

Comparison between cisplatin plus vinorelbine and cisplatin plus docetaxel in the treatment of advanced non-small-cell lung cancer: A meta-analysis of randomized controlled trials

GUODONG SHEN^{1,2}, GENG BIAN², HAIYING YU², MIN GAO¹, DONGMEI KANG¹,
GAN SHEN^{1,2} and SHILIAN HU^{1,2}

¹Geriatrics Department, Anhui Provincial Hospital;

²Anhui Provincial Key Laboratory of Tumor Immunotherapy and Nutrition Therapy, Hefei, Anhui 230001, P.R. China

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Abstract. Whether cisplatin plus vinorelbine (VC) or cisplatin plus docetaxel (DC) are equally effective in the treatment of advanced non-small-cell lung cancer (NSCLC) remains controversial. The aim of this study was to compare the VC and DC regimens in the first-line treatment of advanced NSCLC. A search was conducted through PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE and the Chinese Biomedical Literature database (CBM). The language of the publication was not considered to be a limitation. The recruited trials were evaluated for eligibility and quality and the data were extracted and analyzed. The endpoints were overall response, survival rate and toxicity. We analyzed 9 randomized controlled trials (RCTs), including a total of 1,886 patients. Patients receiving DC therapy exhibited a significantly higher response rate [relative risk (RR)=0.83, 95% CI: 0.73-0.95 and P=0.007] and 2-year survival rate (RR=0.65, 95% CI: 0.50-0.84 and P=0.001). However, the 1-year survival rate for the two cisplatin-based regimens were comparable (RR=0.90, 95% CI: 0.81-1.01 and P=0.07). Patients receiving the VC regimen more frequently developed grade 3/4 leucopenia, anemia and vomiting, whereas those receiving DC chemotherapy were more prone to grade 3/4 diarrhea. The incidence of grade 3/4 neutropenia, thrombocytopenia and nausea were similar between the two arms. In conclusion, our study indicated that DC is superior to the VC regimen in terms of tumor response rate, 2-year survival rate and safety for the first-line treatment of advanced NSCLC.

Introduction

Lung cancer is the leading cause of cancer-related mortality, resulting in over one million deaths annually worldwide (1). Non-small-cell lung cancer (NSCLC) accounts for >80% of lung cancer cases. However, approximately two-thirds of patients have inoperable locally advanced (stage IIIB) or metastatic (stage IV) disease at the time of diagnosis, with a 1-year survival rate of <20% (2,3). It was demonstrated that the integrated basic treatment with chemotherapy is crucial in advanced NSCLC. Platinum-based doublet regimens are considered to be the standard treatment for advanced NSCLC (4-7). With the development of third-generation cytotoxic agents, such as taxanes, gemcitabine and vinorelbine, doublet chemotherapies consisting of platinum plus a third-generation agent are currently considered to be the standard regimens and are recommended as first-line chemotherapy for advanced NSCLC by the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Net (5,8,9). Vinorelbine was the first agent to demonstrate a survival benefit when combined with cisplatin and it consequently became a standard regimen for the first-line treatment of NSCLC (10). Docetaxel was the first drug approved for the second-line treatment of NSCLC (5). Docetaxel plus cisplatin (DC) treatment was shown to have better survival benefits compared with vinorelbine plus cisplatin (VC) treatment (11) and may therefore be used as a first-line agent in combination with platinum. Although third-generation anticancer drugs in combination with cisplatin may have the best efficacy in terms of longer survival and milder toxicity profiles, their use is currently controversial (5,12). Consequently, we conducted a systemic overview on published phase II and III randomized controlled trials (RCTs) comparing VC and DC in the first-line treatment of advanced NSCLC, with study endpoints such as tumor response rate, overall survival and toxicity.

Materials and methods

Search strategy. An electronic search was conducted through PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE and the Chinese Biomedical

Correspondence to: Professor Shilian Hu, Geriatrics Department, Anhui Provincial Hospital, 17 Lujiang Road, Hefei, Anhui 230001, P.R. China
E-mail: hushilian@126.com

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Table I. Baseline characteristics of the 9 trials comparing VC with DC in the treatment of advanced non-small-cell lung cancer.

| Patient no. | Treatment regimen | Mean age (years) | Disease stage (%IIIB/IV) | Quality scores | Year (refs.) |
|-------------|--|------------------|--------------------------|----------------|--------------|
| 404 | Vin 25 mg/m ² d1, 8, 15 and 22 + cispl 100 mg/m ² d1 ^a | 61 | 33/67 | 3 | 2003 (11) |
| 408 | Doc 75 mg/m ² d1 + cispl 75 mg/m ² d1 | 61 | 33/67 | | |
| 118 | Vin 30 mg/m ² d1, 8 + cispl 100 mg/m ² d1 | 57 | 0/100 | 3 | 2005 (15) |
| 115 | Doc 75 mg/m ² d1 + cispl 100 mg/m ² d1 | 58 | 0/100 | | |
| 33 | Vin 25 mg/m ² d1, 8 + cispl 20 mg/m ² d1-3 | 56 | 46/54 | 2 | 2006 (16) |
| 26 | Doc 37.5 mg/m ² d1, 8 + cispl 20 mg/m ² d1-3 | 55 | 27/73 | | |
| 48 | Vin 25 mg/m ² d1, 8 + cispl 60 mg/m ² d1 | 65 | 17/83 | 3 | 2007 (17) |
| 46 | Doc 160 mg/m ² d1 + cispl 60 mg/m ² d1 | 60 | 20/80 | | |
| 45 | Vin 30 mg/m ² d1, 8 + cispl 25 mg/m ² d1-3 | 51 | 58/42 | 3 | 2007 (18) |
| 42 | Doc 75 mg/m ² d1 + cispl 30 mg/m ² d1-3 | 47 | 60/40 | | |
| 33 | Vin 25 mg/m ² d1, 8 + cispl 75 mg/m ² d1 | - | 55/45 | 2 | 2007 (19) |
| 34 | Doc 75 mg/m ² d1 + cispl 75 mg/m ² d1 | - | 59/41 | | |
| 35 | Vin 25 mg/m ² d1, 8 + cispl 27 mg/m ² d1-3 | 62 | 63/37 | 2 | 2007 (20) |
| 32 | Doc 37.5 mg/m ² d1, 8 + cispl 27 mg/m ² d1-3 | 61 | 63/37 | | |
| 190 | Vin 30 mg/m ² d1 iv, 80 mg/m ² d8 oral + cispl 80 mg/m ² d1 | 59 | 20/80 | 3 | 2009 (21) |
| 191 | Doc 75 mg/m ² d1 + cispl 75 mg/m ² d1 | 62 | 15/85 | | |
| 44 | Vin 30 mg/m ² d1, 8 + cispl 80 mg/m ² d1 | 62 | 20/80 | 2 | 2009 (22) |
| 42 | Doc 75 mg/m ² d1 + cispl 75 mg/m ² d1 | 61 | 19/81 | | |

^a28 days per cycle; the remaining, 21 days per cycle. Vin, vinorelbine; doc, docetaxel; cispl, cisplatin; VC, vinorelbine plus cisplatin; DC, docetaxel plus cisplatin; yrs, years; d, day; iv, intravenous.

Literature database (CBM) up to May, 2013, for trials comparing VC to DC in the management of advanced NSCLC. The following terms were used: 'non-small-cell lung cancer', 'carcinoma, non-small-cell lung', 'chemotherapy' and 'randomized controlled trials'. The language of the publication and year of publication were not considered to be limitations. The reference lists of the original and review articles were also investigated for additional literature.

Inclusion criteria. Studies were considered eligible if they compared VC to DC chemotherapy for advanced NSCLC. The patients involved were required to have pathological or cytological confirmation of advanced (stage IIIB/IV) NSCLC, with a performance status of 0-2 on the World Health Organization (WHO) scale, or a Karnofsky performance status of $\geq 80\%$. Only the full-published studies (RCTs) were selected, whereas conference or meeting abstracts were excluded. The quality of the trials was assessed using the three-question instrument described by Jadad *et al* (13). The quality scores are listed in Table I.

Data extraction. The following information was independently extracted: first author, year of publication, quality scores, number of patients, chemotherapy regimens, mean age, percentage of stage IIIB and IV disease, overall RR, 1- and 2-year survival and specific toxicity data, such as leucopenia, neutropenia, thrombocytopenia, anemia, nausea and vomiting and diarrhea. Disagreements were resolved through discussion with an independent expert. The characteristics of the meta-analysis for each treatment group were assessed as

follows: overall response rate, overall 1- and 2-year survival and number of patients with grade 3/4 specific toxicity data, such as leucopenia, neutropenia, thrombocytopenia, anemia, nausea and vomiting and diarrhea. Since they are considered milestones in survival result analyses of NSCLC chemotherapy, 1- and 2-year survival were selected as primary endpoints. An attempt was made to contact the authors of each unpublished study on whether there had been any update of the trial following its presentation. The response was evaluated according to the Response Evaluation Criteria in Solid Tumors (14) or the WHO criteria and classified as complete response (CR), partial response (PR), stable disease and progressive disease. Overall response was defined as the sum of CR and PR. Toxicity profiles were graded according to the National Cancer Institute Common Toxicity Criteria or the WHO criteria.

Statistical analysis. The analyses were tested by pairwise comparisons between the VC arm of the identified trials and the respective DC arm. The relative risk (RR) for overall response to treatment, 1- and 2-year survival and the odds ratio (OR) for different types of toxicity were calculated using Review Manager software, version 5.0.3 (The Cochrane Collection, Oxford, UK). $P < 0.05$ was considered to indicate a statistically significant difference. An RR of > 1 reflected a favorable outcome in the VC arm regarding response and 1- or 2-year survival rate; an OR of > 1 indicated a higher toxicity in the VC arm. The heterogeneity of the studies was also assessed and $P < 0.1$ was defined as heterogenous. If the test indicated heterogeneity across studies, the random effects

Table II. Summary of grade 3/4 toxicities in VC and DC for advanced non-small-cell lung cancer.

| Toxicity | No. of studies | No. of cases | | Test of homogeneity | | OR (95% CI) | P-value |
|------------------|----------------|--------------|---------|---------------------|---------|--------------------------------|---------|
| | | VC | DC | I ² (%) | P-value | | |
| Leucopenia | 8 | 338/822 | 298/817 | 21 | 0.26 | 1.26 (1.02, 1.54) ^a | 0.03 |
| Neutropenia | 6 | 561/829 | 524/830 | 65 | 0.01 | 1.46 (0.93, 2.29) ^b | 0.10 |
| Thrombocytopenia | 8 | 33/907 | 19/898 | 0 | 0.88 | 1.69 (0.97, 2.96) ^a | 0.06 |
| Anemia | 6 | 146/686 | 51/683 | 48 | 0.09 | 3.40 (2.42, 4.76) ^a | <0.0001 |
| Nausea | 4 | 88/752 | 72/758 | 77 | 0.004 | 0.94 (0.37, 2.38) ^b | 0.90 |
| Vomiting | 6 | 99/831 | 66/832 | 47 | 0.10 | 1.58 (1.14, 2.20) ^a | 0.006 |
| Diarrhea | 6 | 15/829 | 49/826 | 0 | 0.71 | 0.31 (0.18, 0.55) ^a | <0.0001 |

^aFixed effects model. ^bRandom effects model. VC, vinorelbine plus cisplatin ; DC, docetaxel plus cisplatin; OR, odds ratio; CI, confidence interval.

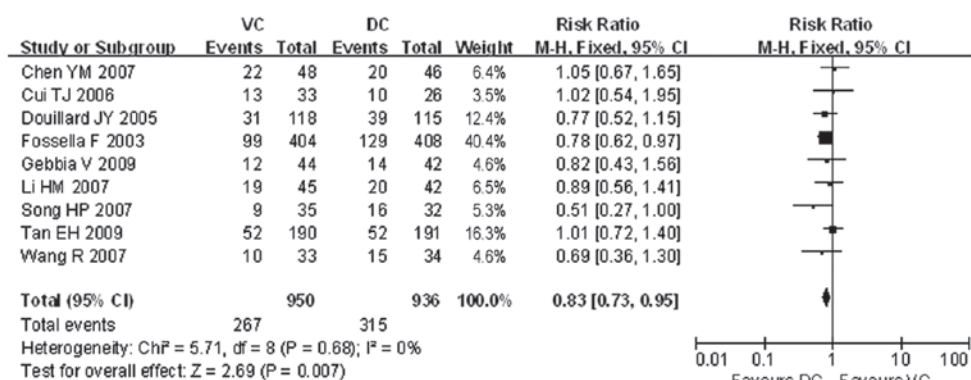


Figure 1. The overall response rate analysis of vinorelbine plus cisplatin (VC) or docetaxel plus cisplatin (DC) for advanced non-small-cell lung cancer (NSCLC). The fixed effects model was applied. Relative risk (RR) ratio and 95% confidence interval (CI) for each study are also plotted on the graph.

model (Der Simonian and Laird) was selected. Otherwise, we used the fixed effects model (Mantel-Haenszel) to analyze two treatment groups. All toxicities were analyzed in the trials stating the relative toxicities in a per-patient manner; trials not reporting on the relative toxic effects or reporting in a different way (e.g., reporting toxicities per treatment cycle) were excluded from the toxic effects evaluation.

Results

Characteristics of the included trials. A total of 9 RCTs that met the inclusion criteria were selected (11,15-22), of which 7 trials were phase II (15-20,22) and the remaining were phase III RCTs (11,21). The details of these trials are summarized in Table I. Randomization was stated in all trials; however, only 5 described the detailed methods of randomization. None of the trials were double-blind and all trials reported withdrawals and drop-outs. Overall, 1,886 patients were randomized to receive VC or DC chemotherapy (950 and 936 patients, respectively).

Response rate. The number of the cases achieving an overall response was presented in all the trials. The intention-to-treat analysis demonstrated that the overall response rate of the VC group was 28.11% and that of the DC group was 33.65%. The patients receiving DC therapy exhibited a significantly

higher response rate (RR=0.83, 95% CI: 0.73-0.95 and P<0.05) (Fig. 1). There was no heterogeneity between the compared groups ($\chi^2=5.71$; P=0.68; I²=0%).

Survival. One-year survival data were available for 7 of the 9 trials (11,17-21), including a total of 1,741 patients (Fig. 2). The 1-year survival rates of the VC and DC group were comparable (RR=0.90, 95% CI: 0.81-1.01 and P=0.07) and there was no heterogeneity ($\chi^2=2.08$; P=0.91; I²=0%). Furthermore, as shown in Fig. 2, patients treated with the DC regimen benefited from a significant reduction in the risk of mortality within the first 2 years (RR=0.65, 95% CI: 0.50-0.84 and P=0.001), as shown in the 2-year survival analysis of 4 trials (11,15,19,20).

Toxicity. All trials provided toxicity profile results. The adverse effects of chemotherapy were described as number of cases experiencing grade 3/4 toxicity. The most frequently reported toxicities included leucopenia, neutropenia, thrombocytopenia, anemia, nausea and vomiting and diarrhea (Table II). VC chemotherapy was more frequently associated with grade 3/4 leucopenia, anemia and vomiting (OR=1.26, 95% CI: 1.02-1.54 and P<0.05; OR=3.40; 95% CI: 2.42-4.76 and P<0.05; and OR=1.58, 95% CI: 1.14-2.20 and P<0.05, respectively), whereas patients receiving DC chemotherapy were more prone to grade 3/4 diarrhea (OR=0.31, 95% CI: 0.18-0.55 and P<0.0001). However, the incidence of neutropenia,

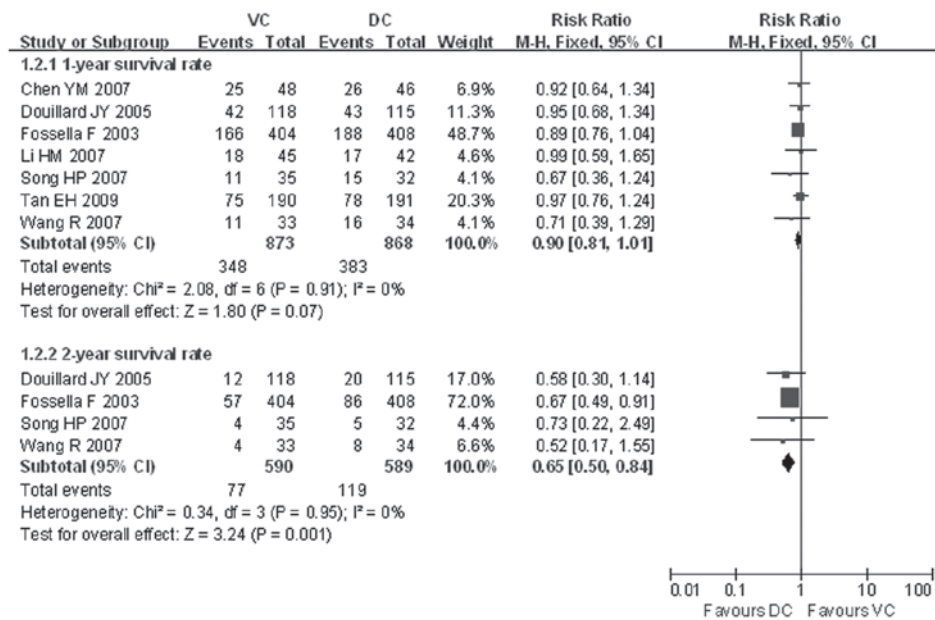


Figure 2. The 1- and 2-year survival analysis of vinorelbine plus cisplatin (VC) or docetaxel plus cisplatin (DC) for advanced non-small-cell lung cancer (NSCLC). The fixed effects model was applied. Relative risk (RR) ratio and 95% confidence interval (CI) for each study are also plotted on the graph.

thrombocytopenia and nausea were not significantly different between the two groups (OR=1.46, 95% CI: 0.93-2.29 and P=0.10; OR=1.69, 95% CI: 0.97-2.96 and P=0.06; and OR=0.94; 95% CI: 0.37-2.38 and P=0.90, respectively).

Discussion

NSCLC is a highly malignant disease exhibiting short survival times in the advanced stages. Improving the treatment for advanced NSCLC has proven to be challenging. Several NSCLC meta-analyses have been published over the last decade (6,23,24). These studies helped to determine a doublet chemotherapy consisting of platinum plus a third-generation agent as the gold standard in the treatment of NSCLC (5,6,8,9,12). In this study, we evaluated agents considered to be the gold standard according to current ASCO guidelines and may therefore be clinically useful in selecting the appropriate treatment for patients with advanced NSCLC.

We observed that patients receiving DC therapy exhibited higher response and 2-year survival rates compared to those who received VC therapy; however there was no significant difference in the 1-year survival rate between the VC and DC groups. Since second-line treatment may affect survival, the unbalanced post-study treatment may have had an impact on the survival analysis of our study. We also observed that VC as well as DC may cause hematological and digestive adverse events, although the VC group was prone to develop leucopenia, anemia and vomiting, whereas the DC group was more likely to develop severe diarrhea. There were no significant differences in the incidence of neutropenia, thrombocytopenia and nausea between the two groups.

One of the major issues with the available data on treatment for advanced NSCLC is the lack of quality of life (QoL) analyses. Although 4 trials in this meta-analysis included a formal QoL assessment, the assessment scales used, including

EuroQoL Five-Dimensional Questionnaire (11), Lung Cancer Symptom Scale (11,17,21) and EORTC QLQ-C30 (22), were different; therefore, the data could not be pooled. The QoL scores were not significantly different between the two groups in any of the trials, although the TAX 326 study demonstrated that the DC regimen relieved the symptoms and improved QoL compared to the VC regimen, according to the EuroQoL Five-Dimensional Questionnaire. Since the primary role of chemotherapy in patients with advanced NSCLC is palliative, the effect on patients' QoL is crucial in determining the overall value of new therapy.

Although there is no evidence that the DC regimen improves QoL compared to the VC regimen, our meta-analysis demonstrated that the DC regimen exhibits certain advantages over the VC regimen as first-line treatment for advanced NSCLC. The DC regimen was also associated with a more favorable safety profile compared to the VC regimen. These findings may be helpful when selecting the appropriate treatment for advanced NSCLC, with the aim of improving the response and survival rates, without increasing toxicity. Recently, with the advances in the research of cancer cell signal transduction, molecular targeted therapy has emerged as a treatment option; such regimens may provide a potential platform on which to add targeted therapy for first-line treatment in the future. Lynch *et al* (25) performed a phase III trial including 676 patients with advanced NSCLC without restrictions posed by histology or epidermal growth factor receptor expression, in which treatment with taxane plus carboplatin alone was compared to taxane plus carboplatin with cetuximab, confirming a remarkable increase in the overall response rate in taxane plus carboplatin with cetuximab over taxane plus carboplatin alone. The difference in overall survival favored cetuximab, although it did not reach a statistical significance. The results of that study cannot be applied to all patients with advanced NSCLC, as it excluded patients with previous

infusion reactions to chimerized/murine monoclonal antibodies, history of acute myocardial infarction, higher than grade 2 peripheral neuropathy and inadequate hematological, hepatic or renal functions. However, such patients represent a substantial population of patients with advanced NSCLC and viable alternatives are required to improve their treatment.

This meta-analysis had certain limitations that should be considered. Our study was limited by the number and quality of the available RCTs. Although it may be difficult for phase II studies to produce reliable survival data, no significant heterogeneity was observed in the response rate or in the 1- and 2-year survival rates among the trials included in the analysis. This result of the 2-year survival analysis supports the decision to include all randomized phase II or III trials with prospectively recorded 2-year survival data. Furthermore, the survival data at 2 years of follow-up and some adverse effects were lacking in several trials, which may have led to a biased estimate.

In conclusion, this meta-analysis revealed that DC therapy exhibited a marginally better response rate and 2-year survival rate and a milder toxicity profile compared to VC. Therefore, the former may be the better choice for patients with advanced NSCLC. However, these results need to be interpreted with caution, as the outcome of these meta-analyses on the basis of summary data derived from the literature may be affected by several biases.

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