Efficacy of Cisplatin and Vinorelbine in Patients with Metastatic Non-Small Cell Lung Carcinoma

Metastatik Küçük Hücreli Dışı Akciğer Karsinomlu Hastalarda Sisplatin ve Vinorelbinin Etkinliği

Ufuk Yılmaz, Huseyin Halilçolar, Yasemin Yıldırım, Sena Yapıcıoğlu, İpek Ünsal, Ceyda Mahleç

Dr. Suat Seren Chest Diseases and Thoracic Surgery Training Hospital, pulmonary, İzmir, Turkey

ABSTRACT

Introduction: Cisplatin-based chemotherapy improved survival and quality of life in lung cancer. The aim of this study is to evaluate the feasibility of the cisplatin-vinorelbine (day 1+8) in patients with metastatic NSCLC.

Material and Method: ECOG performance 0-1, chemotherapy-naive stage IV NSCLC patients were treated with cisplatin (75 mg/m^2, d1) and vinorelbine (30 mg/m^2, d1 and d8, IV) every 21 days for a maximum of 6 cycles in a single center. Between October 2001 and December 2006, a total of 44 NSCLC patients were evaluated.

Results: Characteristics of patients were as follows: Median age 56 years (range 41-72), male 41, female 3 and PS 0=7 / PS 1=37. The histologic diagnosis was adenocarcinoma in 17 patients, squamous cell carcinoma in 5 and undifferentiated NSCLC in 22. Brain metastases were present in 7 patients (16%) prior to starting the treatment. Median number of cycles was 3.0 (range 1-6). Complete responses were seen in 1 patient (2.3%), partial response in 15 (34.1%) and disease stabilization in 19 (43.2%). In a total of 140 cycles, grade 3-4 neutropenia, leucopenia and anemia occurred in 16.5%, 10% and 0.7% respectively. One fatal event was observed. The median survival was 285 days (95% CI [172-397]) and at 1 and 2 years survival were 39% and 9.5%, respectively.

Conclusion: The combination of cisplatin plus vinorelbine is an active regimen with infrequent toxicity in patients with metastatic NSCLC. *(Tur Toraks Der 2008;9:137-40)*

Key words: Chemotherapy, platinum, vinca alkaloid, lung cancer

Received: 30. 03. 2008 *Accepted: 17. 07. 2008*

ÖZET

Giriş: Akciğer kanserinde, sisplatin bazlı kemoterapi hayat kalitesi ve yaşam süresini iyileştirdi. Bu çalışmanın amacı, metastatik küçük hücreli dışı akciğer kanserli hastalarda sisplatin-vinorelbinin (1 ve 8. gün) fizibilitesini değerlendirmektir.

Gereç ve Yöntem: Performans durumu ECOG 0-1 , daha önce kemoterapi almamış evre 4 KHDAK li hastalar, 21 gün ara ile, en fazla 6 kür için sisplatin (75 mg/m^2, g1) vinorelbin (25 mg/m^2 g1 ve g8, IV) ile tek bir merkezde tedavi edildi. Ekim 2001 ile aralık 2006 tarihleri arasında, toplam 44 KHDAK li hasta değerlendirildi.

Bulgular: Hastaların özellikleri aşağıdaki gibidir. Ortanca yaş 56 (aralık 41-72), erkek 41, kadın 3, PS 0 =7 / PS 1=37. Histolojik tanı 17 hastada adenokarsinom , 5'inde skuamöz hücreli karsinom, 22'sinde tiplendirilememiş KHDAK idi. Tedavi başlamadan önce hastaların 7 (%16) sinde beyin metastazı vardı. Ortanca siklus sayısı, 3 (aralık 1-6) idi. Tam yanıt 1 (%2.3) hastada , kısmi yanıt 15 (%34.1) inde, hastalık stabilizasyonu 19 (%43.2) unda görüldü. Toplam 140 siklusda, derece 3-4 nötropeni, lökopeni ve anemi, sırasıyla %16.5, %10, %0.7 oranında görüldü. Bir ölümcül olay görüldü. Medyan yaşam süresi 285 gün (%95 GA [172-397] idi. ve 1 ve 2 yıl yaşam, sırasıyla %39 ve %9.5 idi.

Sonuç: Sisplatin ve vinorelbin kombinasyonu, metastatik KHDAK'li hastalarda sık olmayan toksisite ile aktif bir rejimdir. *(Tur Toraks Der 2008;9:137-40)*

Anahtar sözcükler: Kemoterapi, platin, vinka alkoloid, akciğer kanseri

Geliş Tarihi: 30. 03. 2008 *Kabul Tarihi: 17. 07. 2008*

INTRODUCTION

Lung cancer is the most common form of cancer in men in Turkey according to the Ministry of Health [1]. Approximately 80% of lung cancers are of non-small cell histology, but less than half of all patients with non-small cell lung cancer (NSCLC) present with surgically resectable stages I and II tumors [2]. Close to 70% of patients with NSCLC present with locally advanced or metastatic disease at the time of diagnosis [3]. Chemotherapy is an appropriate form of treatment for many patients with metastatic lung cancer [2,3]. Currently, cisplatin based regimens are considered the standard treatment for advanced NSCLC. Chemotherapy prolongs survival and palliates tumor-related symptoms [2,4].

New chemotherapeutic agents such as gemcitabine, paclitaxel, docetaxel and vinorelbine have been tested in chemo-naive patients with NSCLC, and randomised clinical trials have demonstrated the activity of these new

Address for Correspondence / Yazışma Adresi: Ufuk Yılmaz, Dr.Suat Seren Chest Diseases and Thoracic Surgery Training Hospital, Pulmonary Department, İzmir, Turkey Phone: +90 232 433 33 33 E-mail: drufukyilmaz@e-kolay.net

agents alone or in combination with platinum derivatives for the treatments of locally advanced and metastatic NSCLC [5-8]. Weekly Vinorelbine treatment (Navelbine, Pierre fabre Oncologie, Boulogne, France) has been successfully combined with cisplatin in NSCLC chemotherapy. Response rates of 25-40% and median survival of 33-40 weeks have been obtained in several studies with cisplatin and vinorelbine combination [6,7,9]. In a phase III trial, Gebbia et al. obtained a better therapeutic index by rescheduling vinorelbine administration on days 1 and 8 of 3-week cycles [10].

In our previous study [11], we found that cisplatin (100 mg/m^2) plus vinorelbine (25 mg/m^2, days 1 and 8 of 3-week cycles) regimen in patients with advanced NSCLC is active with an acceptable toxicity profile. But, while the dose of cisplatin was higher than standard, the doses of vinorelbine were relatively lower. In the present study, we administered a standard dose level of vinorelbine (30 mg/m^2 , days 1 and 8) and cisplatin (75 mg/m^2). The aim of the present study is to evaluate the overall survival, response rates and toxicity with this schedule.

PATIENTS AND METHODS

Chemotherapy and radiotherapy-naive patients with histologically or cytologically proven stage IV NSCLC were enrolled. Patients met the following criteria to be eligible; Age ≥16 years, no prior radiotherapy except palliation or chemotherapy, adequate hematological function (WBC>3000/µL, absolute neutrophil count ≥2000 /µL, hemoglobin level ≥10 g/dL, platelet count ≥100.000//µL), hepatic function (bilurubin ≤1.5 mg/dL, AST ≤2.5x the upper limit of normal (ULN) or ≤5 x ULN if liver metastases were present), and renal function (creatinine concentration ≤1.2 mg/d). Patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) < 2 were eligible.

Patients were ineligible for the study if they had experienced any of the following events: Active infection, pregnancy or lactation, hypersensitivity to the study drugs, concommitant or previous malignancies (except for adequately treated basal or squamous cell carcinoma of skin, carcinoma in-situ of the cervix, or localized low grade prostate cancer), severe co-morbidities, symptomatic brain metastasis, life expectancy of ≥12 weeks.

The protocol was approved by the institutional review board. Each patient provided written informed consent.

Pretreatment evaluation consisted of medical history, physical examination, complete blood count, biochemical screen, electrocardiogram, chest X-ray, CT of the chest, brain and upper abdomen (or ultrasonography) and bone scintigraphy.

Treatment plan: Cisplatin was administered at a dose of 75 mg/m^2 on day 1 of each cycle with prehydration. Intravenous vinorelbine was supplied as a 10 mg/ml solution for injection on days 1 and 8 of each cycle at a dose of 30 mg/m^2 every 21 days. The drug was reconstituted to a total volume of 50 ml with N-saline, and then given into the site injection port of a freely flowing saline infusion over 6-10 min; the saline infusion was continued to flush the vein. Treatment was planned to continue for a maximum of six cycles unless halted by disease progression, unacceptable toxicity or patient refusal. Routine prophylactic anti-emetics with setrons and dexamethasone (IV) were administered to cover day 1 cisplatin/i.v. vinorelbine.

Treatment was to be modified in the case of hematological and/or non-hematological toxicities according to a prespecified system. Hematological toxicity including neutropenia or thrombocytopenia at grade ≥2 on day 1 would result in treatment delay and reassessment after1 week. On day 8, the same levels of toxicity would result in the omission of the planned IV vinorelbine dose. Neurological toxicity at grade 2 would result in a 50% dose reduction, and at grade 3/4, in treatment discontinuation. Hepatic toxicity at grade 2 on day 1 would result in delay and reassessment 1 week later, and at grades 3 or 4, treatment would be discontinued. Modification of the cisplatin dose was assessed by serum creatinine level as follows: ≤1.2 mg. no modification; 1.21-1.50 mg., 25% dose reduction; >1.50 mg., delay of both vinorelbine and cisplatin and reassessment 1 week later. Toxicity affecting hearing at grade 2 would result in a 50% reduction of the cisplatin dose, and at grade 3/4, in treatment discontinuation. Doses were not modified for nausea/vomiting.

Assessments: Before each cycle, the following assessments were made; medical history, physical examination, blood chemistry, blood count, chest x-ray, electrocardiogram, toxicity (graded according to the WHO criteria), performance status and clinical tumor assessment. Complete blood counts were made on day 8 and 15 to define toxicity. Patients were assessable for response if they had received at least one full treatment course, and revisited our hospital in the second treatment course. The protocol required chest x-ray and/or computed tomographic response assessment after two and four cycles of treatment and at the end of therapy. Tumor responses and toxicity were evaluated in patients according to the WHO criteria [12,13].

Data were collected prospectively, and evaluated retrospectively.

Statistics: The primary objective was to determine the survival with cisplatin plus vinorelbine. Overall survival was calculated from the first day of treatment until the date of death from any cause or the last follow-up examination. Survival time was assessed at the last date of follow-up. Survival curves were calculated by the Kaplan-Meier method. Survival was characterized by the median and the probability of being alive at 12 and 24 months (based on Kaplan-Meier estimates). Ranges, 95% CI on the treatment estimates were computed. The cut-off date for the survival analysis was 8 March 2007.

RESULTS

A total of 46 patients with NSCLC were enrolled from October 2001 to December 2006. 44 patients were eval-

uated. Two patients were not evaluable because we could not find their data files. Patient baseline characteristics are shown in Table 1.

A total of 140 cycles were administered during the study with a median of three cycles per patient (range 1-6). Both cisplatin and i.v. vinorelbine scheduled on day 1 were delayed by up to 1 week in 6% of cycles. The cisplatin and vinorelbine doses were reduced in 6 patients as a result of hematological toxicities. Only two patients were treated with docetaxel as second-line therapy.

On the reference date, eight patients were still alive. The median overall survival was 285 days (40.7 weeks) (95% CI 172-397 days) and the 1 and 2-year survival probability was 39% and 9.5%, respectively (Figure 1). Response rates are shown in Table 2.

Hematological toxicity is listed in Table 3. Six patients (13%) experienced febrile neutropenia seven times. All patients were hospitalized and were uneventfully treated with rhG-CSF support and broad-spectrum antibiotics except one patient. One patient with febrile neutropenia died due to renal toxicity and dehydration. Anemia occurred frequently (25% of cycles) but was rarely severe (blood transfusions were required in 5.0% of cycles). Non-hematological toxicity was mild. 3 patients had grade 3 constipation, and 15 patients had grade 3 alopecia, 2 patients had grade 3 renal toxicity.

Table 1. Patient characteristics

Total no. of patients,	n 46	
No. of evaluable patients,	n 44	
Age, years		
Median (range)	56 (41–72)	
Sex	n	(%)
Male	41	(93%)
Female	3	(7%)
ECOG score,	n	(%)
0	7	(16%)
1	37	(84%)
Histology,	n	(%)
Squamous cell	5	(12%)
Adenocarcinoma	17	(38%)
Non-specified NSCLC	22	(50%)
No of pts. with brain metastasis	7	(16%)

Table 2. Response to treatment (evaluable patients; n=44)

Response	**No. of patients (%)**	
Objective response rate	16	(36.3%)
Complete responses	1	(2,3%)
Partial responses	15	(34%)
Stable diseases	19	(43.2%)

Table 3. Hematological toxicity profiles in a total of 140 cycles

	Gr 1	Gr 2	Gr 3	Gr 4	Gr 3-4 (%)
Leucopenia	7	8	11	3	10
Neutropenia	4	15	11	12	16.5
Anemia	26	8	1	0	0.7
Thrombocytopenia	0	1	0	0	0

* Gr: Grade

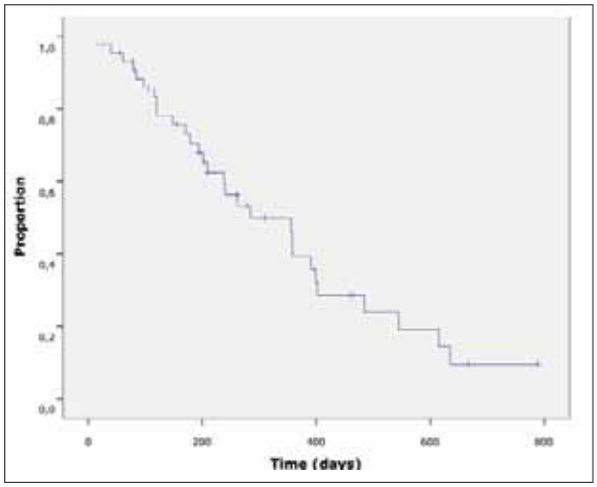

Figure 1. Overall survival for all patients

DISCUSSION

The results of this study showed the clinically meaningful efficacy of vinorelbine-cisplatin combination in metastatic NSCLC. The response rate of 36.3% and the median survival of 285 days are within the range of results demonstrated in earlier trials, which had a schedule of vinorelbine weekly or day 1 and 8 [6,7,9,15].

Cisplatin-based doublet regimens are still the standard therapy for well performing patients in the management of advanced NSCLC [14]. In a randomized ECOG trial, four doublets (cisplatin/docetaxel, cisplatin/paclitaxel, cisplatin/gemcitabine and carboplatin/docetaxel) were compared for survival, but the comparison yielded identical results The one statistically significant difference was an improvement in time to progression for cisplatin/gemcitabine [5]. In another randomized, multinational phase III study, docetaxel plus platinum combinations were not statistically significant different with vinorelbine plus cisplatin in terms of survival for advanced NSCLC [8].

Several phase III trials have demonstrated the value of cisplatin/vinorelbine combinations in advanced NSCLC [6,7,9,15]. The SWOG schedule, i.e. weekly vinorelbine (25 mg/m^2/week) with cisplatin (100 mg/m^2) 4 weeks, has been for widely reported to have excellent activity but an excess of hematological toxicity [7]. In this study, there was a 12% partial response rate for cisplatin arm. Cisplatin and vinorelbine (P-VNB) arm had a 26% response rate (2% complete responses and 24% partial responses, P=.0002). There was a statistically significant advantage with regard to progression-free survival (median, 2 vs 4 months; P=.0001) and overall survival (median, 6 vs 8 months; P=.0018) for the P-VNB arm [7]. One-year survival was 20% for cisplatin alone and 36% for the combination arm.

Le Chevalier et al. included 612 patients with advanced NSCLC [6]. Patients in this trial were randomized to receive P-VNB or cisplatin/vindesine (P-VND) or vinorelbine (VNB) alone. The median duration of survival was 40 weeks in the P-VNB arm, compared with 32 weeks in the P-VND arm and 31 weeks in the VNB arm. The comparison of survival among the three groups demonstrated an advantage for P-VNB compared with P-VND (P=.04) and VNB (P=.01). In the other study, the cisplatin and vinorelbine combination increased objective response rates and time to progression in comparison with vinorelbine alone, but did not influence the survival of patients (9).

The weekly regimen of vinorelbine in combination with cisplatin every 4 weeks may not be optimal since the dose of vinorelbine to be given on day 15 had to be omitted in a number of patients. In Gebbia et al phase III trial, the tri-weekly schedule of cisplatin plus vinorelbine day 1 and 8 is equelactive but more tolerated than classical weekly vinorelbine schedule [10].

Our previous trial of cisplatin (100 mg/m^2) and vinorelbine (25 mg^2/m^2, days 1 and 8) have been performed in patients with advanced NSCLC. This regimen was associated with a median survival time of 36 weeks, 1-year survival rate of 28.7% and a objective response of 27%. The major toxicity was hematological with grade 3-4 neutropenia in 16.4% of cycles and febrile neutropenia in 9% of patients [11].

In the current study, our treatment protocol was shown to produce comparable response rates and median survivals with the previous studies. It was also comparable in terms of one and two year survival. As expected, the most common toxicity in this study was myelosuppression, with grade 3 and 4 neutropenia occurring in 16.5% of cycles. However, grade 3 or 4 neutropenia was transient and of short duration, leading to seven episodes of febrile neutropenia in six patients. Nevertheless, all episodes were successfully treated, with the exclusion of one patient with renal toxicity. Anemia occurred frequently (25% of cycles) but was rarely severe, and blood transfusions were required in only 5.0% of cycles. There was no difference in myelotoxicity between two schedules of cisplatin and vinorelbine in our two studies. Non-hematological toxicity related to study treatment was manageable except in one patient. One patient died because of the renal toxicity and febrile neutropenia.

In conclusion, the combination of cisplatin (75 ng/m^2, day 1) plus vinorelbine (30 mg/m^2, days 1 and 8) is an active and tolerable regimen in patients with metastatic NSCLC.

Acknowledgements: The authors thank Mr. Mustafa Delibas for conducting statistic studies.

REFERENCES

1. Erkeklerde en çok görülen on kanser türü, 1999. http://www.saglik.gov.tr/TR/Belgegoster.aspx. Accessed December 25, 2008
2. Non-small cell lung Cancer Colloborative Group. Chemotherapy analysis in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomized clinical trials. Br Med J 1995;311:899-909.
3. Molina JR, Adjei AA, Jett JR. Advances in chemotherapy of non-small cell lung cancer. Chest 2006;130:1211-19.
4. Clegg A, Scott DA, Hewitson P, et al. Clinical and cost-effectiveness of paclitaxel, docetaxel, gemcitabine, and vinorelbine in non-small cell lung cancer: a systematic review. Thorax 2002;57:20-8.
5. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Eng J Med 2002;346:92-8.
6. Le Chevalier T, Brisgand D, Douillard JY, et al. Randomized study of vinorelbine and cisplatin versus vindesine and cisplatin versus vinorelbine alone in advanced non-small cell lung cancer: Results of a European Multicenter Trial including 612 patients. J Clin Oncol 1994;12:360-7.
7. Wozniak AJ, Crowley J, Balcerzak SP, et al. Randomized trial comparing cisplatin with cisplatin plus vinorelbine in the treatment of advanced non-small cell lung cancer: a Southwest Oncology Group Study. J Clin Oncol 1998;16:2459-65.
8. Fossella F, Pereria JR, Von Pawel J, et al. Randomized, multinational phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small cell lung cancer. J Clin Oncol 2003;21:3016-24.
9. Depierre A, Chastang CI, Quoix E, et al. Vinorelbine versus vinorelbine plus cisplatin in advanced NSCLC: a randomized trial. Ann Oncol 1994;5:37-42.
10. Gebbia V, Galeta D, Carusa M, et al. Weekly vinorelbine plus cisplatin versus day 1+8 vinorelbine with cisplatin in advanced non-small cell lung cancer. End results of a phase III trial. Lung Cancer 2005;49:O-090 (abstract).
11. Yılmaz U, Utkaner G, Yalnız E, Kara S, et al. Cisplatin and vinorelbine for advanced stage non-small cell lung cancer. Tuberculosis and Thorax 2000;48:312-6 (Turkish).
12. Miller AB, Hoogstraten B, Staquet M, et al. Reporting results of cancer treatment. Cancer 1981;47:207-14.
13. WHO Handbook for Reporting Results of Cancer Treatment. WHO offset publication no 48, Geneva; Switzerland, World Health Organization. 1979
14. Pfister DG, Johnson DH, Azzoli CG, et al. American Society of Clinical Oncology treatment of unresectable non-small-cell lung cancer guideline. Update 2003. J Clin Oncol 2004;22:330-53.
15. Kelly K, Crowley J, Bunn Jr PA, et al. Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non-small-cell lung cancer. A southwest oncology group trial. J Clin Oncol 2001;19:3210-8.