of patients had distant metastatic disease.

Treatment

The duration of treatment was similar in the three arms of the study. The median duration of treatment was 14.6 weeks for vinorelbine alone, 15.4 weeks for vinorelbine/cisplatin, and 14.4 weeks for vindesine/cisplatin.

The dose intensity was determined by dividing the given dose by the expected dose. The expected dose was the calculated full dose for the period of time that a patient was receiving treatment. For vinorelbine alone, the dose intensity was 83%. In the vinorelbine/cisplatin arm, the dose intensities for the two agents were 71% and 96%, respectively. In the vindesine/cisplatin arm, the dose intensity was 98% for both agents. The addition of cisplatin to the vinorelbine regimen had a relatively minor effect on the dose intensity of the latter agent.

Second-line treatment was allowed. A total of 362 patients received some form of second-line therapy, including surgery in 26 individuals, thoracic radiation therapy in 245, and second-line chemotherapy in 195. The analysis of survival did not take into account these second-line treatments.

Response Rates

Of the 612 patients enrolled, 38 were excluded from the analysis of response. The reasons for exclusion included ineligibility in 24 patients, lack of treatment in 6, incorrect treatment in 3, and lack of documentation in 5.

Table 1 shows the objective response data by treatment group. The response rate was significantly higher with vinorelbine/cisplatin than with vindesine/cisplatin (P < .02) or vinorelbine alone (P < .001). The median duration of objective response was 9.2 months for vinorelbine/cisplatin, 9.9 months for vindesine/cisplatin, and 7.8 months for vinorelbine alone.

Survival Rates

Approximately 16 months after the close of the trial, 73 patients (12%) were still alive and 4 had been lost to follow-up. The median survival duration was 31 weeks in the vinorelbine-alone arm, 40 weeks in the vinorelbine/cisplatin arm, and 32 weeks in the vindesine/cisplatin arm (Table 1). The 1-year survival rates were 30%, 35%, and 27%, respectively. Using the log-rank test adjusted for treatment center, survival was superior with vinorelbine/cisplatin as compared with vinorelbine alone (P = .01) or vindesine/cisplatin (P = .04). For patients with stage IV disease only, the median survival time was 36 weeks with vinorelbine/cisplatin as opposed to 27 weeks with each of the other regimens (unadjusted log-rank P = .007).

Toxicity

Toxicity data are summarized in Table 2. Hematologic toxicity mainly consisted of neutropenia, experienced at grade 3 or 4 in 53% of patients in the vinorelbine-alone group, 79% in the vinorelbine/cisplatin group, and 48% in the vindesine/cisplatin group. This was a direct
consequence of the dosage schedules in the three arms. Despite the significantly higher rate of neutropenia in the vinorelbine/cisplatin arm vs the other two arms (P < .005), only two patients died of septic complications in each of the three treatment groups. Thus, the rate of septic death was low (1%) in each group.

Thrombocytopenia was experienced by 3% of patients in each cisplatin group, but in none of those receiving vinorelbine alone.

Grade 3 or 4 neurologic toxicity was significantly more common with vindesine/cisplatin than with either vinorelbine regimen (Figure 1). Notably, cisplatin did not seem to increase the neurotoxicity of vinorelbine.

Nausea and vomiting were common in the groups receiving cisplatin, but became less frequent during the course of the study as ondansetron (Zofran) became progressively more available at the participating centers. Nausea and vomiting were reported in 12% of patients receiving vinorelbine alone, compared with 58% of those receiving vinorelbine/cisplatin and 59% of those receiving vindesine/cisplatin.

The incidence of alopecia was 14% with vinorelbine alone, 32% with vinorelbine/cisplatin, and 38% with vindesine/cisplatin.

**Discussion**

In this study, all three chemotherapy regimens showed activity in patients with advanced non-small-cell lung cancer. However, the response rate, 1-year survival rate, and median survival time were significantly superior (from both statistical and clinical standpoints) in patients receiving vinorelbine/cisplatin. It is noteworthy that the vinorelbine/cisplatin arm demonstrated superior efficacy when compared with the contemporary standard therapy of vindesine/cisplatin.

In addition, the results achieved with vinorelbine alone were similar to those obtained with vindesine/cisplatin. Given the activity shown by single-agent vinorelbine, this treatment is a reasonable option for patients who might not tolerate or choose a cisplatin-containing regimen. In combination with cisplatin, vinorelbine had significantly less neurotoxicity than did vindesine. Although the group randomized to vinorelbine/cisplatin had substantially more patients with grade 3 or 4 neutropenia, the rates of septic complications were similar, and the rate of septic death was low (1%) in each arm. The overall toxicity in the vinorelbine-alone arm was substantially less than that in the cisplatin arms.

Both cisplatin-containing regimens used the same dosage schedule for this agent. The fact that vinorelbine/cisplatin provided superior efficacy (with less toxicity) demonstrates that this combination is more active in the treatment of advanced non-small-cell lung cancer than is the combination of vindesine/cisplatin. The results of this large-scale, randomized, phase III clinical trial therefore suggest that the combination of vinorelbine/cisplatin should be preferred over the other two regimens and that it should be given strong consideration as a reference regimen in the treatment of advanced non-small-cell lung cancer.

**Multicenter North American Study**

In 1990, there was no standard therapy for stage IV non-small-cell lung cancer in the United States. Although cisplatin-based chemotherapy had shown a survival benefit, questions remained regarding the degree of the benefit and the deleterious impact on quality of life. Consequently, North American investigators undertook a phase III clinical trial to determine the role of vinorelbine in advanced non-small-cell lung cancer, with attention given to quality of life as well as survival.[3]

**Materials and Methods**

To be eligible for the trial, patients were required to have definite metastatic disease (stage IV non-small-cell lung cancer). Other criteria included: no prior chemotherapy; age ≥ 18 years; performance status ≥ 70%; adequate bone marrow, renal, and hepatic function; and measurable or evaluable disease. Pregnant patients and those with metastatic central nervous system disease were excluded. Patients who had only evaluable disease were required to have some cancer-related symptoms.

The study was designed to compare single-agent vinorelbine vs leucovorin plus fluorouracil (5-FU). Considerable thought went into the choice of 5-FU as a comparative agent. Specifically, cisplatin was not used because the investigators believed that its toxicity was so great that vinorelbine would have an unfair advantage in quality-of-life assessments.

Furthermore, the regimen of leucovorin/5-FU had shown efficacy in colon cancer and breast cancer, although it had not been studied extensively in non-small-cell lung cancer. Finally, leucovorin/5-FU was a regimen with which practicing medical oncologists in North America had considerable
experience. It was believed that this regimen could be delivered safely and uniformly in the outpatient setting. Best supportive care (ie, no chemotherapy) was not selected as a comparator because the investigators believed that this alternative would not be acceptable to North American physicians or patients at that time.

Patients were randomized in a 2:1 ratio to receive vinorelbine or leucovorin/5-FU. An early stop rule stipulated that the study could be terminated if treatment with leucovorin/5-FU did not produce at least two responses in the first 25 patients evaluable for response. The 2:1 randomization was used to ensure that adequate safety and efficacy information would be available for vinorelbine, even if the 5-FU arm proved to be inactive and the study had to be terminated early. Vinorelbine was administered at a dose of 30 mg/m² given as a 20-minute IV infusion each week. The dose was adjusted on the basis of toxicity. The most common adjustment was anticipated to be for low granulocyte counts. Escalation of the vinorelbine dose to 35 mg/m² was allowed if no toxicity occurred during the first 4 weeks.

In the other arm, leucovorin was administered as a 20-mg/m² IV push, followed by 5-FU, 425 mg/m², as a daily IV push for 5 days in a row, every 4 weeks. Doses were again adjusted on the basis of toxicity. Patients were considered evaluable for analysis if they completed 8 weeks of therapy (receiving at least four doses of vinorelbine or two cycles of leucovorin/5-FU in 8 weeks).

The primary efficacy measures were survival, quality of life, and cancer-related symptoms. Secondary measures of efficacy were response rate, time to treatment failure, Karnofsky performance status, body weight, and pulmonary function tests. Safety data were collected during the course of this study to add to the growing database of clinical experience with vinorelbine in North America.

The study was designed to have 80% power to detect differences in survival between the two treatment arms. The goal was to determine a difference of 12 weeks in survival duration between the vinorelbine group (anticipated to have a median survival time of perhaps 30 weeks) and the leucovorin/5-FU group (anticipated to have a median survival time of perhaps 18 weeks). The analysis was scheduled to be conducted 6 months after the last patient was enrolled. No interim or subsequent analyses were planned.

**Results**

**Patient Accounting and Characteristics** Between 1990 and 1992, a total of 216 patients were randomized at 18 centers in North America. Patient accounting is summarized in Table 3. A total of 144 patients were randomized to the vinorelbine arm and 72 to the leucovorin/5-FU arm. A total of 211 patients were treated (143 with vinorelbine and 68 with leucovorin/5-FU). Demographic and disease characteristics did not differ significantly between these two groups (Table 4).

The number of patients with measurable disease was 127 in the vinorelbine group and 58 in the leucovorin/5-FU group. Nonmeasurable but symptomatic disease was present in 16 patients in the vinorelbine group and 10 in the leucovorin/5-FU group.

Of the 185 patients with measurable disease, evaluable patients (ie, those who received at least four doses of vinorelbine or two courses of leucovorin/5-FU in 8 weeks). Five patients were randomized, but never treated. These patients included two who died before receiving their first dose, one who refused therapy, and one who did not return to the clinic. In addition, seven patients were stratified incorrectly at screening. Also, nine patients had protocol entry violations. Finally, six patients had progression of disease before completing the 8 weeks of therapy necessary to be considered evaluable.

**Treatment** Dose intensity was determined in both treatment arms. Dose intensity was defined as the average dose per week for weeks 1 through 8 in the total patient population. The dose received (mg/m²) during weeks 1 through 8 was divided by 8 to calculate dose intensity. This definition was used for all patients, including those in the study for less than 8 weeks. The dose intensity for vinorelbine was 21 mg/m², which corresponded to 74% of the intended dose for an average of 14 weeks in the study.

**Primary End Points** The estimated median survival time was 30 weeks for the 143 patients in the vinorelbine arm vs 22 weeks for the 68 patients in the leucovorin/5-FU arm. This corresponded to estimated 1-year survival rates of 25.2% for the vinorelbine arm compared with 15.9% for leucovorin/5-FU arm (Table 5).

The difference in median survival time was statistically significant, favoring vinorelbine (unadjusted log-rank P = .03; unadjusted Wilcoxon's rank sum test, P = .008). Patients censored included 24% of patients in the vinorelbine arm compared with 21% in the leucovorin/5-FU arm. The Kaplan-Meier survival estimate showed a consistent survival advantage for vinorelbine from the time of patient entry into the trial through ≥ 400 days (Figure 2).

The Cox proportional hazards model was used to identify the importance of prognostic variables,
including treatment, in predicting survival. According to a PROC PHREG in SAS, important prognostic variables included treatment arm (P = .062), bone metastases (P = .002), Karnofsky performance score (P = .003), weight loss (P = .012), and lactate dehydrogenase greater than 350 U/L (P = .021). Histologic subtype and disease type (measurable vs nonmeasurable) were not significant prognostic factors.

Quality of life was analyzed from the patient’s perspective. Data on cancer-related symptoms were summarized over time, with logistic regression used to make treatment comparisons. Patients in the vinorelbine group tended to remain in the study longer, but those in the leucovorin/5-FU group who remained in the study for a long time tended to have better baseline quality-of-life scores. There was a lower incidence of symptom distress in the vinorelbine arm, but this did not reach statistical significance. Therefore, vinorelbine did not adversely affect symptom distress when compared with leucovorin/5-FU.

Another analysis assessed whether clinicians believed that treatment had palliated selected cancer-related symptoms. Approximately 40% of patients in both arms experienced improvement in baseline symptoms. Palliation of selected cancer-related symptoms did not differ significantly between the two treatment groups. In other words, vinorelbine did not adversely affect palliation of cancer-related symptoms.

Secondary End Points
In the intent-to-treat analysis, the response rate was 12% for vinorelbine compared with 3% for leucovorin/5-FU. In the preferred analysis using only evaluable patients, the response rates were 18% and 8%, respectively. Neither difference achieved statistical significance. The estimated median time to treatment failure was significantly longer in the vinorelbine group than in the leucovorin/5-FU group: 10 vs 8 weeks, respectively (log-rank P = .017; unadjusted Wilcoxon’s rank sum test, P = .02).

The Cox proportional hazards model was used to identify the impact of prognostic variables, including treatment, on the time to treatment failure. Using a PROC PHREG in SAS, significant prognostic variables included treatment arm (P = .02), bone metastases (P < .001), and Karnofsky performance score (P = .01).

Toxicity
Data on hematologic toxicity are summarized in Table 6. Hematologic toxicity was mild with regard to effects on hemoglobin and platelets. Patients hospitalized with neutropenia totaled 10 of 143 (7%) in the vinorelbine group and 4 of 68 (6%) in the leucovorin/5-FU group. Two septic deaths occurred in each group.

Table 7 presents data on nonhematologic adverse experiences considered reasonably or possibly attributable to the study medications. With regard to blood chemistries, serum glutamic-oxaloacetic transaminase was abnormal in 52% of patients in the vinorelbine group and 37% of those in the leucovorin/5-FU group. Abnormal serum glutamate pyruvate transaminase was noted in 55% and 32% of patients in the two groups, respectively. Creatinine, alkaline phosphatase, and total bilirubin were affected in less than 10% of patients in both arms.

Discussion
In this trial, the median duration of survival was distinctly superior with vinorelbine (30 weeks) vs leucovorin/5-FU (22 weeks). Interestingly, the median survival time in the leucovorin/5-FU arm was better than that observed with best supportive care in many previous clinical trials.[2] Although quality-of-life assessments, from both the patients and clinicians’ perspectives, failed to show an advantage of vinorelbine, this treatment was not associated with any negative impact on these end points. Moreover, the favorable safety profile of vinorelbine was striking. In particular, nausea and vomiting were not at all serious problems, and minimal antiemetic therapy was required. (It should also be noted that this trial was conducted before ondansetron and granisetron [Kytril] were available for the control of nausea.) Both vinorelbine and leucovorin/5-FU were administered in the outpatient setting with remarkable safety and simplicity.

Conclusions
In the multicenter, European trial of patients with non-small-cell lung cancer, the combination of vinorelbine/cisplatin provided greater efficacy than vindesine/cisplatin with less toxicity. The North American, multicenter trial was the first to identify a survival benefit with a single agent in this patient population. Compared with leucovorin/5-FU, single-agent vinorelbine was associated with consistently superior survival. The magnitude of the survival benefit and the low occurrence of toxicity indicate that vinorelbine has a definite role in the treatment of advanced non-small-cell lung cancer.
Taken together, the results of these trials demonstrate that vinorelbine can achieve both prolongation of survival and palliation of cancer symptoms in patients with advanced non-small-cell lung cancer. The combination of vinorelbine/cisplatin should be given strong consideration as a reference treatment regimen in this population.

**References:**


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