

# Vinorelbine in advanced non-small-cell lung cancer: Has a survival benefit been achieved in clinical practice?

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## ABSTRACT

### Purpose

Vinorelbine used in conjunction with cisplatin in advanced, inoperable non-small-cell lung cancer has been linked to a survival advantage in this otherwise terminal disease. Survival outcomes achieved in clinical trials, however, may not be matched in practice thus necessitating this practical evaluation.

### Methods

A provincial evaluation of all patients treated with this regimen from September 1994 to July 1996 was conducted by chart review. Survival data was analyzed by the Kaplan-Meier methodology.

### Results

The median survival time and survival rate observed in this practical evaluation was comparable to that achieved in an earlier clinical trial. A paradoxical trend between lower dose intensity of both vinorelbine and cisplatin and improved survival was noted ( $p < 0.0005$ ). Hematological toxicity was common.

### Conclusion

A survival advantage of vinorelbine and cisplatin in this population when compared with best supportive care was observed. Further investigations of different doses and schedules as well as quality of life assessments would complement the finding of this study.

**Key Words:** antineoplastics, phytogetic, lung neoplasms, vinca alkaloids, vinorelbine

## RÉSUMÉ

### Objectif

L'administration conjointe de vinorelbine et de cisplatine dans les cas de cancer du poumon à grandes cellules inopérable a été associée à une meilleure survie dans ces cas de maladie autrement fatale. Cependant, ces avantages au plan de la survie observés lors des essais cliniques pourraient ne pas être reproductibles dans la pratique. C'est pourquoi cette évaluation pratique est nécessaire.

### Méthode

Une évaluation de tous les patients traités par cette association médicamenteuse de septembre 1994 à juillet 1996 a été menée dans la province, à partir de l'analyse des dossiers médicaux des patients. Les données sur la survie ont été analysées au moyen de la méthode de Kaplan-Meier.

### Résultats

Le temps de survie et le taux de survie moyens notés au cours de cette évaluation pratique étaient comparables à ceux observés lors des essais cliniques antérieurs. Une tendance paradoxale entre de faibles doses de vinorelbine et de cisplatine et une amélioration de la survie a été notée ( $p < 0,0005$ ). L'hématotoxicité était courante.

### Conclusion

On a remarqué un avantage au plan de la survie avec l'administration conjointe de vinorelbine et de cisplatine dans cette population, en comparaison aux meilleurs soins de soutien. Des études de doses et de schémas posologiques plus poussées et des évaluations de la qualité de vie viendraient compléter les résultats de cette étude.

**Mots clés:** alcaloïde de la pervenche, antinéoplasiques, phyto-gène, néoplasmes pulmonaires, vinorelbine

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## INTRODUCTION

Over the past decade, intensive research efforts have attempted to define the standard of care for advanced non-small-cell lung cancer (NSCLC). Studies have produced conflicting results, warranting further investigations. Two recent meta-analyses confirmed that chemotherapy offers a survival advantage over best supportive care.<sup>1,2</sup> It has been challenged whether the reputed survival gain is great enough to justify the ensuing chemotherapeutic side effects. To quantify the associated gains and costs, various regimens have

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been compared. The inconsistent findings from these studies have made it difficult to establish which regimen most reliably prolongs survival with the fewest associated complications.<sup>3-5</sup>

The provincial standard protocol for treating advanced NSCLC is vinorelbine (NVB) and cisplatin (DDP). This combination achieved the most promising results with a median duration of survival of 40 weeks in one widely recognized multi-institution trial conducted by LeChevalier et al.<sup>3</sup> Some of the admittance criteria for this trial included: age 75 years, World Health Organization (WHO) performance status (PS) of 2, normal blood count, and no prior chemotherapy. These requirements dictate patient population characteristics which, in turn, impact strongly on both chemotherapeutic response and side effects.<sup>6</sup> Eligibility criteria in practice may be less stringent than in clinical trials and, therefore, the outcomes achieved may not equal those initially reported in the trials.<sup>6</sup>

The goal of this evaluation was to assess past survival outcomes achieved in the clinical setting with the NSCLC palliative chemotherapy protocol of NVB with DDP.

## METHODS

This provincial evaluation studied all patients who received NVB in conjunction with DDP for the palliative treatment of advanced, inoperable NSCLC and who were followed until either completion of NVB therapy or death. The standard regimen for this indication includes a weekly NVB infusion with additional DDP administered on alternate weeks. Table I lists the dosing information of each agent. The standard NVB

dose is administered only if the granulocyte count on the day of treatment is  $1.5 \times 10^9$  cells/L. If the count is  $<1.5 \times 10^9$  cells/L but  $1 \times 10^9$  cells/L, the dose is reduced by 50%. If the count is  $<1 \times 10^9$  cells/L, the chemotherapy is deferred for one week. A six-course trial is normally allotted before response to this regimen is assessed. Subsequent six-course trials are considered only if signs of radiological or symptomatic improvement are evident.

Patients were excluded if they were currently enrolled in a clinical trial; if they were receiving chest radiotherapy in conjunction with or subsequent to chemotherapy; or were given an alternative chemotherapeutic agent after receiving NVB and DDP.

This longitudinal study commenced in September 1994, when NVB was first used provincially, and continued until time of data analysis in July 1996. Outcome parameters included survival time and incidence of granulocytopenia, febrile neutropenia, infections, and alopecia. Data was collected from patient charts by reviewing medication orders, laboratory reports, physician progress notes, and nursing assessments, as well as from the provincial cancer registry database. Treatment related complications were documented using the standardized National Cancer Institute of Canada Clinical Trials Group Toxicity Criteria (see Appendix A).

Dose intensity was calculated by determining the dose actually received compared with the full dose which would have been received, if tolerated. Survival time was calculated from the first day of NVB therapy to the date of death. Chi-square analysis was used to detect any survival differences amongst the following subsets: sex, age, stage, and dose intensity for each of NVB and DDP. Stratification of results by histology was not performed because sub-classification of poorly differentiated NSCLC is too inconsistent to justify any findings.<sup>7</sup> Level of statistical significance was set at  $p < 0.05$ .

## RESULTS

### Patient population

A total of 107 patients were eligible for review. Thirteen patients were excluded from analysis for the following reasons: concurrent enrolment in a trial (4 patients), therapy in progress at the time of analysis (3 patients), treatment with chest radiotherapy concomitant with the chemotherapy (3 patients), treatment with chest radiotherapy subsequent to a completed course of the chemotherapy (1 patient), treatment with an alternative chemotherapeutic agent after an initial trial of NVB and DDP (1 patient), or lost to follow-up (1 patient). Table I

**Table I. Relevant characteristics of evaluable patient population**

Attribute	Number of patients (n=94)
Sex	
male	51
female	43
Stage	
iiia	4
iiib	12
iv	76
local recurrence	2
Histology	
squamous cell	24
adenocarcinoma	54
large cell	9
not otherwise specified	7
Mean age (years)	57

outlines relevant characteristics of the 94 evaluable patients.

**Survival**

The overall Kaplan-Meier survival curve is shown in Figure 1. Median survival times (MST) and survival rates at six-month increments are shown in Table II. Survival times did not differ significantly amongst sex, age, or stage subsets. However, a significant survival advantage was seen in those patients who received the lowest dose intensity of each of NVB and DDP ( $p < 0.0005$  and  $p = 0.002$ , respectively, for survival curve differences). Figure 2 reveals the trend between dose intensity of NVB and DDP ( $p < 0.0005$  for trend).

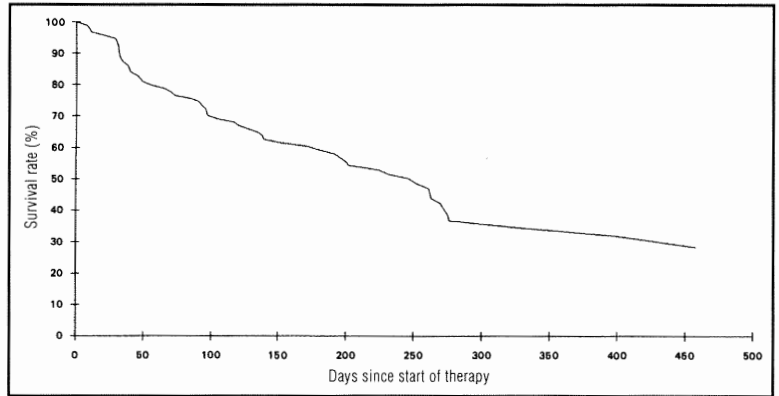
**Dose intensity**

A treatment course consisting of consecutive weekly standard doses, or 100% dose intensity, was administered to 18 individuals. Of these, 15 had only one or two courses of therapy, which was too early for hematological toxicity to have manifested (granulocyte nadir = 7–10 days), therefore no dose adjustments were indicated.<sup>8</sup> By comparison, only three of the 76 patients who proceeded beyond the initial two courses tolerated 100% dose intensity.

The average dose per administration reflects the weekly reductions of the standard dose of NVB due to granulocytopenia as dictated by the protocol. Dose deferrals were a consequence of either granulocytopenia, complicating medical conditions, or patient-elected drug holidays. These deferrals prolonged the actual length of therapy by a median value of 1.4 times that of an uninterrupted treatment period. While the average dose per administration was only slightly lower than standard, the dose intensity was substantially reduced, largely due to dose deferrals (see Table III).

**Duration of therapy**

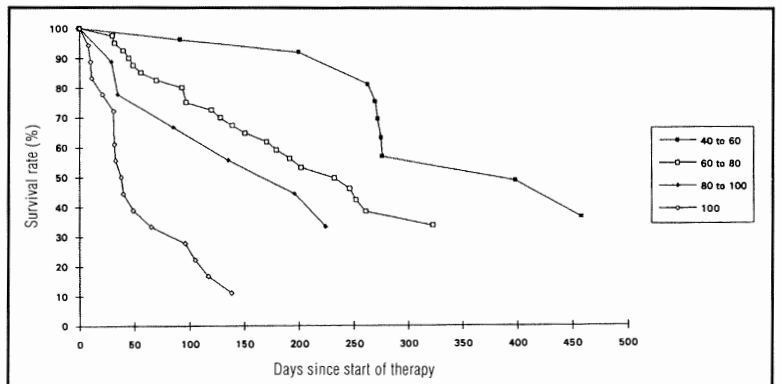
The number of courses of chemotherapy per patient ranged from 1 to 19. All 15 patients who received only 1 or 2 courses of therapy are deceased. Documented reasons for early withdrawal from therapy include: complications related to the progression of the malignancy (3), quality of life preservation (3), unrelated medical emergencies (2), and death (1). No such documentation was provided for the other 6 patients.



**Figure 1. Survival of patients receiving vinorelbine in combination with cisplatin for the palliative treatment of advanced NSCLC.**

**Table II. Median survival time (MST) and survival rates among evaluable patients**

Median survival time (wk)	35
Survival rate (%) at:	
6 months	59
1 year	33



**Figure 2. Survival of patients stratified by dose intensity (%) of vinorelbine ( $p < 0.0005$ ).**

**Table III. Treatment protocol and administered dose intensity**

	Standard dosage per administration (mg/m <sup>2</sup> )	Average dosage per administration (mg/m <sup>2</sup> )	Dose intensity* (%)
Vinorelbine	30	28.6 <sup>†</sup>	66.7% <sup>†</sup>
Cisplatin	60	60.0 <sup>†</sup>	66.7% <sup>†</sup>

\* Given dose divided by expected dose. Calculated full dose for the time that the patient was on treatment (4).

<sup>†</sup> Median value of all patients.

The total number of treatment courses administered to each patient is depicted in Figure 3. The graph reflects the proportion of patients who proceeded beyond each 6 course trial period.

### Alopecia

Figure 4 illustrates the incidence of hair loss amongst the 60 documented assessments. There were no statistically significant differences amongst the groups when stratified for sex and age. It is noteworthy, however, that all 5 patients who experienced complete head hair loss, for reasons that could not be otherwise explained by concomitant palliative cranial radiotherapy, were over 50 years of age.

### Granulocytopenia

Table IV reveals that the majority of patients experienced some degree of granulocytopenia throughout the course of therapy. The 15 patients who received only 1 or 2 courses (i.e. days 1 and 8 of therapy) were excluded because an assessment of hematological toxicity would be premature with the granulocyte nadir occurring between days 7–10.<sup>8</sup> It was postulated that laboratory results signifying insufficient white blood cells to perform a differential constituted the most severe case of granulocytopenia experienced by the given individual. The incidence of the associated complications, relative to granulocytopenia, was notably less frequent as demonstrated in Figure 5. The 24 documented cases of these complications were as follows: 10 cases of febrile neutropenia (11%), 14 cases of infection treated with antibiotics (15%). There were no deaths as a direct consequence of either the infections or febrile episodes. No relationship between age and the incidence of either granulocytopenia or its associated complications was found.

### DISCUSSION

Survival outcomes achieved in the heterogeneous population of practice were similar to those met in the population controlled clinical trials. The median survival time (MST) and 1-year survival rate reported in our review are similar to the MST of 40 weeks and 1-year survival rate of 35% attained in a major clinical trial.<sup>4</sup> This supports earlier hypotheses that polychemotherapy offers a survival advantage over the median of 17 weeks achieved with best supportive care.<sup>1,2</sup>

As previously alluded to, a comparative analysis of survival outcomes achieved in clinical trials and in practice is of limited

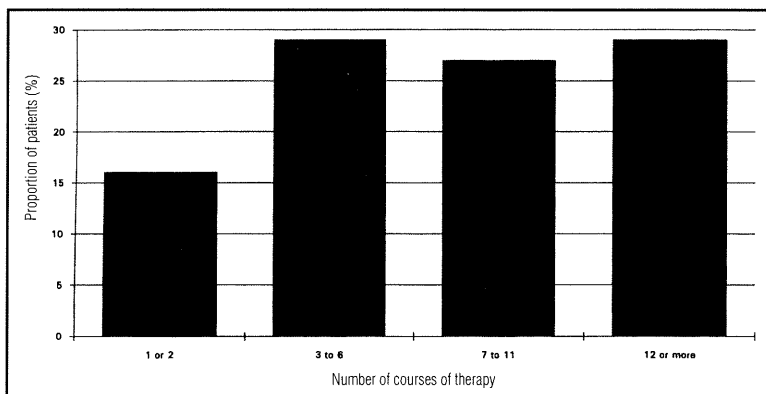


Figure 3. Total duration of therapy.

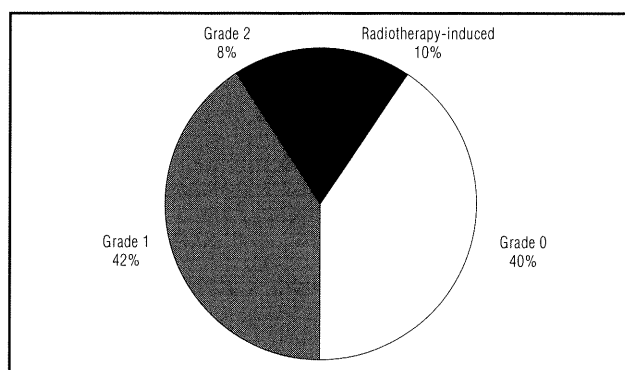


Figure 4. Incidence of alopecia.

Table IV. Cases of granulocytopenia among evaluable patients

Granulocytopenia by grade	Number of cases*	Grade as a % of adjusted cases
Grade 4	29	37
Grade 3	20	25
Grade 2	7	9
Grade 1	3	4
ICD †	13	16
All Grades	72	91

\* Total cases =79. Only the most severe case experienced throughout the course of therapy is used in this calculation. Adjusted number of cases =72.

† Insufficient cells present to perform a WBC differential.

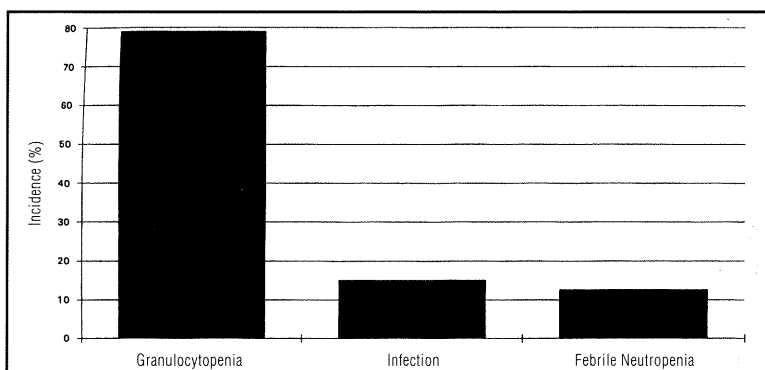


Figure 5. Incidence of granulocytopenia\* and associated complications†.

\*Denotes granulocytopenia grades 3, 4, and I.C.D.

†Denotes infection grades 2 and 3; febrile neutropenia grade 3

reliability. Primarily, the heterogeneous population of practice has many confounding factors influencing individual prognosis.<sup>6,7,9</sup> Results may easily be skewed in an uncontrolled population. Although this evaluation of practice yielded results comparable to the trials, a different practice population may not achieve the same outcomes.

The quantitative results from this evaluation verify the earlier predicted survival times; however, the qualitative nature of the extended survival was not investigated. Chemotherapy may negatively impact patients' quality of life due to its associated side effects or, rather, improve quality of life by palliating the symptoms associated with the disease.<sup>9</sup> In keeping with the intent of palliative chemotherapy to preserve the quality of life of its recipients, a careful analysis of both quantitative and qualitative outcomes is warranted.

The survival outcomes in this evaluation were met with a similar dose intensity of NVB (67% vs. 71% in practice and a major trial,<sup>4</sup> respectively) but a substantially lower dose intensity of DDP (67% vs. 96%). As well in this study, the paradoxical relation between survival and dose intensity is suggestive that a survival benefit can still be achieved with a less intensive dosing schedule.

Rarely was full dose intensity of either agent administered so it may be inferred that the current protocol is not well-tolerated in terms of granulocytopenia. A reduction in dose and/or dosing frequency may improve tolerability of the regimen.

Alternative dosing regimens currently under investigation have demonstrated promising results by maintaining a survival benefit with less toxic effects.<sup>10-13</sup> Options worth future consideration include: reduced doses administered over several days, weekly alternating full and half doses, or longer dosing intervals. Further clinical trials are warranted to determine a tolerable regimen which will not compromise survival benefit.

Tumour response may be roughly estimated from the duration of therapy because treatment is continued only if there is subjective evidence of response. It may be inferred that patients who proceed beyond each six-course trial are tumour responsive. However, the decision to pursue further treatment is determined by more than simply a subjective assessment of tumour response. Contributing factors include patient's health status, complicating medical conditions, or tolerance of side effects. Duration of therapy may, in fact, be a stronger reflection of the patient's willingness to continue therapy than an actual function of tumour response. Patients often elect to continue therapy based on the perceived benefit of the drug contributing to survival in contrast with the treatment effects and impact on quality of life.

Cases of alopecia encountered with this combination chemotherapeutic regimen may be attributed to NVB

since DDP is generally not associated with this toxic effect.<sup>14,15</sup> The risk of complete head hair loss due to NVB appears to be slight but some degree of mild hair thinning may be expected. The incidence of 50% for all grades was higher than the 19.2%–31.7% reported in earlier clinical trials.<sup>3,16,17</sup>

The incidence of alopecia in this evaluation may not be a true reflection of that attributed solely to the chemotherapy. Some of the reported cases may be a consequence of natural aging because it is difficult to ascertain, in retrospect, whether hair loss which pre-dated treatment was a consideration with each patient assessment.

While granulocytopenia was experienced by a large proportion of patients treated with the regimen, relatively few developed associated complications. The incidence of grade 3 or 4 granulocytopenia in this evaluation was 79%, which was similar to the 78.7% incidence in the LeChevalier trial.<sup>3</sup> There was, however, a slightly greater incidence of septic complications in this practical review than in the trial (7% vs. 4%, respectively).

Although comparatively infrequent, febrile neutropenia and sepsis are both potentially life-threatening and their occurrence disrupts the course of treatment, at the very least. The use of colony-stimulating factors may be warranted to offset the risk of these complications. However, the use of hematopoietic growth factors solely to support the administration of escalated doses of chemotherapy does not appear to be indicated.<sup>11</sup> Another option for the management of septic complications is the use of prophylactic antibiotic therapy in severely neutropenic patients. A future consideration could be the development of criteria to govern when prophylactic antibiotic therapy is indicated with this myelosuppressive regimen.

There were several limitations to this trial. First and foremost, the review was retrospective in nature and, because of this, the information may be incomplete. As well, while the results were stratified for stage, other prognostic indicators such as WHO performance status histological type, and extent and rate of tumour growth could not be accounted for with this retrospective design. Indeed it could be argued that the inverse relationship between dose intensity and survival could have been due to the aggressiveness of tumour growth with those patients with more aggressive growth dying before dose reductions or deferrals could take place. Unfortunately this information was not available. Additionally, the exclusion of patients who had received alternative treatments may be criticized since the study was intended to be an evaluation of outcomes achieved in clinical practice. However, because there were only 5 such patients, this was unlikely to markedly affect the results.

In summary, a survival benefit similar to that of earlier trials has been achieved in clinical practice with the

use of NVB and DDP. A future impact assessment on quality of life would complement this quantitative evaluation of survival.

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## Appendix A.

National Cancer Institute of Canada Clinical Trials Group Toxicity Criteria					
Grade	0	1	2	3	4
Granulocytes	2.0 10 <sup>9</sup> /L	1.5-1.9	1.0-1.4	0.5-0.9	<0.5
Febrile Neutropenia	—	—	—	Absolute gran. count <1.0 x 10 <sup>9</sup> /L, fever 38.5°C, treated with (or ought to have been treated with) IV antibiotics	—
Infection	none	mild, no active treatment	moderate, localized infect req. active treatment	severe, systemic infect req. parenteral treatment	—
Alopecia	no loss	mild hair loss	pronounced or total head hair loss	total body hair loss	—