Treatment of Advanced Non-small Cell Lung Cancer with Vinorelbine in Elderly Thai Patients

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The present study evaluated the efficacy and toxicity of vinorelbine as single chemotherapy for elderly Thai patients with advanced non-small cell lung cancer (NSCLC). Twenty-eight patients with no prior chemotherapy and ECOG performance status of 0-2 were enrolled in the study. There were 20 males and 8 females with a median age of 72 years, and the median ECOG performance status was 1. Eight cases were stage IIIB and 20 cases were stage IV. Fourteen cases were adenocarcinoma, 13 were squamous cell and one was large cell NSCLC. These patients received vinorelbine 25 mg/m^2 on day 1 and 8. This treatment produced partial reponse in 5 of 25 evaluable patients (20%). Median survival time was 40 weeks. Hematologic toxicity caused 9% grade 3 anemia, 1.5% grade 4 neutropenia and 0.5% grade 4 neutropenia.

Conclusion : *Chemotherapy is a valuable treatment option for elderly patients with advanced NSCLC. Single agent vinorelbine is able to induce an overall response with a low toxicity level in elderly Thai patients with advanced NSCLC.*

Keywords : *Non-Small Cell Lung Cancer, Vinorelbine, Chemotherapy for elderly patients NSCLC.*

J Med Assoc Thai 2004; 87(4): 367-71

Non-small cell lung cancer (NSCLC) frequently occurs in more than 50% of patients aged over 65 years, and in 30% of patients aged 70 or more[1]. For patients with advanced NSCLC, cisplatin based chemotherapy can improve survival and quality of life when compared with best supportive care, but it has been demonstrated only in cisplatin-containing regimens[2]. However, the inclusion criteria of these studies only selected patients aged under 70 with a good performance status. Most of the elderly patients had comorbidities and reduction in functional reserve that might be unsuitable for cisplatin-based chemotherapy[3]. Based on these clinical findings in elderly patients, single agent chemotherapy was the first investigative approach[4].

Vinorelbine is a semisynthetic compound of the vinca alkaloid group that inhibits mitosis by targeting microtubules and thus blocks the spindle formation[5]. Vinorelbine, as a monotherapy, is well tolerated and a proven activity in advanced NSCLC, especially in elderly patients, with response rates of 12% to 39% and median survival of five to ten months [5-12]. A randomized phase III multicentre trial (ELVIS-Elderly Lung Cancer Vinorelbine Italian Study) compared single agent vinorelbine to best supportive care[9]. The response rate of the vinorelbine arm was 20% with mild toxicity, and it also showed that vinorelbine improves the quality of life and survival compared with best supportive care.

In Thai clinical practice, many patients with advanced non-small cell lung cancer are elderly and physically unsuitable for polychemotherapy. Vinorelbine has a proven efficacy in elderly patients, but the physical or health status of elderly Thai patients is not as good as Western patients of the same age. Thus, the authors designed a phase II prospective study to confirm whether or not the efficacy of vinorelbine can improve survival in elderly Thai patients with advanced NSCLC.

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Patients and Method

Patient selection

The eligibility criteria for inclusion in the present study were cytohistologically confirmed NSCLC, stage IIIB (with pleural effusion) or stage IV disease, presence of measurable lesions, aged 65 or more and an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2. All patients gave informed consent.

Exclusion criteria were previous chemotherapy or radiation therapy, history of another cancer, presence of brain metastasis, and reduced renal (serum creatine > 2mg/dl) and hepatic function (serum total bilirubin > 2mg/dl or SGOT or SGPT > 5 times of normal upper limit).

Staging procedures and treatment schedule

Before entering the study, all patients had to undergo a medical history and complete physical examination, complete blood count and blood chemistry (BUN, creatinine, electrolytes and liver function test), chest X-ray, CT scan of the thorax and upper abdomen, and a bone scan if indicated for the baseline tumor measurement. CT scan of the thorax was performed after the 4^{th} and 6^{th} cycle of treatment in order to assess the overall response according to the WHO criteria[13]. Hematologic parameters were performed weekly, and serum chemistry and chest X-rays were repeated at every cycle to closely monitor potential toxicity and progression of disease.

Vinorelbine was administered at a dose of 25 mg/m^2 on day 1 and 8. It was diluted with 50 ml of normal saline and infused intravenously over 10 minutes, before 250 ml of normal saline was given. The cycle was repeated every 3 weeks until any one of the following termination criteria occurred; death, progressive disease, intolerance to any side effect or complication of vinorelbine. At day 1 and 8, the minimum requirement for the administration of vinorelbine was an absolute neutrophil count of $1,500/mm^3$ or more, and platelet count of $100,000/mm^3$ or more. If the absolute neutrophil count was less than $1,500/mm^3$, and the platelet count less than $100,000/mm^3$, the treatment was withheld for one week; and if postponed more for than two weeks, it was terminated. If the patient had WHO grade 3 or 4 toxicities, the dosage of the next cycle was reduced to 20 mg/m^2.

Study statistics

The objective of this phase II prospective trial was to study the efficacy of vinorelbine in the treatment of elderly patients with advanced NSCLC in terms of response and overall survival rate according to the 'intent-to-treat' analysis. The evaluation of efficacy was based on data by clinical examination, chest X-ray and thoracic CT scan. Efficacy was evaluated after four cycles of treatment and reevaluated after the completion of treatment at 6 cycles according to the WHO criteria[13]. A univariate analysis of survival data was performed according to the Kaplan-Meier product-limit estimate.

Results

Between April 2001 and February 2003, 28 eligible patients were observed and registered on the trial. The characteristics of the patients are listed in Table 1. The median age for the 28 eligible patients (8 women, 20 men) was 72 years (range 65-82). The majority of patients had an ECOG performance status of 1 and the most common histologic tumor type was adenocarcinoma (50%). At the time of inclusion, 20 patients (71.4%) had metastatic stage IV disease, whereas, only 8 patients (28.6%) had stage IIIB disease, and 5 of 8 patients (62.5%) had stage IIIB disease with pleural effusion. Metastatic sites essentially included the lung (61.5%), bone (23.1%), liver (7.8%), adrenal gland and heart (3.8% each). Sixteen patients had only one metastatic site.

Table 1. Patient Characteristics

Characteristics	Number of patients	%
Number of entered patients	28	100
Median age, years (range)	72 (65-82)	
Sex		
Male	20	71.4
Female	8	28.6
ECOG Performance status		
0	3	10.7
1	22	78.6
2	3	10.7
Histopathology		
Squamous cell carcinoma	13	46.4
Adeno carcinoma	14	50
Large cell carcinoma	1	3.6
Stage		
IIIB	8	28.6
IV	20	71.4
Metastatic site		
Lung	16	61.5
Bone	6	7.8
Liver	2	7.8
Adrenal gland	1	3.8
Heart	1	3.8

A total of 102 cycles was administered to the patients with a median number of 4 cycles (range 1-6). The mean dose of vinorelbine was 24.6 mg/m^2. Three patients could not be evaluated for response: two due to early death within one and four weeks after the first course administration and one was lost to follow-up. The objective response rate of 20% (partial response) was seen in the 25 evaluable patients. Stable disease was noted in 11 patients (44%) and progression in 9 (36%) (Table 2). The median survival time was 40 weeks. (Fig. 1)

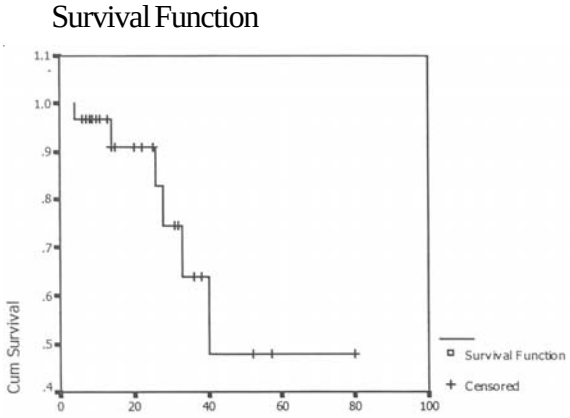

Fig. 1 Survival Time

Toxicity

Toxicity was measured each week during treatment, for a total of 204 observations. It was evaluated for all 28 patients. Two early deaths were reported and they were possibly not related to the toxic effect of vinorelbine. For these two patients, one death occurred within one week after the first cycle from an uncertain cause, and the other was due to congestive heart failure within four weeks after the first cycle.

The most severe toxicity was granulocytopenia, but this was a rare event (Table 2). Grade 3 and 4 toxicity of leukopenia and granulocytopenia were found in only 4 of 204 observations (2%). There was no documented toxic death or infection due to granulocytopenia. Anemia was generally mild to moderate in toxicity (19.6%), but there was grade 3 anemia in only 4.4% of patients and no thrombocytopenia. Nonhematologic toxicity was generally mild and uncommon and consisted of peripheral neuropathy (1 patient), phlebitis (2 cases), and constipation (1 case).

Table 2. Treatment effects

No. of eligible patients	28		
No. of evaluable patients	25		
Partial response (%)	5(20)		
Stable disease (%)	11(44)		
Progressive disease(%)	9(36)		
WHO Hematologic toxicity (%)	Grade II	Grade III	Grade IV
Anemia	40(19.6)	9(4.4)	0
Leukopenia	10(4.9)	3(1.5)	1(0.5)
Thrombocyto penia	0	0	0

Discussion

This phase II study of elderly Thai patients suffering advanced NSCLC showed that vinorelbine is an active drug in this indication, with a 20% overall response rate (20% partial response and 44% stable disease) and median survival time of 40 weeks. The evaluation of toxicity showed that vinorelbine was well tolerated and managable. In the present study, vinorelbine was a confirmed activity comparable to that observed in previous studies (Table 3). Veronesi et al reported a 39.1% response rate in the older subgroup of 83 patients (23 of whom were aged 70 years or more) treated with vinorelbine at a dose of 25-30 mg/m^2, and their overall median survival time was 9 months[7]. In phase II trials by Colleoni el al[10] and Tononi et al[11], patients of 65 years or more were included, and vinorelbine was given at a dosage of 25 mg/m^2. The response rate was 16% and 12% with a median survival time of 5 months and 10 months respectively. In another phase II study by Gridelli et

Table 3. Studies of single-agent vinorelbine in elderly patients with advanced NSCLC

Study	Number of patients	Age(years)	Regimen(mg/m^2)	ORR(%)	MST(months)
Veronesi el al [7]	23	> 70	25,30	39	NR
ELVIS [9]	76	> 70	30	20	7
Colleoni el al [10]	25	> 65	25	16	5
Tononi el al [11]	25	> 65	25	12	10
Gridelli el al [12]	43	> 70	30	23	9

ORR =overall objective response rate; NR =not responsive; ST = Median survival time

al, 43 elderly patients with advanced NSCLC received vinorelbine at a dose of 30 mg/m^2 per week for 12 weeks[12]. Toxicity was mild and the overall response rate was 23%, with a median survival time of 9 months. A randomized phase III multicentre trial (ELVIS-Elderly Lung Cancer Vinorelbine Italian Study) compared single agent vinorelbine at 30 mg/m^2 to best supportive care, and vinorelbine showed a response rate of 20%, with a median survival time of 7 months versus 5 months. The mean dose of vinorelbine in the present study was lower than that in previous studies (24.6 mg/m^2 versus 30 mg/m^2), but it had comparative efficacy in both response and survival.

In conclusion, the results of the present trial can be generalized to state that chemotherapy is a valuable treatment option for elderly patients with advanced NSCLC. Single agent vinorelbine is able to induce an overall response with a low toxicity level in elderly Thai patients with advanced NSCLC.

Acknowledgement

Partial support of vinorelbine from Baxter Healthcare (Thailand) Co.,Ltd.

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การรักษามะเร็งปอดชนิดเซลล์ไม่เล็กระยะแพร่กระจายด้วยยาเคมีบำบัด Vinorelbine ในผู้ป่วยไทยสูงอายุ

สิริกุล ศรฤทธิ์ชิงชัย, สุมิตรา ทองประเสริฐ, ชัยยุทธ เจริญธรรม, บุษยมาส ชีวสกุลยง, สุทธิรักษ์ มูลประการ

การศึกษาเพื่อประเมินประสิทธิภาพ และผลข้างเคียงของยาเคมีบำบัด Vinorelbine ในการรักษามะเร็งปอดชนิดเซลล์ไม่เล็กระยะแพร่กระจายในผู้ป่วยไทยสูงอายุ ผู้ป่วยใหม่ซึ่งไม่เคยได้รับยาเคมีบำบัดจำนวน 28 ราย เข้ารับการรักษา แบ่งเป็นชาย 20 ราย หญิง 8 ราย อายุเฉลี่ย 72 ปี และค่าเฉลี่ยของ ECOG performance status เท่ากับ 1 ผู้ป่วย 8 ราย เป็นระยะ IIIB และ 20 ราย เป็นระยะ IV ผู้ป่วย 14 รายเป็น adenocarcinoma 13 ราย เป็น squamous cell และ 1 ราย เป็น large cell ผู้ป่วยจะได้รับยาเคมีบำบัด vinorelbine 25 mg/m^2 ในวันที่ 1 และ 8 ของช่วงการรักษาแต่ละชุด 21 วัน ผลการรักษาพบว่าผู้ป่วย 5 รายจากจำนวน 25 ราย ตอบสนองต่อการรักษาเป็น แบบ partial response (20%) ค่าเฉลี่ยของการรอดชีวิตเท่ากับ 40 สัปดาห์ ผลข้างเคียงที่สำคัญคือ การกดการทำงานของไขกระดูก ผู้ป่วยร้อยละ 9 มีอุบัติการณ์ของเม็ดเลือดแดงต่ำเกรด 3 ผู้ป่วยร้อยละ 1.5 มีเม็ดเลือดขาวต่ำเกรด 3 และพบอุบัติการณ์เม็ดเลือดขาวต่ำเกรด 4 ร้อยละ 0.5

***สรุป** : การรักษามะเร็งปอดชนิดเซลล์ไม่เล็กระยะแพร่กระจายในผู้ป่วยไทยสูงอายุ ด้วยยาเคมีบำบัด Vinorelbine มีการตอบสนองต่อการรักษาและผลข้างเคียงจากยาเคมีบำบัดต่ำ*