Title: Phase I and II trials of vinorelbine with carboplatin for patients 75 years of age or older with previously untreated non-small-cell lung cancer

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Running Title: NSCLC in the elderly

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Abstract

Background: The safety and efficacy of platinum-based combination chemotherapy for elderly patients with advanced non-small-cell lung cancer (NSCLC) remains unclear. We conducted Phase I and Phase II trials of a combination of vinorelbine and carboplatin for patients ≥ 75 years of age with advanced NSCLC. **Patients and Methods:** Previously untreated patients (≥75 years of age) with Stage IIIB or IV NSCLC were enrolled. Based on a 4-week cycle, vinorelbine was given on days 1 and 8, and carboplatin on day 1. Dose-limiting toxicity (DLT) was defined as grade 4 hematologic toxicity lasting 4 days or more; febrile neutropenia; grade 3 or worse non-hematologic toxicities; or the omission of vinorelbine administration on day 8 in the first cycle. **Results:** A total of 13 patients was enrolled in Phase I. DLT was grade 4 neutropenia lasting 4 days or more, observed in 2 of 4 patients at level 4. Phase II study used the dose of level 3 (20 mg/m^2 vinorelbine, area under the curve [AUC] = 4 mg/ml/min carboplatin). A total of 42 patients was enrolled. The response rate was 14.6% of 41 assessable patients (95% confidence interval [CI] 3.8-25.4). The median time to progression was 98 days (95% CI 61-135) and median survival time was 366 days (95% CI 321-411). All toxicities were mild and manageable. **Conclusion:** Use of 20 mg/m^2 vinorelbine on days 1 and 8 followed by carboplatin AUC = 4 mg/ml/min on day 1 every 4 weeks warrants a Phase III study for elderly patients with advanced NSCLC.

Introduction

Lung cancer is currently a leading cause of cancer death in developed countries.[1,2] The risk of lung cancer increases with age. It has been reported that patients ≥ 70 years of age account for 47% of all lung cancer cases,[3] and it should be noted that while the incidence and the mortality from lung cancer has decreased among patients ≤ 50 years of age, it has increased in older patients.[4]

Platinum-based chemotherapy is currently recommended as the standard treatment for patients with advanced NSCLC.[5] However, it is unclear whether it should be recommended as the standard regimen for elderly patients with advanced NSCLC. Its efficacy for such a population has been questioned because of the perceived higher risk of toxicity.[5] On the other hand, large elderly-specific randomized trials have recommended that single-agent chemotherapy with a third-generation agent (e.g., vinorelbine, gemcitabine, taxanes) be used for elderly patients with advanced NSCLC.[5]

Vinorelbine is a semisynthetic vinca alkaloid, which showed significantly superior survival over best supportive care (median survival time 27 weeks vs. 21 weeks, $p = 0.04$) in a landmark Phase III trial in elderly patients with advanced NSCLC.[6] Since then, vinorelbine monotherapy has become one of the most important chemotherapy regimens for elderly patients.[5,7] Carboplatin is a platinum derivative with less renal toxicity and causes less nausea and vomiting than cisplatin.[8] We therefore considered that vinorelbine and carboplatin could be an effective combination for elderly patients with previously untreated NSCLC and planned Phase I and II trials of this combination regimen. The aim of the Phase I study was to determine the best dose of this regimen and that of the

Phase II study was to investigate its activity.

Patients and methods

Eligibility Criteria

The eligibility criteria for this study were as follows: histologically or cytologically confirmed stage IIIB or IV NSCLC in the sixth edition UICC TNM classification of malignant tumors, ≥ 75 years of age, no prior chemotherapy or radiation therapy, measurable lesions, Eastern Cooperative Oncology Group performance status of 0 or 1, life expectancy of 12 weeks or longer, adequate organ functions (leukocyte count ≥ 4000/μl, hemoglobin ≥ 10 g/dl, platelet count ≥ 100,000/μl, serum bilirubin level ≤ 1.5 mg/dl, serum alanine aminotransferase and aspartate aminotranferase levels ≤ 2 times the upper limit of normal, serum creatinine levels ≤ 1.5 mg/dl). Exclusion criteria included: myocardial infarction within the previous 3 months; uncontrolled angina pectoris or arrhythmia; symptomatic brain metastasis; uncontrolled hypertension or diabetes; active infection, pulmonary fibrosis, pleural effusion or ascites requiring drainage; or cerebrovascular disease. The ethics committees of participating centers approved the study protocol. Written informed consent was obtained from each patient. This study is an independent collaborative (non-sponsored) group study.

Assessment of Treatment

Before treatment, all patients underwent a complete medical history and physical examination, chest radiography, chest and abdominal computed tomography (CT) scans, a radionuclide bone scan, a brain CT or magnetic

resonance imaging scan, an Electrocardiography and arterial blood gas analysis. Laboratory tests included a complete blood count with white blood cell differential, liver function tests, serum electrolytes, serum creatinine, blood urea nitrogen, and urinalysis. The physical examination and laboratory tests were performed at least twice a week. Chest radiography and/or CT were repeated every cycle to evaluate tumor response.

Tumor response was classified according to the WHO criteria.[9] A complete response (CR) was defined as the disappearance of any evidence of tumors for at least 4 weeks. A partial response (PR) was defined as ≥ 50% reduction in the sum of the products of the greatest perpendicular diameters of all lesions for at least 4 weeks. No change (NC) was defined as < 50% reduction or < 25% increase in the products of the greatest perpendicular diameters of all lesions without any evidence of new lesions. Progressive disease (PD) was defined as an increase of ≥ 25% or the appearance of new lesions. Response duration was measured from the start of the treatment to disease progression. Toxicities were assessed by use of the National Cancer Institute Common Toxicity Criteria version 2.0 (NCI-CTC, ver 2.0). [10]

Study Design

Treatment consisted of fixed doses of carboplatin and escalating vinorelbine doses. Vinorelbine was diluted in 50 ml normal saline and administered within 10 minutes on days 1 and 8. Carboplatin was diluted in 250 ml normal saline and administered after vinorelbine in 60 minutes on day 1. The treatment schedule was repeated every 4 weeks.

If a patient had a leukocyte count < 2000/μl and/or a neutrophil count < 1000/μl on day 8, the treatment scheduled for day 8 was not given. The next cycle started after the leukocyte and platelet counts reached > 3000 and 100,000/μl, respectively. After a delay of 2 weeks, if toxicity persisted, the treatment was stopped. Recombinant human granulocyte colony stimulating factor could be given if grade 3 or worse leukocytopenia or neutropenia occurred. Prior to treatment, all patients received prophylactic anti-emetic therapy with a type-3 serotonin receptor antagonist and dexamethasone.

Phase I study: Carboplatin dose was fixed at area under the curve (AUC) = 4 mg/ml/min for all patients, and vinorelbine was started at a dose of 10 mg/m^2 and increased by 5 mg/m^2. Dose-limiting toxicity (DLT) was defined as grade 4 hematologic toxicity lasting 4 days or more; febrile neutropenia; grade 3 or worse non-hematologic toxicities with the exception of nausea, vomiting, anorexia and alopecia; and the omission of vinorelbine administration on day 8 in the first cycle. At least three patients were enrolled at each dose level. The vinorelbine dose was increased to the next level if no patient displayed any DLT. If two of the three patients showed DLT, then this level was defined as the maximum tolerated dose (MTD). If one of the three patients showed DLT, three additional patients were enrolled at the same level. If none of these additional patients showed DLT, the dose was increased to the next level. If one or more of the three additional patients had DLT, this dose was defined as the MTD. The recommended dose for the Phase II study was the level below the MTD.

Phase II study: Combination chemotherapy with vinorelbine and carboplatin at the recommended dose was repeated every 4 weeks until the patient refused the treatment or showed progressive disease. An 80% reduction in carboplatin dose was allowed for grade 4 leukocytopenia or neutropenia lasting 4 days, febrile neutropenia, or grade 4 thrombocytopenia during the previous cycle. A Simon two-stage minimax design was chosen for definition of the total number of patients required for this study. Assuming an overall response rate of 25% for standard therapy, a target response rate of 25% was established. Alpha = 0.05, beta = 0.20, and the estimated required number of patients was > 40. If three patients or more had not achieved PR in an interim analysis when 22 patients were accrued, the Phase II study would be discontinued.

Results

Patients Characteristics

Fifty-five patients were enrolled from November 1999 to November 2005 and their characteristics are listed in Table 1. Thirteen patients were entered in the Phase I study, and 42 in the Phase II study. In the Phase II study, one patient was not assessable because of staging violation. Twenty-one patients (38.9%) were stage IIIB and 33 patients (61.1%) were stage IV. Thirty-six patients (66.7%) had adenocarcinoma, and 13 (24.1%) had squamous-cell carcinoma.

Phase I Study

The dose-escalation schedule and major toxicity profile are summarized in Table 2. No DLT was observed in patients treated with dose levels 1, 2 or 3. Two

level-4 patients experienced DLT (grade 4 neutropenia lasting 4 days or more); therefore, level 4 was defined as MTD and level 3 provided the recommended dose (vinorelbine: 20 mg/m^2, carboplatin: AUC = 4 mg/ml/min). Grade 3 or 4 non-hematologic toxicity in Phase I was observed in one patient who experienced grade 3 constipation. With regard to clinical response, although not required in Phase I evaluation, we observed PR in one of three patients at dose level 3 and one of four patients at dose level 4. The overall response rate was 15.4%.

Phase II Study

The 41 patients treated in the Phase II study received a total of 96 cycles of therapy: the median was 3 cycles (range 1-6). Eleven (11.4%) of 96 cycles were delayed because of hematologic toxicities. The relative dose intensity of vinorelbine was 95.8% (184/192). Leukopenia was the reason for the omitted dose of vinorelbine on day 8 in all cases.

Results of the Phase II study are summarized in Table 3. Objective responses were observed in 6 (14.6%) of 41 assessable patients (95% CI 3.8-25.4). The median time to progression was 98 days (95% CI 61-135) and median survival time was 366 days (95% CI 321-411). One-year survival was 52.9% (95% CI 36.2-69.6) and 2-year survival was 16.3% (95% CI 3.0-29.6).

Toxicities observed during the treatment are listed in Table 4. The principal hematologic toxicity > grade 3 was neutropenia, experienced by 26 patients (63.4%). Neutropenias were all reversible and there was no febrile neutropenia. One patient suffered grade 4 anemia; no patient experienced grade 3 or 4

thrombocytopenia. No patient required blood transfusion. There was no treatment-related death.

Discussion

We evaluated the toxicity and the efficacy of combination chemotherapy with vinorelbine and carboplatin in patients ≥ 75 years of age with previously untreated advanced NSCLC. Our Phase I study found the recommended doses of vinorelbine and carboplatin to be 20 mg/m^2 and AUC = 4 mg/ml/min, respectively. The response rate in the Phase II study was 14.6% (95% CI 3.8-25.4), and all toxicities were mild and controllable.

Single-agent chemotherapy with third-generation agents (e.g., vinorelbine, gemcitabine, taxanes) has been considered as the standard treatment for elderly patients with advanced NSCLC, based on the results of several Phase III trials.[6,7,11] Recently, two randomized Phase III trials evaluated the efficacy of platinum-based combination chemotherapy in an elderly population. Quoix E et al. demonstrated that combination chemotherapy with weekly paclitaxel (90 mg/m^2, day 1, 8,15) and carboplatin (AUC = 6 mg/ml/min, day 1) improved the overall survival compared with single-agent chemotherapy with gemcitabine or vinorelbine, though the toxicity of the combination regimen was higher.[12] However, Abe et al. found in their first interim analysis that the survival of weekly docetaxel (20 mg/m^2, days 1, 8, 15) and cisplatin (25 mg/m^2, days 1, 8, 15) in combination was not superior to that of docetaxel (60 mg/m^2, day 1): the study was terminated early (JCOG0803/WJOG4307L).[13] In this trial, the combination regimen was again more toxic. Indeed, the American Society of Clinical

Oncology states in their guidelines that the evidence does not support the selection of a specific first-line chemotherapy drug or combination treatment based on age alone. They also emphasize that older patients may experience more toxicity from cytotoxic chemotherapy than younger patients, but they may garner an equal amount of benefit, and physiologic age is more important in treatment selection.[5] Considering these reports, a more effective and safe combination chemotherapy regimen is required for elderly patients with advanced NSCLC.

Aging is associated with physiological changes in functional status, organ function, and drug pharmacokinetics. Furthermore, toxicities might be more severe in older patients because of the decline in organ functions.[14,15] Kudoh et al. demonstrated that docetaxel improved clinical outcomes in elderly patients with advanced NSCLC compared with vinorelbine. A subset analysis of this trial showed that toxicities were more severe in the subset containing patients ≥ 75 years of age compared with the younger subset.[11] In the JCOG0803/WJOG4307L trial, three quarters of patients recruited were ≥ 75 years of age. This study evaluated the cisplatin combination regimen, and the older subgroup showed severe toxicities. Cisplatin is thought to be slightly more effective than carboplatin, but it also has more adverse effects.[5] Thus, when developing a new combination regimen for the elderly, safety might be one of the most important factors although dose intensity is usually significant in clinical trials.

The recommended dose in this study was 20 mg/m^2 vinorelbine on days 1 and 8, and carboplatin, target AUC = 4 mg/ml/min, on day 1. This dose intensity

was lower than that in previous trials,[14,15] which might be the reason for the moderate response rate in this trial. However, patients eligible for this trial were ≥ 75 years of age, older than in previous Phase III trials. We previously reported a Phase II trial of carboplatin (AUC = 5) and irinotecan for patients aged ≤ 74 years with previously untreated NSCLC. Grade 3 or 4 neutropenia was experienced by 60% of patients.[16] As aging is associated with decreases in marrow reserve, we decided to use a dose of AUC = 4. This regimen is adequate for the elderly population.

In this study, we found a discrepancy between the very low response rate and the relatively short progression-free survival with a moderate overall survival. Of the 41 patients, 25 received second-line treatment, including 16 cytotoxic agents and nine epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs). Overall survival was 595 days with EGFR-TKI and 360 days with cytotoxic agents; thus, patients receiving EGFR-TKI as a second-line treatment appear to have longer survival. Unfortunately, we did not monitor EGFR mutations in our patients.

In conclusion, we have evaluated the safety and efficacy of combination chemotherapy with vinorelbine and carboplatin in patients ≥75 years of age with previously untreated advanced NSCLC. This combination was feasible and showed a moderate response rate in this population, and might be promising for elderly patients. A randomized trial is warranted.

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Table 1. Patient Characteristics

	Phase I	Phase II
No. of patients	13	42
Assessable	13	41
Age, years		
Median	80	78
Range	76-83	76-86
Sex		
Male	10	31
Female	3	10
Performance status		
0	5	18
1	8	23
Stage		
IIIB	7	14
IV	6	27
Histology		
Adenocarcinoma	6	30
Squamous cell carcinoma	3	10
Large-cell carcinoma	1	0
Undifferentiated	3	1

Table 2. Results of Phase I study

Dose level	No. of patients	Vinorelbine (mg/m^2)	Carboplatin target AUC	Hematologic toxicity (≥ NCI CTCAE grade 3/4)			
				Anemia	Anemia	Anemia	Anemia
1	3	10	4	0/0	0/0	0/0	0/0
2	3	15	4	0/0	0/0	0/0	0/0
3	3	20	4	2/0	2/0	2/0	2/0
4	3	25	4	1/0	1/0	1/0	1/0

Table 3. Results for Phase II study (n=41)

Response	No. of patients	%	95%CI
Partial response	6	14.6	3.8-25.4
Stable disease	25	60.9	47.3-73.5
Progressive disease	10	24.4	11.2-37.6

Table 4. Toxicity in 41 Patients in Phase II (n=41)

	Grade 2		Grade 3		Grade 4	
	n	%	n	%	n	%
Leukopenia	10	24.4	14	34.1	4	9.8
Neutropenia	8	19.5	10	24.4	16	39.0
Anemia	8	19.5	7	17.1	1	2.4
Thrombocytopenia	2	4.8	0		0	
Nausea/vomiting	1	2.4	0		0	
Diarrhea	2	4.8	0		0	
ALT/AST	2	4.8	0		0	
Phlebitis	2	4.8	0		0	

Abbreviation: ALT; alanine aminotransferase, AST; aspartate aminotransferase.