

Pemetrexed versus vinorelbine treatment of advanced non-squamous non-small cell lung cancer in elderly patients

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Abstract. Pemetrexed, a multitargeted antifolate agent, has been shown to have clear activity in non-squamous non-small cell lung cancer (NSCLC). The aim of this retrospective study was to evaluate the efficacy and toxicity of pemetrexed vs. vinorelbine in NSCLC elderly patients. Chemotherapy-naïve patients aged ≥ 70 years with stage IIIB/IV non-squamous NSCLC and performance status ≤ 2 were eligible for inclusion in this study. Patients were selected to receive pemetrexed 500 mg/m² (day 1) or vinorelbine 25 mg/m² (days 1 and 8) every 21 days. In total, 62 patients were enrolled in the present study. Thirty-six patients were treated with pemetrexed, and 26 with vinorelbine. The median number of cycles received was six in the pemetrexed group vs. four in the vinorelbine group. Pemetrexed demonstrated a significantly higher disease control rate (DCR) (80.5 vs. 65.3%; $P=0.011$), and an improvement in progression-free survival (6.5 vs. 4.0 months; $P=0.018$) compared to vinorelbine. Neutropenia occurred in more patients in the vinorelbine group compared to the pemetrexed group, grade 3-4 neutropenia was observed in 53.8 and 11.1% of patients in the two groups, respectively ($P<0.001$). Pemetrexed-treated patients experienced lower frequencies of anemia, thrombocytopenia and non-hematologic toxicities compared to vinorelbine-treated patients. The toxicity profiles for the two treatment groups were mild and tolerable. In conclusion, pemetrexed improved DCR, progression-free survival, and presented a lower incidence of treatment-related adverse events compared to vinorelbine, although overall survival was not significantly improved. As a result, pemetrexed monotherapy might be considered as a

good option in the treatment of elderly patients with advanced non-squamous NSCLC.

Introduction

Lung cancer is the most common type of malignancy and constitutes the leading cause of cancer death worldwide. Non-small cell lung cancer (NSCLC) comprises 85% of all lung cancer cases, and ~55-65% of patients present with advanced or stage III/IV disease at the time of diagnosis (1). The prognosis in patients with untreated advanced NSCLC is extremely poor, with a median survival time of ≤ 6 months.

Among the patients who are newly diagnosed with NSCLC, 30-40% of them are aged ≥ 70 years (2). The management of this cohort of patients constitutes a challenge for medical oncologists. Elderly patients are a specific population that requires special care, due to the fact that they have metabolic changes and increased likelihood of comorbidities. They are characterized by relatively inferior immune system and functions of the major organs, which should be taken into consideration when selecting the appropriate chemotherapy in the clinical setting. Clinical trials on the treatment of advanced NSCLC in the elderly are limited, and no optimal regimen has been identified. The Multicenter Italian Lung Cancer in the Elderly Study (MILES) phase III randomized trial (3) compared the efficacy and toxicity of the combination of vinorelbine plus gemcitabine with single-drug treatment in elderly patients with advanced NSCLC. Tumor response and overall survival were not observed after combination therapy, while increased toxicity was reported. Thus, monochemotherapy is believed to be a priority in the treatment of elderly patients with advanced NSCLC.

Pemetrexed is a novel antifolate cytotoxic chemotherapy agent that targets multiple folate-dependent enzymatic pathways, which inhibit multiple enzymes involved in purine and pyrimidine synthesis, thereby effectively inhibiting both DNA and RNA synthesis (4). As a promising drug, pemetrexed has demonstrated good antitumor activity in the treatment of various solid tumors in previous clinical studies (5). The aim of this retrospective study was to evaluate the efficacy of

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pemetrexed vs. vinorelbine in elderly patients with previously untreated advanced non-squamous NSCLC.

Patients and methods

Eligibility criteria. Consecutive patients aged ≥ 70 years with histologically- or cytologically-diagnosed stage IIIB/IV non-squamous NSCLC were included in this study. Detailed inclusion criteria were the following: at least one measurable lesion, life expectancy of >3 months, Eastern Cooperative Oncology Group (ECOG) performance status 0-2; adequate marrow reserve (leukocyte count $\geq 3.8 \times 10^9/l$ and absolute neutrophil $\geq 1.5 \times 10^9/l$, platelets $\geq 90 \times 10^9/l$ and hemoglobin ≥ 90 g/l) and hepatic [alanine aminotransferase (ALT) and aspartate aminotransaminase (AST) <1.5 -fold of the upper limit of normal value, total bilirubin <1 -fold of the upper limit of normal value), as well as renal (<45 ml/min in calculated creatinine clearance rate) functions. This study was conducted according to ICH Good Clinical Practice guidelines and written informed consent was obtained from the patients or their families.

Treatment plan. Patients in the pemetrexed group received pemetrexed 500 mg/m^2 as >10 -min intravenous infusion on day 1 of a 3-week cycle. Premedication was as follows: $1,000 \mu\text{g}$ vitamin B12 injected at the beginning of 1 week prior to day 1 of cycle 1 and repeated every 3 cycles, $400 \mu\text{g}$ folic acid ingested orally on a daily basis starting 1 week prior to the first cycle of chemotherapy and continued until 3 weeks after the therapy completion, 4 mg dexamethasone ingested orally twice per day from the day before to the day after each dose of pemetrexed. Patients in the vinorelbine group were administered tri-weekly vinorelbine 25 mg/m^2 intravenous infusion on days 1 and 8.

Vinorelbine treatment was delayed on day 8 when leukocyte count, platelet count and hemoglobin level were $<2.0 \times 10^9/l$, $<50 \times 10^9/l$ and <60 g/l, respectively, and was withheld until the patient had a minimum leukocyte count of $3.8 \times 10^9/l$, a minimum platelet count of $90 \times 10^9/l$ and a hemoglobin level of ≥ 90 g/l, respectively. Patients were withdrawn from the study when >5 weeks had elapsed from day 1 of any cycle until these criteria were satisfied. The presence of grade 4 neutropenia led to a reduction in the doses of pemetrexed and vinorelbine by 100 mg/m^2 and 5 mg/m^2 , respectively, in the subsequent cycle. Treatment was interrupted at any time in the event of progressive disease. Treatment was discontinued when the patient experienced unacceptable toxicity, withdrew consent or refused treatment.

Assessments. Prior to treatment, the patients underwent a complete medical history and physical examination, fiberoptic bronchoscopy, cervical to abdominal computed tomography (CT), a brain magnetic resonance imaging (MRI), an electrocardiogram (ECG), pulmonary function tests and a radionuclide bone scan. Laboratory examinations included a routine blood, liver and renal function tests, as well as routine electrolyte analysis. Baseline tumor measurements were taken ≤ 2 weeks before treatment. The physical and laboratory examinations were performed weekly. Chest CT was repeated every two cycles to evaluate tumor response and the Response

Evaluation Criteria in Solid Tumors (RECIST) were recommended (6). Toxic-effect grades were based on version 3.0 of the National Cancer Institute Common Terminology Criteria (7).

Statistical analysis. The primary objective was to determine whether pemetrexed improved survival compared to vinorelbine. Overall survival was calculated from the initiation of treatment to the date of death due to any cause or last follow-up. Progression-free survival was calculated from the initiation of treatment to the date of disease progression, recurrence or death due to any cause. Survival curves were constructed according to the Kaplan-Meier method and were compared using the log-rank test. The χ^2 test was used in the response rate comparison and toxicity analysis. Statistical analyses were performed using the Statistical Package for Social Science (SPSS) 16.0 and two-sided P-values of <0.05 were considered to indicate statistically significant difference.

Results

Between January 2009 and March 2011, 62 patients were included the study. Among them, 36 patients were treated with pemetrexed monochemotherapy regimen, and 26 with the single-agent vinorelbine. Demographic and clinical characteristics of patients are summarized in Table I.

The median number of cycles received was six in the pemetrexed group (range, 3-10) and four in the vinorelbine group (range, 2-6), which was significantly different ($P=0.035$). In total, 20 (55.6%) of the 36 pemetrexed-treated patients completed ≥ 6 cycles and 14 (53.8%) of the 26 vinorelbine-treated patients completed ≥ 4 cycles of chemotherapy.

Second-line treatment was administered to 57 patients (92.0%; 33 pemetrexed-treated and 24 vinorelbine-treated patients). Among the patients initially treated with vinorelbine, 7 patients received second-line pemetrexed treatment; while 16 pemetrexed-treated and nine vinorelbine-treated patients received albumin-bound paclitaxel as second-line therapy. Twenty-five patients (40.3%) received second-line gefitinib or erlotinib treatment: 17 patients (47.2%) in the pemetrexed group and 8 patients (30.8%) in the vinorelbine group. Optimum supportive care was provided to the remaining 5 patients.

Response and survival. We did not observe complete response (CR) in the two groups of patients. Disease control rate [(DCR = complete response (CR) + partial response (PR) + stable disease (SD)] was significantly increased in the pemetrexed compared to the vinorelbine group (80.5 vs. 65.3%; $P=0.011$) (Table II). Progressive disease during treatment occurred in 19.4% of pemetrexed-treated patients and in 34.6% of vinorelbine-treated patients, and a statistically significant difference was observed ($P=0.021$).

The follow-up ended on January 31, 2012, with the median follow-up period being 16.5 months (range, 6.5-38). Thirty-six (58.1%) of the 62 patients succumbed to the disease (pemetrexed group, $n=20$; vinorelbine group, $n=16$). The median progression-free survival time with pemetrexed was longer compared to vinorelbine (6.5 vs. 4.0 months, $P=0.018$) (Fig. 1). One-year survival rates were 71.5 and 53.3% for the

Table I. Patient characteristics.

| Characteristics | Pemetrexed, n (%) (n=36) | Vinorelbine, n (%) (n=26) |
|---------------------------|-----------------------------|------------------------------|
| Age, years | | |
| Median (range) | 75 (70-83) | 74.5 (70-84) |
| Gender | | |
| Male | 30 (83.3) | 21 (80.8) |
| Female | 6 (16.7) | 5 (19.2) |
| ECOG performance status | | |
| 0-1 | 34 (94.4) | 25 (96.2) |
| 2 | 2 (5.6) | 1 (3.8) |
| Stage | | |
| IIIB | 11 (30.6) | 8 (30.8) |
| IV | 25 (69.4) | 18 (69.2) |
| Histologic type | | |
| Adenocarcinoma | 35 (97.2) | 24 (92.3) |
| Large cell | 1 (2.8) | 0 (0) |
| Other | 0 (0) | 2 (7.7) |
| Organs involved in cancer | | |
| 1 | 1 (2.8) | 0 (0) |
| 2 | 13 (36.1) | 11 (42.3) |
| 3 | 11 (30.6) | 9 (34.6) |
| ≥4 | 11 (30.6) | 6 (23.1) |
| Comorbid illness | | |
| Presence | 15 (41.7) | 10 (38.5) |
| Absence | 21 (58.3) | 16 (61.5) |

ECOG, Eastern Cooperative Oncology Group.

Table II. Patient response to treatment.

| Response | Pemetrexed, n (%) (n=36) | Vinorelbine, n (%) (n=26) |
|---------------------|-----------------------------|------------------------------|
| CR | 0 (0) | 0 (0) |
| PR | 8 (22.2) | 3 (11.5) |
| SD | 21 (58.3) | 14 (53.8) |
| Progressive disease | 7 (19.4) | 9 (34.6) |
| DCR | 80.5 | 65.3 |

CR, complete response; PR, partial response; SD, stable disease; DCR, disease control rate.

pemetrexed and vinorelbine groups, respectively. The median overall survival times were 16.0 months in the pemetrexed group, and 12.5 months in the vinorelbine group, indicating that pemetrexed prolonged median survival time by 3.5 months, while the overall survival distributions were not statistically significant ($P=0.191$) (Fig. 2).

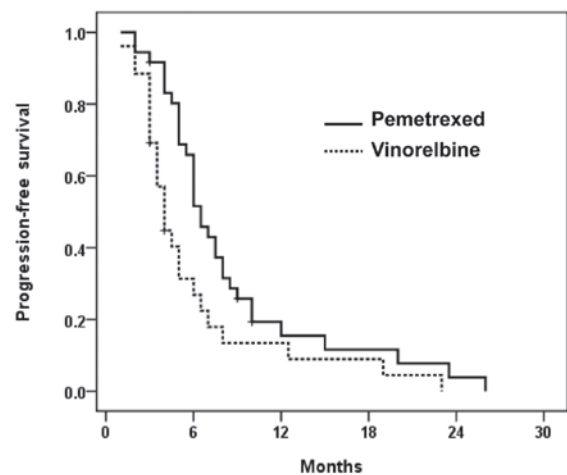


Figure 1. Progression-free survival of patients is shown.

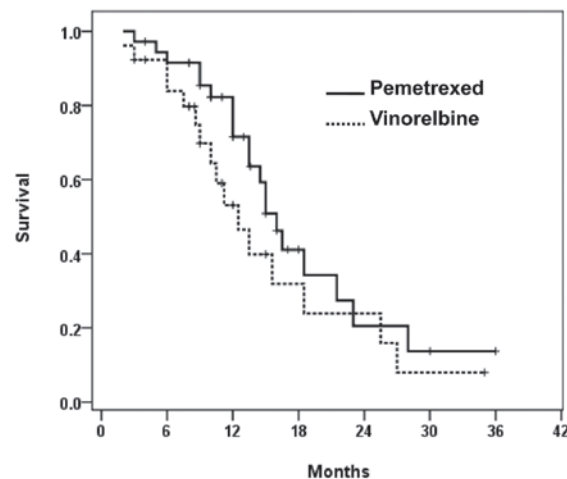


Figure 2. Overall survival of patients is shown.

Toxicity. Toxicity was assessed in all the patients and cycles, and the major toxicities are summarized in Table III. Neutropenia occurred in more patients in the vinorelbine group compared to the pemetrexed group, grade 3-4 neutropenia was noted in 53.8 and 11.1% of patients in the two groups, respectively ($P<0.001$). The frequencies of anemia and thrombocytopenia were higher in the vinorelbine group compared to that in the pemetrexed group, however, no statistically significant differences were identified ($P>0.05$). Nausea/vomiting and infection occurred more frequently in the vinorelbine group compared to the pemetrexed group ($P<0.01$). Overall toxicity in the two treatment groups was generally mild and well-tolerated in elderly patients with advanced NSCLC.

Discussion

The population of elderly patients with NSCLC is on the increase in China as well as in Western countries due to a general increase in life expectancy. NSCLC is a common disease in the elderly population and the provision of optimal treatment to elderly NSCLC patients is becoming an important issue, since age-related impairment of organ function

Table III. Pemetrexed and vinorelbine toxicities.

| Toxicity | Pemetrexed, n (%) (n=36) | | | | Vinorelbine, n (%) (n=26) | | | | P-value |
|------------------------|-----------------------------|----------|---------|---------|------------------------------|-----------|----------|----------|---------|
| | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 1 | Grade 2 | Grade 3 | Grade 4 | |
| Hematologic | | | | | | | | | |
| Neutropenia | 13 (36.1) | 5 (13.9) | 3 (8.3) | 1 (2.8) | 1 (3.8) | 10 (38.5) | 9 (34.6) | 5 (19.2) | 0.000 |
| Anemia | 9 (25.0) | 4 (11.1) | 0 | 0 | 14 (53.8) | 8 (30.8) | 1 (3.8) | 0 | 0.355 |
| Thrombocytopenia | 8 (22.2) | 2 (5.6) | 0 | 0 | 11 (42.3) | 5 (19.2) | 2 (7.7) | 0 | 0.106 |
| Non-hematologic | | | | | | | | | |
| Fatigue | 15 (41.7) | 1 (2.8) | 0 | 0 | 17 (65.4) | 2 (7.7) | 0 | 0 | 0.834 |
| Appetite loss | 7 (19.4) | 1 (2.8) | 0 | 0 | 14 (53.8) | 3 (11.5) | 0 | 0 | 0.623 |
| Nausea/vomiting | 3 (8.3) | 0 | 1 (2.8) | 0 | 6 (23.1) | 3 (11.5) | 0 | 0 | 0.001 |
| Constipation | 2 (5.6) | 2 (5.6) | 0 | 0 | 5 (19.2) | 4 (15.4) | 0 | 0 | 0.725 |
| Diarrhea | 3 (8.3) | 1 (2.8) | 0 | 0 | 3 (11.5) | 0 | 0 | 0 | - |
| ALT/AST | 5 (13.9) | 0 | 0 | 0 | 6 (23.1) | 1 (3.8) | 0 | 0 | 0.130 |
| Creatinine | 1 (2.8) | 0 | 0 | 0 | 1 (3.8) | 0 | 0 | 0 | - |
| Infection | 2 (5.6) | 0 | 0 | 0 | 1 (3.8) | 2 (7.7) | 0 | 0 | 0.007 |
| Peripheral neuropathy | 0 | 0 | 0 | 0 | 1 (3.8) | 0 | 0 | 0 | - |

ALT/AST, alanine aminotransferase/aspartate aminotransferase.

and presence of potentially complicating comorbid conditions should be taken into consideration.

First-line chemotherapy treatment is not frequently administered to elderly patients with advanced stage NSCLC. However, it has become useful in recent years, due to the fact that chemotherapy with a third-generation agent (gemcitabine, taxane or vinorelbine) has significantly improved median survival and quality of life in those patients (3,8-10). In the USA, 28% of elderly stage IIIB/IV NSCLC patients diagnosed in 1997 were administered chemotherapy, which increased to 36% of patients diagnosed in 2002 (11). Combination chemotherapy is used with caution in elderly patients due to the high risk of adverse events and a lower ability to tolerate the potential toxicity, thus single agents are generally accepted by oncologists as first-line therapy. Single-agent pemetrexed has been considered a standard treatment option in previously-treated advanced or metastatic NSCLC, as an objective response and symptomatic benefit in combination with a favorable safety profile were provided (12). However, limited data are available on the efficacy and toxicity of pemetrexed in elderly patients with advanced non-squamous NSCLC.

Our findings show that pemetrexed demonstrated a significantly higher DCR (80.5 vs. 65.3%; $P=0.011$), and an improvement in progression-free survival (6.5 vs. 4.0 months; $P=0.018$) compared to vinorelbine in elderly patients with advanced non-squamous NSCLC. Pemetrexed-treated patients also exhibited an increased 1-year survival rate (71.5 vs. 53.3%) and a longer median survival time (16.0 vs. 12.5 months) compared to vinorelbine-treated patients, while the differences were not statistically significant. Limitations of this study were the limited number of patients and the high proportion of patients (92.0%) subsequently receiving second-line therapy.

In this study, the survival rates following vinorelbine treatment were higher compared to those reported in other studies; single-agent vinorelbine as first-line chemotherapy in elderly

NSCLC patients has previously indicated 1-year survival rates of 13-38% and median survival times of 4.5-9.9 months (3,10,13,14). Notably, the median survival time of 16.0 months with pemetrexed treatment in this study was comparable to that reported for platinum-doublet chemotherapies assessed in recent studies in chemotherapy-naïve non-squamous NSCLC patients, where median survival times of 11.4-17.3 months were reported (15,16). There are at least three possible ways to explain the prolonged median survival time in the two treatment groups in this study. One possibility constitutes the relatively improved prognosis of the included patients. A second possibility is that the increased survival rates could have been a result of the significant proportion of patients receiving second-line treatment. A third possibility is that Asian patients are sensitive to epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKI), 47.2 and 30.8% of patients who were treated with pemetrexed and vinorelbine, respectively, received second-line treatment with gefitinib or erlotinib.

Age is a pivotal factor in the treatment, decision-making and cancer patient outcomes. The physiological hematopoietic capacity affected by aging may lead to an increased susceptibility to cytotoxic therapy. Several studies (?) have been conducted to evaluate cytotoxic agents in elderly patients with advanced NSCLC. The Elderly Lung Cancer Vinorelbine Italian Study (ELVIS) investigated for the first time the effects of vinorelbine on the quality of life and survival of elderly patients with advanced NSCLC in 1999 (13). Compared to optimum supportive care alone, the patients who received vinorelbine had a longer median duration of survival (6.4 vs. 4.8 months) and were significantly more likely to survive up to one year (32 vs. 14%). In addition, patients receiving vinorelbine exhibited improved outcome compared to controls on measures related to lung cancer symptoms and pain as well as on social, cognitive and physical functioning. The conclusive results of the MILES study also recommend that single-agent

vinorelbine or gemcitabine should be preferred over the combination therapy as palliative treatment for elderly patients with advanced NSCLC (3). The WJTOG study investigated the efficacy and safety of docetaxel vs. vinorelbine in elderly patients with advanced NSCLC (10). Compared to vinorelbine, the docetaxel elevated tumor response rate ranged from 9.9 to 22.7% ($P=0.019$) and increased median progression-free survival from 3.1 to 5.5 months ($P<0.001$). There was no statistical difference in the median overall survival with docetaxel vs. vinorelbine (14.3 vs. 9.9 months; $P=0.138$). Docetaxel monotherapy was therefore considered a standard treatment option, while it was associated with increased treatment-related toxicity; the incidence of grade 3-4 neutropenia and leucopenia was 82.9 and 58.0%, respectively.

In the present study, the toxicity profiles for the two treatment groups were mild and tolerable. However, severe neutropenia occurred significantly less often with pemetrexed treatment. The incidence of anemia and thrombocytopenia was also lower in the pemetrexed group compared to the vinorelbine group, while these differences were not statistically significant. In this study, patients treated with pemetrexed also experienced a relatively lower incidence of non-hematologic toxicities compared with patients treated with vinorelbine, a fact indicating that pemetrexed is well-tolerated among patients ≥ 70 years.

In conclusion, pemetrexed treatment improved DCR, progression-free survival, and presented a lower incidence of treatment-related adverse events compared with vinorelbine treatment in elderly patients with advanced non-squamous NSCLC. However, overall survival was not significantly improved. Based on these findings, pemetrexed monotherapy might be considered a good option in the treatment of elderly patients with advanced non-squamous NSCLC.

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