Meta-Analysis of Randomized Clinical Trials Comparing Cisplatin to Carboplatin in Patients With Advanced Non–Small-Cell Lung Cancer

Katsuyuki Hotta, Keitaro Matsuo, Hiroshi Ueoka, Katsuyuki Kiura, Masahiro Tabata, and Mitsune Tanimoto

ABSTRACT

Purpose
It remains undetermined whether cisplatin and carboplatin are equally effective for advanced non–small-cell lung cancer (NSCLC). We therefore did a meta-analysis of trials that compared cisplatin-based chemotherapy with carboplatin-based chemotherapy.

Methods
We performed a literature search to identify trials that had investigated the substitution of carboplatin for cisplatin in the treatment of advanced NSCLC. We evaluated these trials for inclusion, rated methodologic quality, and abstracted relevant data.

Results
Of 1,191 reports, eight trials (2,948 patients) were identified, five of which investigated drug regimens containing platinum plus a new agent. Cisplatin-based chemotherapy produced a higher response rate, but the survival advantage was not significant (hazard ratio \(H_1\) = 1.050; 95% CI, 0.907 to 1.216; \(P = .515\)). Subgroup analysis revealed that combination chemotherapy consisting of cisplatin plus a new agent yields 11% longer survival than carboplatin plus the same new agent (hazard ratio \(H_2\) = 1.106; 95% CI, 1.005 to 1.218; \(P = .039\)). Patients on cisplatin-based chemotherapy frequently developed nausea and vomiting; thrombocytopenia was more frequent during carboplatin-based chemotherapy. No significant difference in treatment-related mortality was observed.

Conclusion
We found that combination chemotherapy consisting of cisplatin plus a new agent yields a substantial survival advantage compared with carboplatin plus a new agent in patients with advanced NSCLC, although we failed to find any survival difference in an analysis that included both new and old agents. The strength of our conclusion is limited because we used abstracted data, and careful interpretation is thus required. Nevertheless, our results raise a critical point that needs to be evaluated in future studies.


INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths in many countries. Approximately one third of patients with non–small-cell lung cancer (NSCLC) have metastatic disease at the time of diagnosis.\(^1\) Cisplatin-based chemotherapy is currently considered to be the standard treatment in advanced NSCLC, with a 10% absolute improvement in the 1-year survival rate compared to supportive care alone.\(^2\) However, many medical oncologists remain skeptical about these data and have not routinely used cisplatin-based chemotherapy to treat patients with advanced NSCLC.\(^3\) This reluctance may be partly explained by the severe toxicity that is associated with cisplatin-based chemotherapy.
In an attempt to circumvent cisplatin-induced toxicities, carboplatin, an analog of cisplatin, was introduced into clinical trials in 1981. Indeed, cisplatin has already been replaced by carboplatin for the chemotherapy of a few other malignancies, such as ovarian cancer. In patients with advanced NSCLC, carboplatin-based chemotherapy has also been extensively investigated. A two-drug combination consisting of carboplatin plus paclitaxel has been frequently used in clinical practice as well as in clinical trials, especially in the United States. However, it is still unclear whether carboplatin has efficacy equivalent to that of cisplatin or not. Go et al reviewed reports directly comparing the effectiveness of cisplatin with that of carboplatin. In their report, carboplatin was shown to possess inferior activity to that of cisplatin in germ cell, head and neck, and esophageal cancers. Furthermore, comparisons between cisplatin and carboplatin in NSCLC have been based on limited data. Accordingly, we performed a meta-analysis to compare the effect of carboplatin-based chemotherapy with that of cisplatin-based chemotherapy on overall survival, response rate, and toxicity in patients with advanced NSCLC.

**METHODS**

**Search for Trials**

We searched for trials that had completed recruitment by December 31, 2001. To avoid publication bias, both published and unpublished trials were identified through a computer-based search of the PubMed database and abstracts from the past 13 conferences of the American Society of Clinical Oncology (ASCO). We searched using the following terms: "lung cancer," "chemotherapy," and "randomized controlled trial." Only references published in English were included. We also examined reference lists of original articles, review articles, and relevant books, and the Physician Data Query registry of clinical trials.

**Selection of Trials**

Trials were eligible if they investigated the substitution of carboplatin for cisplatin in combination chemotherapy for patients with advanced NSCLC. Whatever drug was combined with cisplatin or carboplatin had to be the same cytotoxic agents in both treatment arms. Patients with pathologically confirmed NSCLC who had not previously received chemotherapy were enrolled in these trials.

**Validity Assessment**

We performed an open assessment of the trials and used the instrument reported by Jadad et al. We calculated odds ratios (ORs) to assess objective response rate and toxic events. We constructed 2 × 2 tables from abstracted data for response and for each toxic event. ORs and their variances for the subjects who received cisplatin-based chemotherapy relative to those receiving carboplatin-based chemotherapy were calculated from the tables. An OR above unity indicates that the cisplatin-based chemotherapy achieved worse results than the carboplatin-based chemotherapy. For OR calculations we excluded ineligible subjects from each evaluation.

A hazard ratio (HR) was calculated to assess the survival advantage of the carboplatin-based chemotherapy as compared with the cisplatin-based chemotherapy. The crude log HR value and its variance in each trial were calculated using the abstracted survival probabilities in the Kaplan-Meier curve at specific time points according to the methods proposed by Parmar et al. Minimum and maximum follow-up times were used to estimate censored subjects under the assumption that censoring happens constantly throughout follow-up. If the minimum follow-up time was not available, time zero was substituted for it. As we assumed constant hazard for the two types of therapy within an individual trial, all the survival probabilities available in each trial were used to obtain a representative HR for each trial instead of limiting time points to specified times. HRs were calculated to show how many times higher the probability of death from any cause was in patients receiving a carboplatin-based chemotherapy as compared with those receiving a cisplatin-based chemotherapy. Therefore, an HR greater than unity indicates that the cisplatin-based chemotherapy is better than the carboplatin-based chemotherapy.

A general variance-based method was used to estimate the summary HR, ORs, and their 95% CIs. We looked for heterogeneity among the trials based on standard methods. We also calculated the between-study variation (r²) from the Q statistic according to the method described by DerSimonian and Laird. Based on the statistical significance of the Q test, we applied a random effect model which allows meta-analyses to take into consideration between-study-variation. We also used Begg’s funnel plots and Egger’s test to detect possible publication bias. Meta-regression analysis was applied to detect the source of heterogeneity in the analysis for survival. The factors examined in meta-regression analysis were study quality score, starting year of trial, proportion of patients with performance status 0-1, proportion of stage IV patients, proportion of male patients, inclusion of new agents, number of stratifications in the random allocation, and median age of patients. Cumulative meta-analysis was applied in the event that heterogeneity was probable in an ordinal variable with statistical significance (P < .15).

All statistical analyses were conducted with STATA version 8 software (College Station, TX). We defined a statistical test with a P value less than .05 as significant.
**RESULTS**

**Trial Flow**

The flow chart of our study is shown in Figure 1. One of the nine trials retrieved for more detailed evaluation compared cisplatin plus tirapazamine with carboplatin plus tirapazamine. Since tirapazamine is not a cytotoxic agent and the effectiveness of tirapazamine for advanced NSCLC has not been determined, we excluded this trial from our analysis. Thus, eight trials involving 2,948 patients with advanced NSCLC were ultimately analyzed.

**Characteristics of the Eight Trials**

Baseline characteristics of the eight trials are listed in Table 1. In total, 2,948 patients were randomly assigned to cisplatin-based chemotherapy (1,478 patients) or carboplatin-based chemotherapy (1,470 patients). Patients were stratified by four variables in four trials, by three in one, and by two in three. Clinical stage was used for stratification in all trials.

Of the eight trials, seven were randomized phase III trials, and the remaining one was a randomized phase II trial. There was no placebo-controlled double-blind
trial. Each of the eight trials was reported in a full paper. Old chemotherapy regimens including etoposide, vindesine, mitomycin C, and vinblastine were investigated in three trials, whereas new chemotherapy regimens including paclitaxel, gemcitabine, and docetaxel were investigated in five trials.

We assessed the quality of the eight trials using the three question instrument reported by Jadad et al. There was a statement regarding both randomization and withdrawals in reports on all eight trials, whereas none of the trials were described as double-blind. Therefore, we assigned two points for all trials and judged that study quality was not a source of heterogeneity. Other potential sources of heterogeneity, including use of a new agent as a combination drug, were examined by meta-regression analysis. However, we detected no significant factor.

Response

Data on objective response rate were available in all eight trials (2,805 patients; Table 2). The objective response
rate to cisplatin-based chemotherapy was significantly higher than that to carboplatin-based chemotherapy (OR, 1.36; 95% CI, 1.15 to 1.61; \( P < .001 \)). Neither a funnel plot nor a rank correlation test regarding response rate indicated the existence of publication bias (Z = 1.04; \( P = .30 \)). In combination chemotherapy regimens of platinum plus a new agent (2,251 patients), the results were consistent, with OR estimates for most trials favoring cisplatin-based chemotherapy (OR, 1.38; 95% CI, 1.14 to 1.67; \( P = .001 \)).

### Overall Survival

Data on overall survival were available for all eight trials (2,903 patients; Table 3). Survival analyses were carried out based on intention-to-treat analysis in four trials, whereas 11, five, and five patients, respectively, in the trials reported by Klastersky et al.6 Jelic et al.7 Schiller et al.8 and Mazzanti et al.12 had been excluded from the survival analysis. The most common reason for the exclusion of patients from survival analysis was incorrect clinical stage.

#### Table 3. Survival in the Eight Trials Comparing Cisplatin-Based With Carboplatin-Based Chemotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Chemotherapy Regimen</th>
<th>Intention-to-Treat Analysis</th>
<th>1-Year Survival (%)</th>
<th>Median Survival Time (months)</th>
<th>( P )</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klastersky6</td>
<td>P + E</td>
<td>No</td>
<td>34</td>
<td>7.0</td>
<td>.35</td>
<td>1.20</td>
<td>0.89 to 1.61</td>
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<tr>
<td></td>
<td>C + E</td>
<td></td>
<td>23</td>
<td>6.3</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Jelic7</td>
<td>P + M + Vd</td>
<td>No</td>
<td>38</td>
<td>9.0</td>
<td>.01</td>
<td>0.61</td>
<td>0.48 to 0.77</td>
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<tr>
<td></td>
<td>C + M + Vd</td>
<td></td>
<td>33</td>
<td>8.2</td>
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<tr>
<td>Rosell10</td>
<td>P + T</td>
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<td>31</td>
<td>7.8</td>
<td>NS</td>
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<tr>
<td></td>
<td>C + T</td>
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<td>8.1</td>
<td></td>
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<tr>
<td>Schiller8</td>
<td>P + T</td>
<td>No</td>
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<td>8.8</td>
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<td>36</td>
<td>8.0</td>
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<tr>
<td>Zatloukal9</td>
<td>P + G</td>
<td>Yes</td>
<td>46</td>
<td>11.3</td>
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<td>1.19</td>
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<tr>
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<td>9.4</td>
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<tr>
<td>Fossella11</td>
<td>P + D</td>
<td>Yes</td>
<td>42</td>
<td>10.4</td>
<td>.39</td>
<td>1.12</td>
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<tr>
<td></td>
<td>C + D</td>
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<td>43</td>
<td>10.8</td>
<td></td>
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<td>Mazzanti12</td>
<td>P + G</td>
<td>No</td>
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<td>27</td>
<td>7.2</td>
<td></td>
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<tr>
<td>Paccagnella13</td>
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<td>Yes</td>
<td>36</td>
<td>10.2</td>
<td>.39</td>
<td>1.35</td>
<td>0.92 to 1.97</td>
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<td>27</td>
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**NOTE.** All \( P \) values were extracted from original papers. All HRs were estimated from Kaplan-Meier survival curves in each report. HRs of each trial were calculated based on the method described by Parmar et al. Each HR indicates relative risk with carboplatin-based chemotherapy relative to cisplatin-based chemotherapy. Abbreviations: HR, hazard ratio; P, cisplatin; E, etoposide; C, carboplatin; M, mitomycin C; Vd, vindesine; T, paclitaxel; NS, not significant; G, gemcitabine; D, docetaxel; NA, not assessed; Vb, vinblastine.
Cisplatin-based chemotherapy was associated with only a 5% improvement in overall survival as compared with carboplatin-based chemotherapy, and this difference was not statistically significant (HR, 1.050; 95% CI, 0.907 to 1.216; P = .515; Fig 2). A funnel plot and rank correlation test regarding survival confirmed the absence of publication bias (Z = 0.37; P = .71). On the other hand, subset analysis of the five trials revealed that the combination chemotherapy consisting of cisplatin plus a new agent yielded an 11% superior survival as compared with that of carboplatin plus a new agent. This difference was statistically significant (HR, 1.106; 95% CI, 1.005 to 1.218; P = .039; Fig 3).

Toxicity
Eight trials including 2,899 patients provided toxicity profile results. Complete data for neutropenia were not obtained in two trials and those for nephrotoxicity were not available in one trial. Cisplatin-based chemotherapy frequently led to grade 3 or more of nausea and vomiting (OR, 2.51; 95% CI, 1.76 to 3.56), while grade 3 or greater thrombocytopenia was significantly more frequent with carboplatin-based chemotherapy (OR, 0.58; 95% CI, 0.39 to 0.87). The risk of grade 3 or greater neutropenia and grade 3 or greater nephrotoxicity was almost comparable between the two modalities (OR, 0.94; 95% CI, 0.66 to 1.35 and OR, 2.82; 95% CI, 0.88 to 9.05, respectively). No significant difference in the number of treatment-related deaths was observed between the two modalities; there were 54 treatment-related deaths (3.9%) among 1,380 patients treated with cisplatin-based chemotherapy and 40 (2.9%) among 1,366 patients treated with carboplatin-based chemotherapy. This represents a 1.4-fold increase in the risk of treatment-related death in patients receiving cisplatin-based chemotherapy, but this difference was not statistically significant (OR, 1.36; 95% CI, 0.89 to 2.07). Similar results were obtained for subgroup analysis of the five trials that investigated the two-drug combinations of platinum plus a new agent.

DISCUSSION
In the present meta-analysis, we failed to demonstrate that cisplatin-based chemotherapy produces a significant survival advantage as compared with carboplatin-based chemotherapy in patients with advanced NSCLC. Then, we further analyzed the regimens containing platinum plus a new agent, because the combination chemotherapy regimens consisting of cisplatin plus etoposide, mitomycin C and vindesine, or mitomycin C and vinblastine are outdated, as defined in the ASCO guidelines. In this second analysis, we demonstrated that combination chemotherapy consisting of cisplatin plus a new agent yields a significant survival benefit compared with that of carboplatin plus a new agent. These results suggest that cisplatin has a possible advantage in the treatment of advanced NSCLC compared with carboplatin, if platinum is combined with a new agent.

Physicians should carefully interpret these results when they apply them in clinical practice because toxicity profiles were quite different between the two modalities. Because carboplatin-based chemotherapy frequently led to thrombocytopenia, only patients with adequate hematologic function should be treated with carboplatin-based chemotherapy. On the other hand, only patients with sufficient renal function...
should be allowed to receive cisplatin-based chemotherapy since severe nephrotoxicity was observed in patients receiving cisplatin-based chemotherapy, though only patients with adequate renal function were accrued in this meta-analysis.

We also note that patients receiving cisplatin-based chemotherapy developed nausea and vomiting more frequently, which might lead to a deterioration in quality of life (QOL). Because the primary role of chemotherapy in patients with advanced NSCLC is palliative, the influence on patients’ QOL is an important issue in determining the true value of new therapy. However, formal QOL assessments were performed in only three of the eight trials. Additionally, the compliance for QOL assessment was generally poor. In the report by Fossella et al, only 926 (76%) of the 1,218 accrued patients were assessed for QOL. Accordingly, further studies will be necessary to assess any difference in QOL between the two modalities.

Several technical issues have to be mentioned regarding this meta-analysis. One major limitation is the data source we used. Analyses were based on abstracted data and not on individual patient data (IPD). In general, an IPD-based meta-analysis would give a more robust estimation for the association, therefore, one needs to interpret our results with care, especially for a positive association in a subgroup analysis. Clearly, further investigation using IPD should be conducted to examine main effects as well as other end points, such as interaction between subgroups and main effect. Publication bias is a significant threat to the validity of meta-analysis. Although we detected no evidence of publication bias using graphical and statistical methods, it is difficult to completely rule out this possibility. Heterogeneity among trials can be another limitation of our meta-analysis, although we applied a random-effect model that takes possible heterogeneity into consideration. The absence of a statistically significant difference in the meta-regression analysis we used to examine heterogeneity may justify the analysis. However, as the number of trials was limited, careful interpretation of heterogeneity is necessary. Regarding HR estimation, we applied the Kaplan-Meier curve-based method which has substantially good correlations with alternative methods. We did not find any statistical inconsistencies between results in the original report and in the HR analysis that we did. Therefore, we can say that the overall HR results we obtained in this study are valid.

In conclusion, we demonstrated that combination chemotherapy consisting of cisplatin plus a new agent produces a significant survival advantage compared with that of carboplatin plus the same new agent in patients with advanced NSCLC, although we failed to demonstrate a survival advantage in an overall analysis that included both new agents and old agents. Although our conclusions should be interpreted cautiously, our results nevertheless raise a critical point regarding the long-standing debate on whether cisplatin-based chemotherapy or carboplatin-based chemotherapy is superior for advanced NSCLC. Further evaluation regarding this issue is now strongly needed.

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Authors’ Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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Role of Cisplatin in Lung Cancer


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