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Phase II Trial of Carboplatin, Paclitaxel Plus Vinorelbine in Non-small Cell Lung Cancer Patients

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Abstract. *Background: Vinorelbine was added to carboplatin plus paclitaxel to determine efficacy and toxicity in non-small cell lung cancer (NSCLC) patients with good performance status. Patients and Methods: Vinorelbine 30 mg/m^2 plus paclitaxel 175 mg/m^2 plus carboplatin AUC 5 was administered every three weeks for a maximum of 6 cycles. Results: One out of 37 patients had a complete and 12 a partial remission (35% response rate). Six patients (16%) had disease stabilization and 18 (49%) progressed. Grade III or IV neutropenia occurred in 11 (30%) and febrile neutropenia in 6 (16%) patients. Grade III/IV neuropathy was observed in 6 (16%) patients. The median time to progression was 6 months (95% CI 4.0 – 8.0), and median survival 11 months (95% CI 8.3 – 13.7). One- and two-year survival was 41% (95% CI 24 – 58) and 24% (95% CI 8.7 – 39.1), respectively. Conclusion: This triple-chemotherapy combination is feasible. The response rates justify further investigation in similar patient subgroups.*

Platinum-based chemotherapy regimens are well established as palliative treatment of non-small cell lung cancer (NSCLC). When compared to best supportive care, chemotherapy is able to prolong survival and improves quality of life (1, 2). Large randomized trials demonstrated the equal efficacy of the modern drugs paclitaxel, docetaxel and gemcitabine in combination with cisplatin or carboplatin (3). A favorable toxicity profile of the paclitaxel plus carboplatin combination was reported as compared to cisplatin-based combinations (3). Therefore, paclitaxel plus carboplatin has become one of the standard regimens in treatment of NSCLC and toxicity may allow the addition of further drugs.

The inclusion criteria in most clinical trials have been an ECOG performance status ≤2, which is equal to a Karnofsky performance status (KPS) ≥60%. However, high toxicity rates of platinum-based doublet regimens in patients with KPS ≤70% were demonstrated, which resulted in the exclusion of this patient group in some trials (3). Few clinical trials have addressed treatment options in younger NSCLC patients with advanced disease, but favourable prognostic factors include KPS of ≥70% without significant comorbidity. In such a selected patient population, we investigated the efficacy and toxicity of a triple-chemotherapy regimen consisting of the three-drug combination carboplatin, paclitaxel and vinorelbine.

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Patients and Methods

Patient selection. Chemotherapy-naïve patients with histologically or cytologically confirmed NSCLC stage III B with malignant pleural effusion or stage IV were eligible for this phase II trial. Further inclusion criteria were age between 18 and 70 years, Karnofsky performance status ≥70%, expected survival of >3 months, adequate bone marrow function with a hemoglobin level >10g/dl, platelet count >100/nl, leucocyte count >3/nl, neutrophil count >1.5/nl and written informed consent. Exclusion criteria were the presence of symptomatic brain metastases, pregnancy or lactation, major organ dysfunction including congestive heart failure > NYHA II, symptoms or a history of coronary heart disease, renal or hepatic impairment with serum creatinine ≥1.5 times normal value or serum ASAT or ALAT >3 times normal range and pre-existing neuropathy > grade I, according to CTC criteria.

Chemotherapy. The chemotherapy regimen included vinrelbine 30 mg/m^2 in 250 ml NaCl 0.9% *i.v.* over 15 minutes, followed by

Table I. *Patient characteristics.*

	Number of pts.
All patients	37 (100%)
Female	12 (32%)
Male	25 (68%)
Median age (range)	54 years (34–69)
Karnofsky PS	
100%	6 (16%)
90%	11 (30%)
80%	14 (38%)
70%	6 (16%)
Stage	
IIIB	5 (13%)
IV	32 (87%)
Histology	
Adenocarcinoma	19 (51%)
Squamous cell carcinoma	11 (30%)
Large cell carcinoma	3 (8%)
Unclassified NSCLC	4 (11%)

PS = performance status, NSCLC = non-small cell lung cancer

Table II. *Response to treatment.*

Number of pts.	N=37 (100%)
Complete remission	1 (3%)
Partial remission	12 (32%)
Stable disease	6 (16%)
Progressive disease	18 (49%)

pts.= patients

Table III. *CTC Grade III and IV toxicity.*

Number of pts.	N=37 (100%)
Anemia	1 (3%)
Neutropenia	11 (30%)
Thrombopenia	2 (5%)
Neuropathy	6 (16%)
Infection w/o neutropenia	1 (3%)
Febrile neutropenia	6 (16%)

pts.=patients, w/o= without.

paclitaxel 175 mg/m^2 in 500 ml NaCl 0.9% over 3 hours and carboplatin at a dose of AUC 5 mg x min/ml in 500 ml 5% glucose over one hour. Chemotherapy was administered on day 1. The cycles were repeated on day 22. In the absence of disease progression, a maximum of 6 cycles were administered. The individual dose of carboplatin was determined using Calvert's formula (4): Dose (mg) = AUC x (glomerular filtration rate (GFR) + 25). GFR was determined using Jelliffe's formula (5). All patients received anti-emetic therapy consisting of 5 mg tropisetrone *i.v.* before starting the infusion of chemotherapy. Antihypersensitivity premedication consisted of dexametasone 8mg orally approximately 12 and 2 hours before chemotherapy and clemastine 2 mg *i.v.* plus ranitidine 50 mg *i.v.* before chemotherapy. In case of grade 3 neuropathy during chemotherapy, vinorelbine was deleted and only paclitaxel plus carboplatin was administered in subsequent cycles. In case of febrile neutropenia, secondary prophylaxis with filgrastim at a dose of 5 μg/kg per day starting on day 5 after subsequent chemotherapy cycles was administered subcutanously.

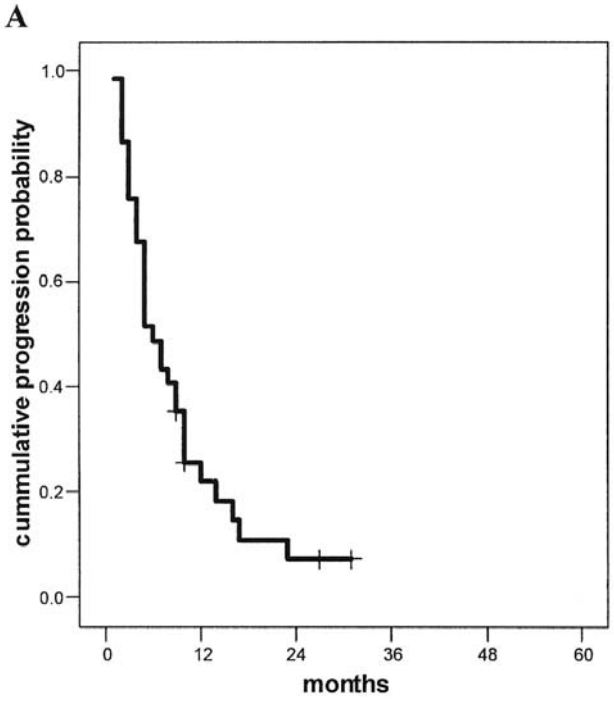
Efficacy evaluation. CT-based tumor response evaluation according to the RECIST criteria (6) was performed before initiation of chemotherapy and after 2, 4 and 6 cycles of chemotherapy. In the follow-up period, CT scans were performed every 12 weeks. Time to progression, response duration and survival were analysed using the Kaplan-Meier method.

Statistical considerations. The number of patients to be included in the study had been calculated according to Simon's optimal two-stage minimax design (7). The criteria for a further evaluation of the regimen in future phase III trials was a response rate exceeding 40%. In case of a response rate below 20%, the study was planned to be terminated early. To minimize the sample size in case of low efficacy according to the minimax design, the response rate was analysed after a first step of 17 evaluable patients. In case of >3 objective responses out of 17 patients in step 1, 20 additional patients were included into step 2. If >10 out of 37 patients had an objective response after this second step, it can be concluded, with an alpha-error of 10%, that the efficacy of the regimen warrants further investigation within future trials.

Results

Patient characteristics. Thirty-seven patients were included in this study. The patient characteristics are listed in Table I. Median age was 54 years, with a range between 24 and 69 years. Six (16%) had a Karnofsky performance status of 100%. Five (13%) had stage IIIB disease with malignant pleural effusion. Fifty-one % of patients had an adenocarcinoma.

Response to treatment. One out of 37 patients had a complete remission lasting for 9 months and 12 (32%) had



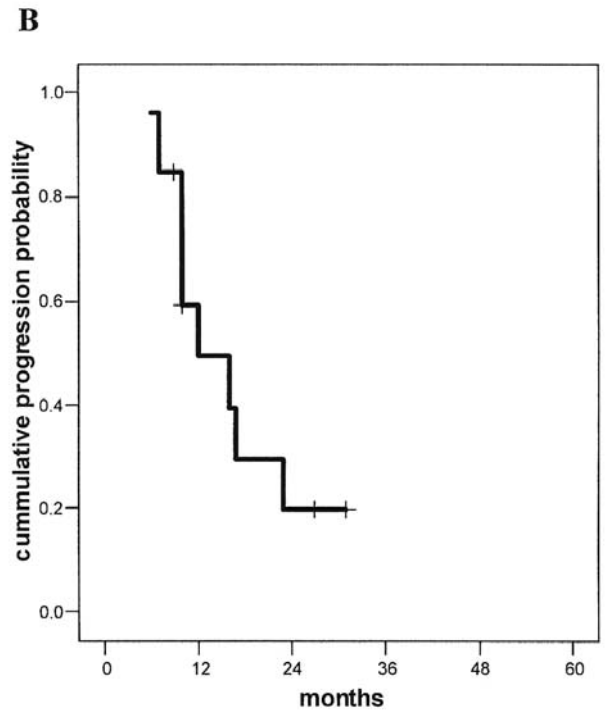


Figure 1. *Kaplan-Meier estimates for progression-free survival (A) and response duration in patients with complete or partial response (B).*

a partial remission (Table II). The objective response rate was 35%. Six (16%) stabilized and 18 (49%) had progressive disease (Table II).

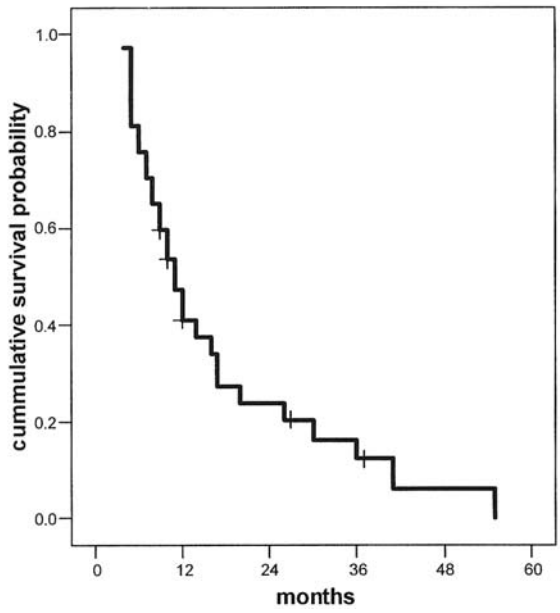


Figure 2. *Kaplan-Meier estimates for overall survival.*

Toxicity and dose reduction. Neutropenia was the most frequent grade III or IV hematological toxicity, which occurred in 11 (30%) patients. In 6 (16%) patients neutropenia was complicated by fever. Grade III or IV thrombopenia and anemia were observed in 2 and 1 patient, respectively. Grade III or IV neuropathy occurred in 6 (16%) patients. In these patients, vinorelbine was deleted and only paclitaxel plus carboplatin was administered in the following chemotherapy cycles. One patient had a grade 3 infection (pneumonia) in the absence of neutropenia (see Table III).

Time to progression, response duration and survival. The median time to progression (TTP) was 6.0 months (95% CI 4.0 – 8.0) and the median response duration was 12 months (95% CI 3.2 – 20.8). One- and 2-year progression-free survival were 21.9% (95% CI 7.5 – 36.3) and 7.3% (95% CI 0 - 17.0), respectively (Figure 1). The median overall survival was 11 months (95% CI 8.3 – 13.7). One- and 2-year overall survival were 40.9% (95% CI 24.1 – 57.7) and 23.9% (95% CI 8.7 – 39.1), respectively (Figure 2).

Discussion

This study investigated the three-drug chemotherapy regimen carboplatin plus paclitaxel plus vinorelbine in a selected favorable patient subset. Earlier randomized trials were not able to show a benefit for three-drug chemotherapy regimens over two-drug regimens. However, several of these

trials did not employ a modern cytostatic agent such as a taxane, vinorelbine or gemcitabine (8 - 10). Two randomized trials have been reported, which investigated three-drug combinations including platinum plus two new agents (11, 12). In an interim analysis of the first study, the superiority of the combination of cisplatin plus gemcitabine plus vinorelbine over cisplatin plus vinorelbine was observed, which resulted in an early termination of the cisplatin/vinorelbine arm. However, this triple-chemotherapy regimen was not superior to cisplatin plus gemcitabine (11). The second trial did not show a difference in survival between the carboplatin/paclitaxel/gemcitabine or carboplatin/paclitaxel/vinorelbine or the two-drug regimens paclitaxel/gemcitabine or gemcitabine/vinorelbine (12). In contrast to our study, this study also enrolled patients with KPS of 60% and age >70 years.

The median age of patients enrolled into this trial was 54 years, which is significantly lower than the median age of about 63 years in many other studies, which also included patients >70 years (3, 12). The objective response rate in our study was 35%. The response rates in other studies varied between 10 and 60%. In addition, the median survival and the 1- and 2-year survival rates of 41% and 24% are promising, when compared to earlier trials. One major reason for these favorable survival data may be a reflection of patients with good prognostic features. It has been demonstrated that KPS is one of the most important prognostic factors for survival in NSCLC (13, 14). Therefore, this regimen should be investigated in a phase III trial prior to broader use. In addition, our regimen may be investigated in neoadjuvant settings.

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