Non-Small Cell Lung Cancer: A Study of Long-Term Survival after Vinorelbine Monotherapy

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ABSTRACT

This study reports the results of 120 patients with inoperable non-small cell lung cancer treated with Navelbine at a dose of 25-30 mg/m²/week in a single-drug chemotherapy regimen. Surgery was contraindicated due to staging or concomitant morbidity. Twenty patients achieved survival greater than or equal to 18 months, and one patient obtained exceptional survival of more than 120 months. The mean dose intensity of Navelbine in long-term survivors was 21.61 mg/m²/week. Objective response to Navelbine was found by multivariate analysis to be a prognostic factor for survival beyond 18 months. Weight loss of more than 5 kg of corporal weight was an unfavorable prognostic factor in patients with metastatic disease. The Oncologist 2000;5:115-119

INTRODUCTION

There is considerable experience in the use of chemotherapy to treat non-small cell lung cancer (NSCLC). As advanced stages (stages IIIB and IV) cannot be cured by surgery, chemotherapy is the reference treatment, especially in patients with evidence of metastatic spread. Among the drugs tested for activity as single-agents, mitomycin C, Adriamycin, ifosfamide, etoposide, cisplatin, taxanes, gemcitabine, and vinca alkaloids have shown antitumoral activity in more than 15% of patients [1-3]. Navelbine (vinorelbine) is the most active of the vinca alkaloids; it induces the highest objective response rates as a single-agent, as has been shown by a study of vinorelbine versus vindesine [4]. The phase II studies of Navelbine produced a consistent objective response rate of approximately 29% [5], while in phase III studies, it remains high at approximately 14% [6, 7], reflecting the difference in selection which is commonly observed between phase II and III studies.

Combination chemotherapies have proved their ability to prolong survival in comparison with palliative treatments, but the extra benefit of a two-drug combination over a single-agent remains low and is not reliably observed in randomized studies [7-9].

The main objective of this study is to describe a group of patients with NSCLC treated at first-line with Navelbine as a single-agent, to identify those having a survival time greater than or equal to 18 months, and then to perform a multivariate analysis of the prognostic factors affecting long-term survival.

MATERIAL AND METHODS

Population

The study recruited 120 patients presenting with advanced stage or localized but inoperable NSCLC who were treated with single-agent Navelbine at two different doses (25 mg/m²/week or 30 mg/m²/week). Patients were treated in the Pneumology Unit of the University Hospital of Besançon from 1985 to 1995 and represented 11.6% of the total of 1,037 comparable subjects who were treated in the unit over that period.

Patients presenting with stage I to IIIA NSCLC were selected for treatment with Navelbine alone for one of the following reasons: poor general health or unconditional contraindication to surgery (forced expiratory ventilation inferior to 1 liter, cardiac insufficiency, elderly, or poor performance status [PS]). Most patients presenting with stage IIIB or IV disease were included in phase II or III studies.

Among these 120 patients, 20 were identified as long-term survivors (16.6%).
**Methodology**

Among the study population, the following prognostic variables were evaluated in order to determine whether they had a significant influence on survival time: age, gender, PS, weight loss, histological type, NSCLC stage, number of metastatic sites, nature of metastatic sites (bone, liver, brain), and response to chemotherapy. These variables were studied according to a witness/case methodology, first through univariate analysis using a chi square test, then by a multivariate analysis using logistic regression. The long-term survivors ($\geq 18$ months) were the cases, while the patients with a survival time less than 18 months made up the witness group. The response to chemotherapy was also studied as a time-dependent variable in a Cox model. Data were entered in DBase III+, and the statistical analysis was performed using the BMDP package [10]. Survival was defined as the time interval in months between the first treatment with Navelbine and the date of death or last contact. Long-term survival was defined as a period greater than or equal to 18 months, most studies having one or two years as long-term survival criteria [11-12]. Response to chemotherapy was evaluated according to World Health Organization criteria [13] by thoracic CT scan, fiberoptic bronchoscopy, and systematic evaluation of metastatic sites at week 9.

For the 20 long-term survivors, the Navelbine dose intensity was calculated according to published methods [14] over 9 and 18 cycles; the mean dose intensity was then compared with published data. Survival curves were generated according to the Kaplan-Meier actuarial method [15].

The following prognostic variables were studied (quantitative variables were changed to dichotomic qualitative variables): age at diagnosis (greater than 65 years versus less than or equal to 65 years); gender (male versus female); PS (0 and 1 versus 2, 3, and 4); weight loss (more than 5 kg versus less than or equal to 5 kg); histological type (adenocarcinoma, squamous cell carcinoma, large-cell carcinoma); stage (IV versus I, II, and III); number of metastatic sites in stage IV (one site versus more than one site); localization of metastatic sites (bone, liver, brain); and type of response to chemotherapy (objective response versus progression, stabilization, and unevaluable response). The multivariate analysis of this last variable was performed by logistic regression as well as according to the Cox model.

**Results**

**Description of Study Population**

The characteristics of the population are presented in Table 1. The population consisted of 114 males and six females with a mean age of 65.6 years (range 39-84 years). Seventy-five percent of patients had a PS of 0 or 1; 37 patients (31.6%) had weight loss greater than 5 kg at presentation.

Histological classification of the tumors showed a predominance of squamous cell carcinomas (85 patients, 70.8%), while 26 patients had adenocarcinomas (21.7%), and nine had large-cell carcinomas (7.5%). Six patients presented with disease at stage I, six at stage II, 40 at stage IIIA, 11 at stage IIIB, and 57 at stage IV. Patients with metastatic disease comprised 47.5% of the population. The distribution of metastatic sites was as follows: lung = 19; bone = 15; liver = 14; pleura-pericardium = 14; adrenal glands = 7; lymph nodes = 6; brain = 4; various = 4; skin = 3. Forty patients had only a single metastatic site, and 17 had two or more.

Twenty-seven patients (22.5%; 95% confidence interval [CI] = [15-30]) obtained an objective response to chemotherapy (four complete responses and 23 partial responses). The outcome of the other patients was categorized as follows: 25 patients were stable, 45 progressed, 21 were not evaluable due to death before week 9 (toxicity or progression), and two were lost to follow-up. These data are summarized in Table 2.

Of the 23 patients who underwent a second line of treatment, 19 were given cisplatin. Among the 20 long-term survivors, 19 patients who relapsed subsequently received either radiotherapy (eight cases), cisplatin-based chemotherapy (five cases), or resection of metastases (one case), while five received no further treatment. Among the five patients treated with cisplatin as second-line chemotherapy, two achieved a partial response, although they had previously progressed on Navelbine; two were stabilized (both had

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**Table 1. Study population characteristics**

<table>
<thead>
<tr>
<th>Variable</th>
<th>$n = 120$</th>
<th>%</th>
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<tr>
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<tr>
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</table>
obtained initial stabilization of disease with Navelbine); and one patient was not evaluable.

Univariate Analysis

There was no significant difference for age, gender, histology, and stage between cases and witnesses. Long-term survival was more often associated with a 0 or 1 PS ($p = 0.02$), with a weight loss less than 5 kg ($p = 0.0049$), and with an objective response ($p < 10^{-4}$) (Table 3).

In the 57 metastatic patients, survival was not influenced by age, PS, weight loss, number of metastatic sites, and bone, hepatic, or cerebral localization, but the objective response value was again significant ($p = 0.015$) (Table 4).

Multivariate Analysis

The variables found to be significant with the univariate analysis were entered into the multivariate logistic regression model in order to study their influence on the ability to achieve a survival time greater than or equal to 18 months. These variables entered were response type, weight loss, and PS (Table 5). Only objective response proved to be an independent prognostic factor for survival with a hazard ratio of $6.37; 95\% \text{ CI} = (2.09-19.4)$ ($p < 10^{-4}$).

By using a Cox model with response as a time-dependent variable, it was confirmed that achievement of a response is an independent prognostic factor in predicting survival after adjustment for weight loss. In the overall population, the relative death risk in the absence of response is $4.91; 95\% \text{ CI} = (2.88-8.34)$, ($p < 10^{-5}$). When the same method is applied to the metastatic population, the relative death risk in non-responders is $2.94; 95\% \text{ CI} = (1.46-5.89)$, ($p = 0.0014$), and weight loss $>5$ kg is shown to be an independent prognostic factor with a relative risk at $1.02; 95\% \text{ CI} = (1.005-1.042)$, ($p = 0.04$), but the PS remains insignificant ($p = 0.08$). Due to the small sample population, the second-line treatment influence on long-term survival has not been evaluated.

Survival

The survival curves are presented in Figure 1. Median survival time was six months, median disease-free survival 2.5 months. Survival at one year, two years, and three years represented 30.8%, 11.7%, and 4.2%, respectively. Ten patients had a duration of response greater than one year, and two had a duration of response greater than two years.

Navelbine Dose Intensity

Navelbine dose intensity in long-term survivors was calculated using Hrynyuk’s method over 9 and 18 cycles. The theoretical weekly dose was 25 to 30 mg/m$^2$/week, depending on protocols in progress. The calculated mean was 21.61 mg/m$^2$/week over nine cycles and 18.90 mg/m$^2$/week over 18 cycles.

DISCUSSION

This analysis establishes a number of points about the treatment of NSCLC. It confirms with a large population that the response rate achieved with single-agent Navelbine...
The response to chemotherapy is paramount: among the 20 long-term survivors in our study, three complete responses and nine partial responses were observed. In the Eastern Cooperative Oncology Group study [12], long-term survival was more often seen in responders: 62% of complete responders and 34% of partial responders survived for more than one year. Similarly, in the study by Sculler [20], the objective response was among the good prognostic factors, together with PS and stage. Nevertheless, in the French database of long-term survivors [21], it had been shown that in contrast to the experience with small-cell carcinomas, long-term survival could be observed in NSCLC even in the absence of treatment.

The age [22, 23], gender [24-26], PS [12, 20, 26], and number and localization of metastatic sites [12, 26, 27], which are generally acknowledged to be prognostic factors in NSCLC, do not emerge as relevant in this long-term survival study. Weight loss greater than 5 kg is an unfavorable prognostic factor only in the metastatic population, as has already been shown by other authors [12, 22].

The prognostic value of stage has not been shown to be significant, although this can be partially explained by the numerous complicating medical conditions in our patient population. Of the 24 patients who suffered from severe cardiovascular and respiratory comorbidities, only three were long-term survivors. Inoperability as a result of functional problems could be an element in counteracting the advantage of presentation with early-stage disease.

The international literature offers relatively few articles concerning long-term survival of inoperable NSCLC, and this reflects the rarity of such an outcome. It is, however, important to emphasize that a percentage of such patients can experience prolonged survival after treatment with single-agent Navelbine; this therapy is given at a low toxicity level, is able to induce an objective response in a worthwhile proportion of patients, and will result in survival greater than 18 months for some of these responders.

**REFERENCES**


