Table 2 Maximum NCI-CTC toxicities by number of patients

	NCI-CTC grade				Grade 3/4 toxicity (% of patients)
	1	2	3	4	
Leukocytes	1	5	8	1	60
Neutrophils	0	2	1	12	87
Platelets	1	1	0	0	0
Hemoglobin	10	4	1	0	7
Nausea	7	1	2	–	13
Vomiting	1	0	1	0	7
Dyspnea	–	2	2	0	13
Neutropenic fever	–	–	5	0	33
Fatigue	2	3	3	0	20
Liver	7	1	0	0	0
Electrolytes	1	0	2	0	13
Worst hematologic toxicity	0	1	2	12	93
Worst non-hematologic toxicity	5	2	8	0	53

turbance (13%), nausea (13%), and vomiting (7%). Grade 3 dyspnea observed in two patients was associated with bacterial pneumonia and docetaxel-related interstitial lung toxicity. No patients experienced hypersensitivity reactions or peripheral edema. Overall, grade 3 or higher hematologic and nonhematologic toxicities were observed in 14 patients (93%) and 8 patients (53%), respectively. No treatment-related death occurred.

Changes in symptom scores during chemotherapy

A total of 39 questionnaires were collected throughout the study. The overall collection rate was 61% (39/64), with rates after the first, second, and third cycle of chemotherapy of 87% (13/15), 38% (5/13), and 43% (3/7), respectively. Changes in symptom and global QOL (face scale) scores up to the third assessment are shown in Fig. 1, where individual scores are presented as relative values as compared with the baseline value. At each assessment, patients exhibited improvement in feeling, appetite, and global QOL; whereas slight deterioration was found in vomiting, cough and sputum. However, there were no significant differences in the changes in these scores during the treatment period. In addition, no relationship was found between relative symptom score and response to treatment.

Pharmacokinetic results

Blood sampling for pharmacokinetic analysis was not performed in three patients because of patient refusal. The C_{max} (1.35 ± 0.32 μg/ml, mean ± SD), $AUC_{0 \rightarrow inf}$ (1.79 ± 0.52 μg h/ml), and $t_{1/2}$ (4.1 ± 2.3 h) in the 12 elderly patients were somewhat lower than those (C_{max}, 1.61 ± 0.59 μg/ml; $AUC_{0 \rightarrow inf}$, 2.44 ± 0.83 μg·h/ml; $t_{1/2}$, 7.5 ± 6.3 h; $n = 6$) in non-elderly patients in a phase I study in Japan (docetaxel dose 60 mg/m^2; infusion time 60–160 min) [15]. Conversely, the CL (38.5 ± 8.5 l/h/m^2) in this study was somewhat higher than that (27.8 ± 11.6 l/h/m^2) in the phase I study. The non-elderly pharmacokinetic participants were required to have an Eastern Cooperative Oncology Group PS of two or less, to be aged between 15 and 75 years old, and to have a leukocyte count ≥4000/μl, a neutrophil count ≥1500/μl, a hemoglobin level ≥9.5 g/dl, a total bilirubin level ≤ 1.5 mg/dl, AST and ALT levels not more than two times the upper limit of the normal range, and a serum creatinine level not more than the upper limit of the normal range [15].

Discussion

This is, to our knowledge, the first study of an every 3-weeks schedule of docetaxel in chemotherapy-naive elderly patients with advanced NSCLC. The percentage

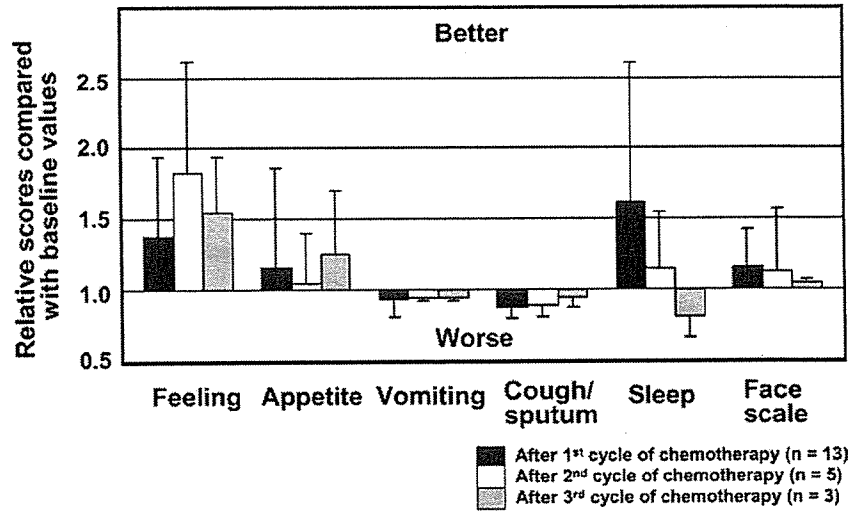

Fig. 1 Changes in relative symptom scores during the treatment period. The histograms represent mean and standard deviation

of patients who are reluctant to receive chemotherapy or who should not be treated with chemotherapy due to poor PS or comorbidity appears to be much higher among elderly patients than among younger patients [3]. In this study, we attempted to estimate the proportion of patients eligible for docetaxel among all elderly patients with advanced NSCLC who visited our hospitals. In a previous study by Oshita et al., 10 of 34 elderly (aged at least 75 years) patients (29%) with lung cancer were eligible for cisplatin-based chemotherapy [12]. In addition, in our retrospective series, 37% of elderly patients with advanced NSCLC underwent either cisplatin-based or non-platinum combination chemotherapy [16]. The results of these studies as well as that (proportion of eligible patients, 43%) of our own suggest that chemotherapy can be administered to approximately 30–40% of elderly patients with advanced NSCLC. However, these findings should be cautiously interpreted because the figures might include a considerable degree of physician discretion with regard to chemotherapy drug and dosing in the elderly.

The initial estimated sample size was 61 patients, which was determined with the efficacy endpoint (one of four primary endpoints) of this study. However, this study was terminated early due to the slow rate of patient accrual. Although the sample size was extremely small, the response rate (40%, 95% CI 15–65%) can be considered at least comparable to that (19%, 95% CI 11–29%) in a phase II study of docetaxel, which was conducted for the application for approval of docetaxel in Japan [4]. In that study, advanced NSCLC patients with a median age of 67 years (range 40–80 years) received docetaxel at a dose of 60 mg/m^2. In addition, the median survival time (15.6 months) in the present study is superior to that in the previous phase II study (9.8 months) [4], although four of nine patients with stage III disease underwent additional thoracic radiotherapy.

The major toxicity in our study was myelosuppression, with grade 3 or higher leukopenia and neutropenia, and grade 3 neutropenic fever observed in 60%, 87%, and 33% of patients, respectively. The incidence and severity of myelosuppression in our study were similar to those (49%, 87%, and 11%, respectively) in the Japanese phase II study [4]. However, hematologic toxicity was easily manageable, and did not lead to treatment-related death. Concerning non-hematologic toxicities, grade 3 or higher fatigue was more frequently observed in our study (20%) than in the phase II study (4%). However, there were no differences in the incidences of other non-hematologic toxicities between the two studies. In this study, relative symptom and global QOL scores did not decline during the treatment period. However, particularly after the second cycle of chemotherapy, only a small number of patients answered the questionnaire, adding limited information to this assessment.

It is believed that the pharmacokinetic profiles of docetaxel are not affected by patient age [6]. Compared with the result of a Japanese phase I study of docetaxel conducted in non-elderly patients [15], the values of C_{max}, $AUC_{0 \rightarrow inf}$, and $t_{1/2}$ were slightly lower in our study, with a slight increase in CL. We cannot explain why docetaxel was cleared more rapidly in this study population. In addition, we have no clear explanation for the relationship between relatively increased total body clearance of docetaxel and high incidence of severe neutropenia. It seems difficult to compare the pharmacokinetic profiles of docetaxel between these studies, since docetaxel in the phase I study was infused at a dose of 60 mg/m^2 over 60–160 min.

In conclusion, 43% of elderly patients with advanced NSCLC received single-agent docetaxel without a reduction in their symptoms in our study, although careful attention should be paid to the physiologic changes associated with ageing to ensure safe administration of anticancer drugs to the elderly. Based on the result of the "ELVIS" study, vinorelbine monotherapy has been considered the treatment of choice for elderly patients with advanced NSCLC [17]. Docetaxel monotherapy also appears to be useful for the treatment of elderly patients with advanced NSCLC, although the validity of the results is limited due to the small sample size. In future studies the endpoint should be limited and the age range should be reconsidered (e.g., 70 years or more). In addition, comorbidity, number of medications, and functional and cognitive status should be evaluated to ascertain the "physiologic age" of the elderly.

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

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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 = 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 = 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.

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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.[4] Indeed, cisplatin has already been replaced by carboplatin for the chemotherapy of a few other malignancies, such as ovarian cancer.[5] In patients with advanced NSCLC, carboplatin-based chemotherapy has also been extensively investigated.[6-14] 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.[14] However, it is still unclear whether carboplatin has efficacy equivalent to that of cisplatin or not. Go et al[15] 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.[16]

Data Abstraction

To avoid bias in the data abstraction process, two observers (K.H. and H.U.) independently abstracted the data from the trials and compared results. The following information was obtained from each source article: year of publication, study period, number of patients, sex, clinical stage, performance status, chemotherapy regimen, objective response rate, overall survival, and specific toxicity data. New chemotherapy agents were defined as docetaxel, paclitaxel, vinorelbine, gemcitabine, and irinotecan.[17]

All data were checked for internal consistency, and disagreements were resolved by discussion among the investigators. All principal investigators of the trials were contacted to confirm or update the published data. For response assessment, we used only trials that included patients with measurable or assessable disease, and that were analyzed with well-accepted criteria. Toxicity profiles were reported according to the WHO's criteria or the cooperative groups' criteria.

Quantitative Data Synthesis

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.[18] 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.[19] We also calculated the between-study variation (τ^2) from the Q statistic according to the method described by DerSimonian and Laird.[20] 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[21] and Egger's test[22] 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,[16] 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.[23] Since tirapazamine is not a cytotoxic agent and the effectiveness of tirapazamine for advanced NSCLC has not been determined,[24] we excluded this trial from our analysis. Thus, eight trials involving 2,948 patients with advanced NSCLC were ultimately analyzed.[6-13]

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,[6-11,13] and the remaining one was a randomized phase II trial.[12] There was no placebo-controlled double-blind

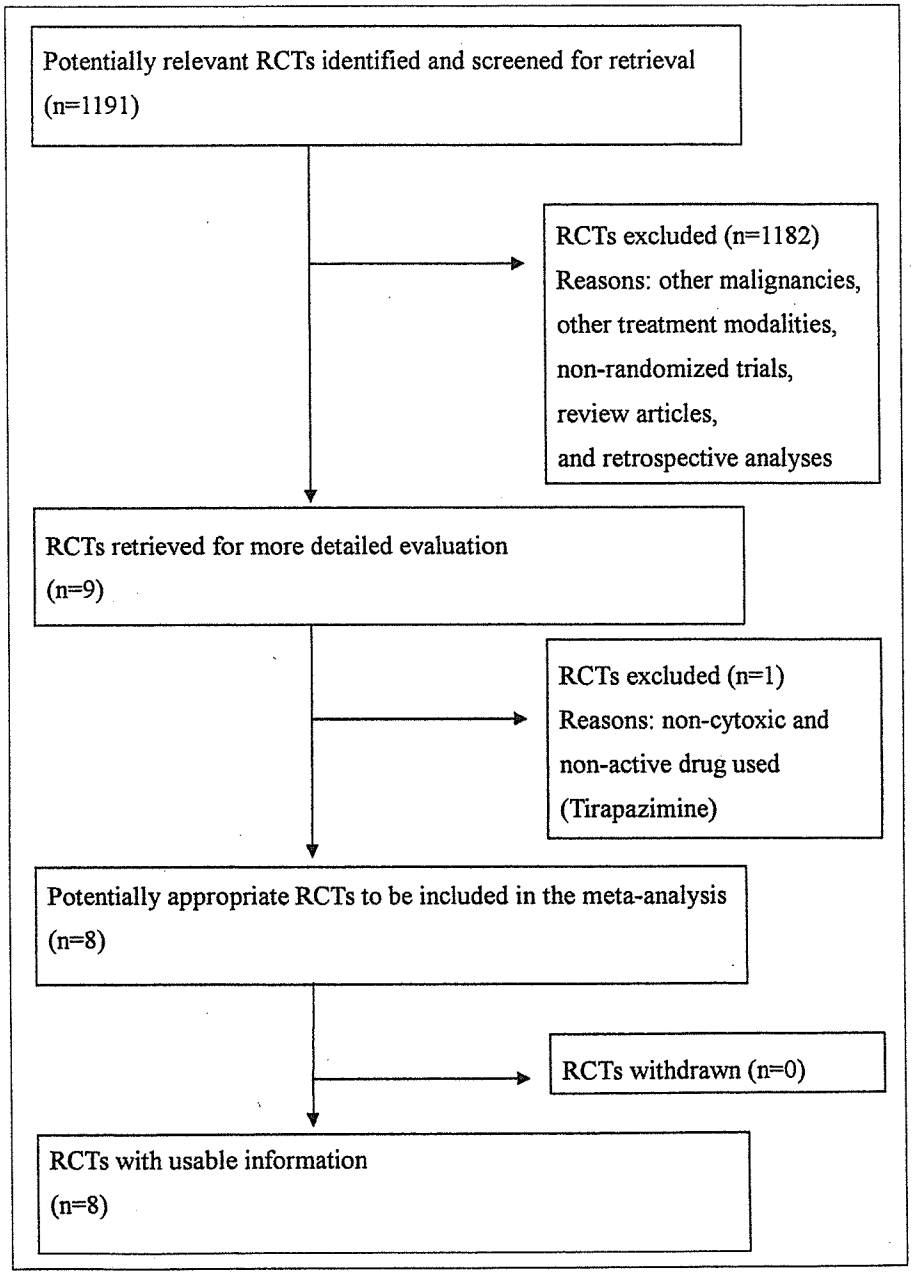

Fig 1. A flow chart showing the progress of trials through the review. RCT, randomized controlled trials.

Table 1. Characteristics of the Eight Trials Comparing Cisplatin-Based With Carboplatin-Based Chemotherapy

Study	Year	No. of Randomly Assigned Patients	Chemotherapy Regimen	Male (%)	PS 0-1 (%)	Stage IV (%)
Klastersky[6]	1990	120	P 120 mg/m², d1 + E 100 mg/m², d1-3; q3-4wks	89	74	54
		119	C 325 mg/m², d1 + E 100 mg/m², d1-3; q3-4wks			
Jelic[7]	2001	114	P 120 mg/m², d2 + M 8 mg/m², d1 + Vd 3 mg/m², d1; q4wks	91	60	44
		107	C 500 mg/m², d2 + M 8 mg/m², d1 + Vd 3 mg/m², d1; q4wks			
Rosell[10]	2002	309	P 80 mg/m², d1 + T 200 mg/m², d1 (3-hr); q3wks	83	83	60
		309	C AUC = 6, d1 + T 200 mg/m², d1 (3-hr); q3 wks			
Schiller[8]	2002	303	P 75 mg/m², d2 + T 135 mg/m², d1 (24-hr); q3wks	63	95	88
		299	C AUC = 6, d1 + T 225 mg/m², d1 (3-hr); q3wks			
Zatloukal[9]	2003	87	P 80 mg/m², d1 + G 1,200 mg/m², d1,8; q3wks	77	68	60
		89	C AUC = 5, d1 + G 1,200 mg/m², d1,8; q3wks			
Fossella[11]	2003	408	P 75 mg/m², d1 + D 75 mg/m², d1; q3wks	72	96	67
		406	C AUC = 6, d1 + D 75 mg/m², d1; q3wks			
Mazzanti[12]	2003	62	P 80 mg/m², d2 + G 1,200 mg/m², d1,8; q3wks	78	83	59
		63	C AUC = 5, d2 + G 1,200 mg/m², d1,8; q3wks			
Paccagnella[13]	2004	75	P 100 mg/m², d1 + M 8 mg/m², d1 + Vb 4 mg/m², d1,8; q3wks	50	50	78
		78	C 300 mg/m², d1 + M 8 mg/m², d1 + Vb 4 mg/m², d1,8; q3wks			

Abbreviations: PS, performance status; P, cisplatin; d, day; E, etoposide; q, every; wks, weeks; C, carboplatin; M, mitomycin C; Vd, vindesine; T, paclitaxel; AUC, area under the plasma concentration-time curve; G, gemcitabine; D, docetaxel; Vb, vinblastine.

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,[6,7,14] whereas new chemotherapy regimens including paclitaxel, gemcitabine, and docetaxel were investigated in five trials.[8-12]

We assessed the quality of the eight trials using the three question instrument reported by Jadad et al.[16] 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

Table 2. Responses in the Eight Trials Comparing Cisplatin-Based With Carboplatin-Based Chemotherapy

Study	Year	Chemotherapy Regimen	No. of Responding Patients	No. of Patients Eligible for Evaluation	Objective Response (%)	OR	95% CI
Klastersky[6]	1990	P+E	27	100	26	1.99	0.99 to 3.97
		C+E	16	102	16		
Jelic[7]	2001	P+M+Vd	40	109	37	1.05	0.60 to 1.84
		C+M+Vd	36	101	36		
Rosell[10]	2002	P+T	80	284	28	1.17	0.81 to 1.70
		C+T	70	279	25		
Schiller[8]	2002	P+T	60	288	21	1.29	0.85 to 1.97
		C+T	49	290	17		
Zatloukal[9]	2003	P+G	36	87	41	1.71	0.92 to 3.20
		C+G	26	89	29		
Fossella[11]	2003	P+D	129	408	32	1.47	1.08 to 2.01
		C+D	97	406	24		
Mazzanti[12]	2003	P+G	26	62	42	1.60	0.76 to 3.40
		C+G	18	58	31		
Paccagnella[13]	2004	P+M+Vb	31	72	43	1.20	0.62 to 2.35
		C+M+Vb	27	70	39		

Abbreviations: OR, odds ratio; P, cisplatin; E, etoposide; C, carboplatin; M, mitomycin C; Vd, vindesine; T, paclitaxel; G, gemcitabine; D, docetaxel; Vb, vinblastine.

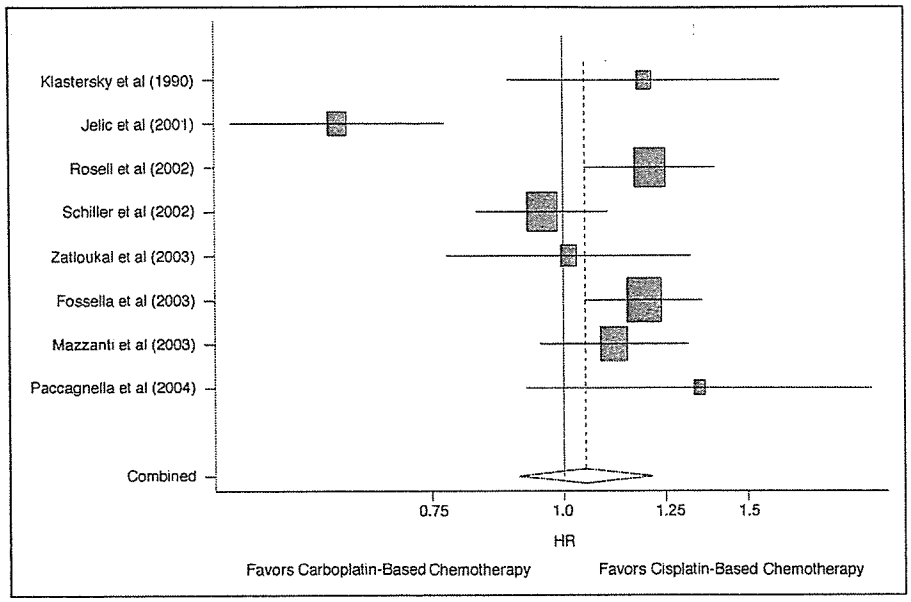

Fig 2. Overall survival with cisplatin-based compared with carboplatin-based chemotherapy. The summary hazard ratio (HR) was 1.050 (95% CI, 0.907 to 1.216; $P = .515$) indicating a 5.0% increase in hazard events in carboplatin-based chemotherapy compared to cisplatin-based therapy.

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),[8-12] 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, 24, 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

Study	Chemotherapy Regimen	Intention-to-Treat Analysis	1-Year Survival (%)	Median Survival Time (months)	*P*	HR	95% CI
Klastersky[6]	P+E	No	34	7.0	.35	1.20	0.89 to 1.61
	C+E		23	6.3			
Jelic[7]	P+M+Vd	No	19	8.0	.01	0.61	0.48 to 0.77
	C+M+Vd		38	9.0			
Rosell[10]	P+T	Yes	38	9.8	.02	1.21	1.05 to 1.40
	C+T		33	8.2			
Schiller[8]	P+T	No	31	7.8	NS	0.96	0.83 to 1.10
	C+T		34	8.1			
Zatloukal[9]	P+G	Yes	33	8.8	.90	1.01	0.77 to 1.32
	C+G		36	8.0			
Fossella[11]	P+D	Yes	46	11.3	NA	1.19	1.05 to 1.36
	C+D		38	9.4			
Mazzanti[12]	P+G	No	42	10.4	.39	1.12	0.95 to 1.32
	C+G		43	10.8			
Paccagnella[13]	P+M+Vb	Yes	36	10.2	.39	1.35	0.92 to 1.97
	C+M+Vb		27	7.2			

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.[18] 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.

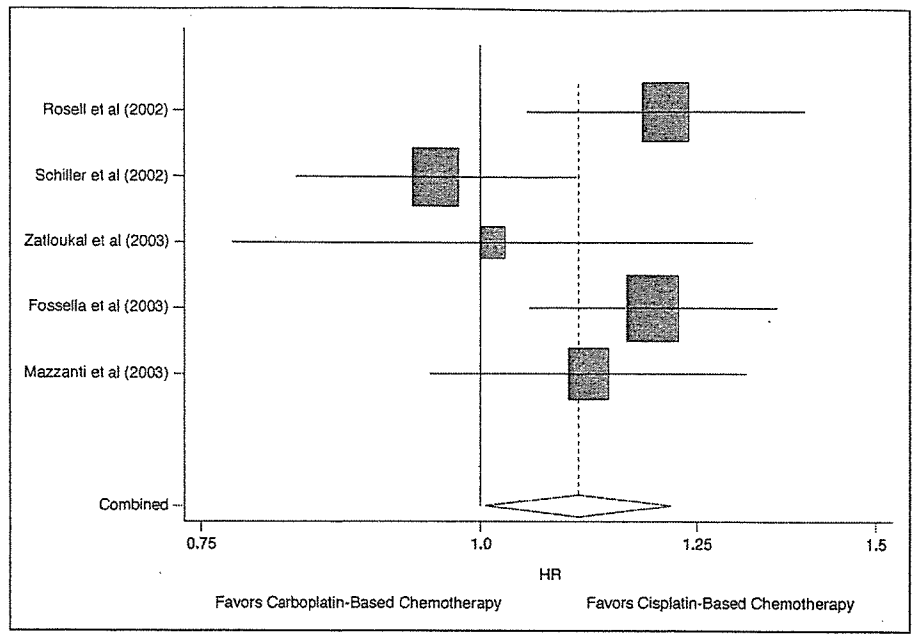

Fig 3. Overall survival with cisplatin plus new agents compared with carboplatin plus new agents. The summary hazard ratio (HR) was 1.106 (95% CI, 1.005 to 1.218; P = .039) indicating a 10.6% increase in hazard events in carboplatin-based chemotherapy compared to cisplatin-based chemotherapy.

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[8-12] 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[6,13] and those for nephrotoxicity were not available in one trial.[9] 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.[8-12]

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 platinum plus etoposide,[6] mitomycin C and vindesine,[7] or mitomycin C and vinblastine[13] are outdated, as defined in the ASCO guidelines.[17] 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.[10,11,13] Additionally, the compliance for QOL assessment was generally poor. In the report by Fossella et al,[11] 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,[25] 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.[18] 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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ORIGINAL REPORT

Role of Adjuvant Chemotherapy in Patients With Resected Non–Small-Cell Lung Cancer: Reappraisal With a Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

Purpose
The role of adjuvant chemotherapy in patients with resected non–small-cell lung cancer (NSCLC) remains to be defined. This study was aimed at re-evaluating the effectiveness of adjuvant chemotherapy in patients with resected NSCLC, by performing a meta-analysis of relevant trials.

Methods
We performed a literature search to identify trials reported after the publication of a meta-analysis in 1995, comparing patients with NSCLC receiving chemotherapy after surgery with those undergoing surgery alone. The hazard ratio (HR) was estimated to assess the survival advantage of adjuvant chemotherapy.

Results
Eleven trials conducted on a total of 5,716 patients were identified by the literature search. In these trials, hazard ratio estimates suggested that adjuvant chemotherapy yielded a survival advantage over surgery alone (HR, 0.872; 95% CI, 0.805 to 0.944; $P = .001$). In a subset analysis, both cisplatin-based chemotherapy (HR, 0.891; 95% CI, 0.815 to 0.975; $P = .012$) and single-agent therapy with tegafur and uracil (UFT; HR, 0.799; 95% CI, 0.668 to 0.957; $P = .015$) were found to yield a significant survival benefit. The toxicities of adjuvant chemotherapy were found to be generally mild.

Conclusion
This is the first updated meta-analysis demonstrating the importance of cisplatin-based chemotherapy and single-agent UFT therapy as adjuvant chemotherapy in the treatment of resected NSCLC. Although the results must be carefully interpreted because of one limitation (the meta-analysis was performed with abstracted data), they raise critical issues that must be resolved in future studies.

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INTRODUCTION

Lung cancer is the leading cause of cancer death in many countries.[1] Surgery remains the best treatment modality for potential cure in patients with non–small-cell lung cancer (NSCLC), and, at present, one-third of all patients are suitable candidates for surgery at the time of initial presentation. However, taking into account the annual incidence of lung cancer worldwide, which is estimated to be more than a million, the social burden of this category of patients is large.[2] Moreover, the long-term survival rate even after surgical resection is rather disappointing.[3]

To improve the postoperative survival of NSCLC patients, the development of effective postoperative therapy is essential. Prospective randomized trials investigating the role of postoperative adjuvant chemotherapy in NSCLC have been performed since the 1960s. A meta-analysis of adjuvant

chemotherapy trials reported in 1995 revealed a hazard ratio (HR) of 0.87 for patients treated with cisplatin (CDDP) -based chemotherapy.[4] However, this result was only of marginal significance. Furthermore, this meta-analysis had the following limitations: the trials evaluated included those using outdated chemotherapy regimens, including a small number of accrued patients, and recorded poor treatment compliance.

Subsequently, many randomized trials investigating the role of adjuvant chemotherapy using more active chemotherapy regimens and larger numbers of accrued patients have been conducted.[5-15] Recently, very large-scale trials have been reported from Japan, Chile, and Italy.[10,11,15] However, these trials yielded conflicting data in regard to the survival benefit. Therefore, we performed a meta-analysis using data from these trials to investigate the effect of adjuvant chemotherapy on the overall survival in patients with resected NSCLC.

METHODS

Research Objective

The primary objective of this study was to assess the survival advantage gained by adding adjuvant chemotherapy to surgery in patients with resectable NSCLC.

Searching for Trials

To update the data, we intended to eliminate the trials accrued in the previous meta-analysis published in 1995.[4] Therefore, only those trials for which patient recruitment was completed after January 1, 1992, were eligible. To avoid publication bias, both published and unpublished trials were identified through a computer-based search of the PubMed database and abstracts from the previous 12 Annual Meetings of the American Society of Clinical Oncology. We conducted the search using the following search terms: "lung cancer," "chemotherapy," "adjuvant," and "postoperative." Only references published in English were included. The search was also guided by a thorough examination of reference lists of original articles, review articles, and relevant books.

Selection of Trials

We included only those trials in which patients were randomly assigned to at least two arms—surgery followed by chemotherapy or surgery alone—and that included only patients with pathologically proven NSCLC who underwent a curative resection. Although optional thoracic irradiation was allowed as one of the adjuvant treatments, trials initially designed to randomly assign patients to surgery, followed by chemotherapy plus radiation, or surgery plus radiation, were considered ineligible. Trials that evaluated immunotherapy as adjuvant therapy and that were designed mainly to evaluate neoadjuvant chemotherapy and/or radiotherapy, were also excluded from the analysis.

Validity Assessment

We performed open assessments of the trials and used the instrument reported by Jadad et al.[16] The Jadad score that we used was the original version reported in 1996. It included three simple questions: (1) was the study described as randomized? (2) Was the study described as double blind? (3) Was there a description of withdrawals and dropouts? The overall scores for these three items were calculated for each trial. Briefly, we gave a score of 1 point for each "yes" and 0 for each "no." There were no in-between scores.

Data Abstraction

To avoid bias in the data abstraction process, two observers (K.H. and H.U.) independently abstracted the data from the trials and compared the results. The following information was culled from each report: year of publication, number of patients, sex, pathological stage, performance status, chemotherapy regimen, treatment compliance, overall survival, and specific toxicity data. An attempt was also made to contact all the principal investigators of the trials to confirm or update the published data. In general, treatment compliance was defined as the number of patients who received the all planned courses of chemotherapy as a percentage of all the assessable patients in the trials evaluating cisplatin-based chemotherapy, and as the number of patients treated for the planned treatment period as a percentage of all the assessable patients in the trials evaluating single-agent therapy with tegafur and uracil (UFT).

Quantitative Data Synthesis

The HR was estimated to assess the survival advantage conferred by adjuvant chemotherapy. The crude log HR and its variance in each trial were calculated using the abstracted survival probabilities at each time-point from the Kaplan-Meier (KM) curves, according to the methods of Parmar et al.[17] The HR provided in the report was used wherever available with 95% CIs. The minimum and maximum follow-up periods were used to estimate the number of censored subjects under the assumption that censoring occurs consistently throughout the follow-up period. If the minimum follow-up time was not available, time zero was substituted for it. Assuming a constant hazard for 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 the time points to specified times. The HRs were calculated to estimate how many times higher the probability of death from any cause would be in patients receiving adjuvant chemotherapy after surgery, compared with that in patients undergoing surgery alone. Therefore, an HR below unity was taken to indicate that adjuvant chemotherapy after surgery was superior to surgery alone. Trials including two experimental arms were treated as two independent trials.[9,13]

The general variance-based method was used to estimate the summary HRs and their 95% CIs. We also calculated the between-study variation (τ^2) from the Q statistic, according to the method described by DerSimonian and Laird.[18] We decided to apply a random effect model, which allows meta-analyses to take between-study variations into consideration based on the statistical significance of the Q test. We also used Begg's funnel plots[19] and Egger's test[20] to identify possible publication bias. Meta-regression analysis was applied to detect the source of heterogeneity in the analysis.[21] The factors examined in the meta-regression analysis were the study quality score,[16] inclusion of platinum agents in the regimen, inclusion of UFT, type of report (abstract form or original article), year of start of the trial, disease stage in the enrolled patient (I, II, or III), proportion of patients with a performance status (PS) score of 0-1, and proportion of male patients. Cumulative meta-analysis was applied in the event of heterogeneity being probable in an ordinal variable with statistical significance ($P < .15$). Subgroup meta-analysis was performed for platinum-based therapy and single-agent UFT therapy. The probable sources of heterogeneity ($P < .20$) for categorical variables were also evaluated by subgroup meta-analysis.

All the statistical analyses were conducted using the Stata version 8 software (Stata Corp, College Station, TX). We defined a statistical result with a P value of less than .05 as significant.

RESULTS

Trial Flow

Our computer-based search of the PubMed database, and manual search of the abstracts and relevant articles yielded 527, four, and two reports, respectively, published throughout a 12-year period. These included 31 potentially relevant randomized clinical trials that evaluated postoperative adjuvant therapy in patients with resected NSCLC. Of the 31 possibly appropriate trials, 20 were excluded from our meta-analysis, including seven that assessed immunotherapy and eight which assessed radiotherapy and two vitamins as adjuvant therapy, and three trials which were initially designed to randomize patients into surgery followed by chemotherapy plus radiation, or surgery followed by radiation.

One of the remaining 11 trials, a British one[12] was a unique trial, because all clinically operable patients were included in the trial, whether or not they had undergone curative resection. However, since the majority of patients in the trial did in fact have an R0 (complete resection) or R1 operation (microscopically incomplete resection), and only two (0.5%) of the total of 381 patients had pathological stage IV disease, we included this trial in our analysis. Thus, ultimately, data from 11 trials were included in this meta-analysis.[5-15]

Characteristics of the 11 Trials

The baseline characteristics of the 11 trials are listed in Table 1. In total, 5,716 patients were randomized to surgery followed by adjuvant chemotherapy (2,873 patients), or to

Table 1. Characteristics of the 11 Trials Included in This Meta-Analysis

Study	Year Published	Year of Start of Accrual	No. of Randomly Assigned Patients in CH Arm	No. of Randomly Assigned Patients in Control Arm	Pathological Stage	% Stage III	% of N2 Positive	No. of Treatment Arms	Chemotherapy Regimen	% Compliance
Xu et al[5]	2000	1989	35	35	I-III	70	NR	2	P (20 mg/m^2); d 1-5 + C (300 mg/m^2) + V (1.4 mg/m^2) + A (50 mg/m^2) + L (50 mg/m^2); d 1 + U (600-900 mg/d); 1 year	91
Mineo et al[7]	2001	1988	33	33	IB	0	0	2	P (100 mg/m^2); d 1 + E (120 mg/m^2); d 1-3	76
Tanaka et al[6]	2001	1991	176	191	I	0	0	2	U (300-400 mg/d); 1 year	51
Tada et al[8]*	2002	1992	85	87	I	0	0	2	U (400 mg/d); 1 year	77
			47	48	II-III	65	54	2	P (80 mg/m^2); d 1 + Vd (3 mg/m^2); d 1,7→U (400 mg/d); 1 year	49
Endo et al[14]	2003	1992	110	111	I-II	0	0	2	U (400 mg/d); 2 years	52
Imaizumi[13]†	2003	1992	50	50	I	0	0	3	U (400 mg/d); 2 years	79
			50			0	0		P (80 mg/m^2); d 1 + Vd (3 mg/m^2); d 1,8 + U (400 mg/d); 2 years	61
Scagliotti et al[10]	2003	1994	606	603	I-IIIA	28	25	2	P (100 mg/m^2) + M (8 mg/m^2); d 1 + Vd (3 mg/m^2); d 1,8	69
Waller et al[12]	2003	1995	192	189	I-IV‡	34	21	2	P (80 mg/m^2); d 1 + Vd (3 mg/m^2); d 1,8, or P (80 mg/m^2); d 1 + Vn (30 mg/m^2); d 1,8; or P (50 mg/m^2) + M (6 mg/m^2); d 1, + I (3 g/m^2); d 1, or P (50 mg/m^2) + M (6 mg/m^2); d 1, + Vb (6 mg/m^2); d 1	64
Arriagada et al[11]	2004	1995	932	935	I-III	39	26	2	P (80-120 mg/m^2); d 1 + E (100 mg/m^2); d 1-3, or + Vn (30 mg/m^2), or + Vb (4 mg/m^2), or + Vd (3 mg/m^2); weekly	74
Kato et al[15]	2004	1994	498	501	I	0	0	2	U (250 mg/m^2); 2 years	61
Tada et al[9]	2004	1994	59	60	IIIA	100	100	2	P (80 mg/m^2); d 1 + Vd (3 mg/m^2); d 1,8	58

Abbreviations: CH, chemotherapy; NR, not recorded; P, cisplatin; d, day; C, cyclophosphamide; V, vincristine; A, adriamycin; L, lomustine; U, UFT; E, etoposide; Vd, vindesine; M, mitomycin; Vn, vinorelbine; Vb, vinblastine.

*Patients with pathological stage I and II-III were accrued to separate trials.

†Patients were randomly assigned to three arms, including the control arm.

‡Only two patients had pathological stage IV.

surgery alone (2,843 patients). Four trials were reported in abstract form only.[6,9,12,13] In the adjuvant chemotherapy arm, CDDP was used in eight trials including 3,907 patients, and vindesine was frequently combined with CDDP (six of the eight trials). Single-agent UFT was also frequently used in five trials including 1,809 patients.

We assessed the quality of all the trials using the instrument reported by Jadad et al.[16] There was a statement on both randomization and withdrawal in all the trials; however, none of the trials was described as double-blind. Therefore, we used two points for all the trials and decided to abandon cumulative meta-analysis in the further analysis.

Overall Survival

Data on survival were available for all trials (5,538 patients, Table 2). A total of 178 randomized patients in four trials were excluded from the survival analysis.[6,10,14,15] The main reasons for this exclusion were problems with data integrity, incomplete resection, incorrect clinical stage, and incorrect pathological diagnosis; on the other hand, postoperative deaths were not generally excluded from the survival analysis. The accuracy of the HRs estimated from the KM curves was assessed by comparing them with the HRs recorded in the original reports, and three trials were eligible for the assessment (Scagliotti et al,[10] Arriagada et al,[11] and Waller et al[12]). The HRs and their CIs based on the KM curves were 0.94 (0.80 to 1.12), 0.87 (0.77 to 0.98), and 1.07 (0.82 to 1.38), and the HR in the reports for the same trials were 0.96 (0.81 to 1.13), 0.86 (0.76 to 0.98), and 1.02 (0.77 to 1.35), respectively.

Adjuvant chemotherapy yielded a survival improvement as compared with surgery alone (HR, 0.872; 95% CI, 0.805 to 0.944; $P = .001$; Fig 1). A rank correlation test regarding survival did not indicate the existence of any publication bias ($z = -1.34$, $P = .180$). CDDP-containing regimens (3,786 patients) showed consistent results, with the HR estimates in most trials favoring adjuvant chemotherapy (HR, 0.891; 95% CI, 0.815 to 0.975; $P = .012$; Fig 2). In addition, single-agent UFT therapy (1,751 patients) showed a significant survival benefit, with an HR of 0.799 (95% CI, 0.668 to 0.957; $P = .015$; Fig 3).

Table 2. Survival in the 11 Trials

Author	Chemotherapy Regimen	Intention-to-Treat Analysis	Median Follow-Up Time (months)	No. of Patients§	No. of Events	5-Year Survival (%)	*P*	HR	95% CI
Xu et al[5]	PCVALU	Yes	NR	35	18	49	NS	0.62	0.33 to 1.18
	S alone			35	24	31			
Mineo et al[7]	PE	Yes	62	33	14	63	.04*	0.62	0.28 to 1.35
	S alone			33	21	45			
Tanaka et al[6]	U	No	76	163	28	82	.11*	0.78	0.52 to 1.17
	S alone			168	35	76			
Tada et al[8]	U	Yes	91	85	14	75†	.04*	0.70	0.36 to 1.35
	S alone			87	24	58†			
	PVd	Yes		47	NR	38	.54*	0.90	0.55 to 1.49
	S alone			48	NR	37			
Endo et al[14]	U	No	64	109	24	79	.70*	0.88	0.65 to 1.19
	S alone			110	27	75			
Imaizumi[13]	PVdU	Yes	78	50	10	88	.05*	0.53	0.18 to 1.57
	U			50	17	68	.84*	1.14	0.51 to 2.57
	S alone			50	18	66			
Scagliotti et al[10]	MVP	No	65	548	279	NR	.59	0.96	0.81 to 1.13
	S alone			540	289	NR			
Waller et al[12]	P-based	Yes	35	192	99	58	.90	1.02	0.75 to 1.35
	S alone			189	99	60‡			
Arriagada et al[11]	P-based	Yes	56	932	469	45	< .03	0.86	0.76 to 0.98
	S alone			935	504	40			
Kato et al[15]	U	No	73	491	123	88	.04	0.71	0.52 to 0.98
	S alone			488	110	85			
Tada et al[9]	PVd	Yes	NR	59	47	28	.89*	0.92	0.58 to 1.44
	S alone			60	43	36			

NOTE. The HRs in each trial were calculated based on the method described by Parmar et al.
Abbreviations: HR, hazard ratio; P, cisplatin; C, cyclophosphamide; V, vincristine; A, adriamycin; L, lomustine; U, UFT; S, surgery; E, etoposide; Vd, vindesine; M, mitomycin; Vn, vinorelbine; Vb, vinblastine; NR, not recorded; NS, not significant.
*Log-rank tests are presented.
†8-year survival.
‡2-year survival.
§HRs were abstracted from original reports. Other HRs were estimated from Kaplan-Meier survival curves in each report.

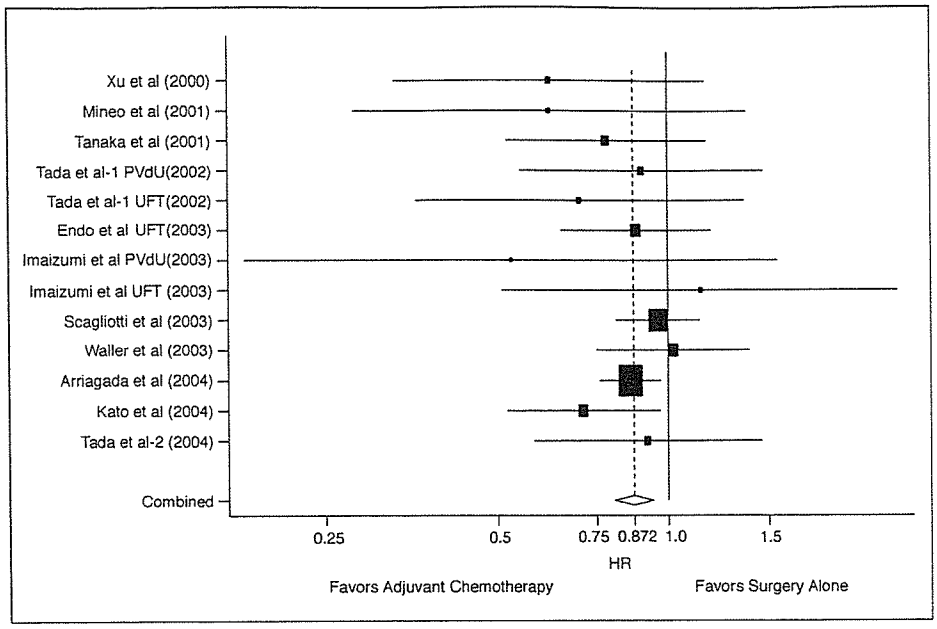

Fig 1. Overall survival with adjuvant chemotherapy compared with surgery alone. The summary hazard ratio (HR) was 0.872 (95% CI, 0.805 to 0.944; $P = .001$) for adjuvant chemotherapy compared with surgery alone. PVdU, cisplatin, vindesine, and tegafur-uracil; UFT, tegafur and uracil.

Regarding survival, the test of heterogeneity yielded a $Q_{12} = 7.730$ ($P = .806$, $\tau^2 < 0.001$), indicating a lack of heterogeneity among the trials. However, we decided to use a random-effect model in the following subsequent analysis to remove the effect of potential heterogeneity. In the meta-regression analysis, inclusion of stage II patients (0.18, $P = .081$) and stage III patients (0.14, $P = .159$) was identified as a potential source of heterogeneity. The actual summary HR in the trials that included stage II patients was 0.903 (95% CI, 0.826 to 0.987; $P = .024$), and that in the trials in which stage II patients were not included was 0.753 (0.627 to 0.905; $P = .002$). Similar results were obtained for stage III disease—the HR was 0.899 (95% CI, 0.821 to 0.984; $P = .021$) in the trials that included stage III patients, and 0.781 (95% CI, 0.657 to 0.929; $P = .005$) in those in which stage III patients were not included.

Toxicity

The toxicity profiles were obtained for 2,594 (90%) of the 2,873 patients assigned to the adjuvant chemotherapy arms. Toxicities were generally mild and acceptable. Grade 4 neutropenia, grade 4 thrombocytopenia, grade 3 or more severe

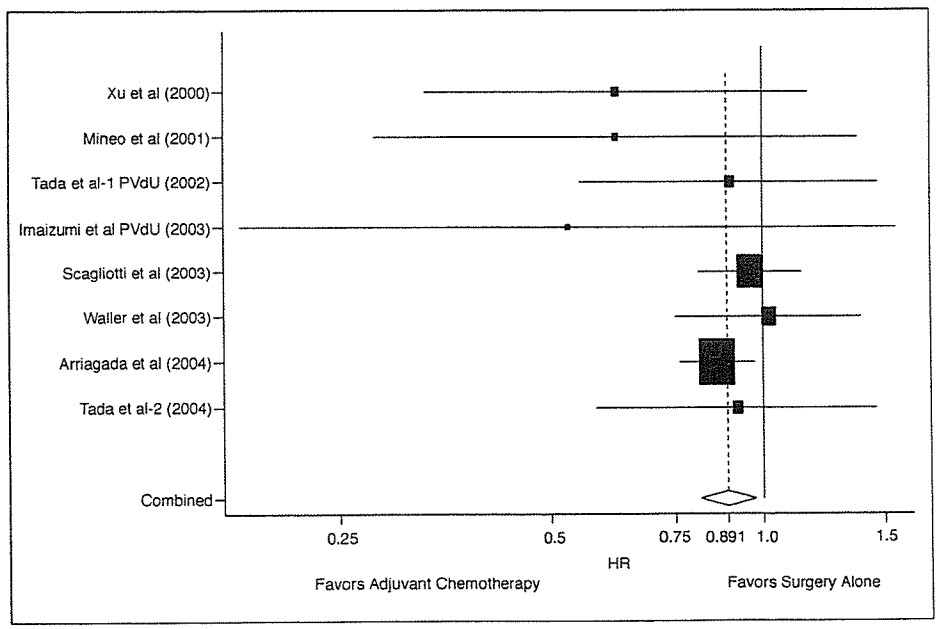

Fig 2. Overall survival with adjuvant cisplatin–based chemotherapy compared with surgery alone. The summary hazard ratio (HR) was 0.891 (95% CI, 0.815 to 0.975; $P = .012$) for adjuvant chemotherapy compared with surgery alone. PVdU, cisplatin, vindesine, and tegafur-uracil.

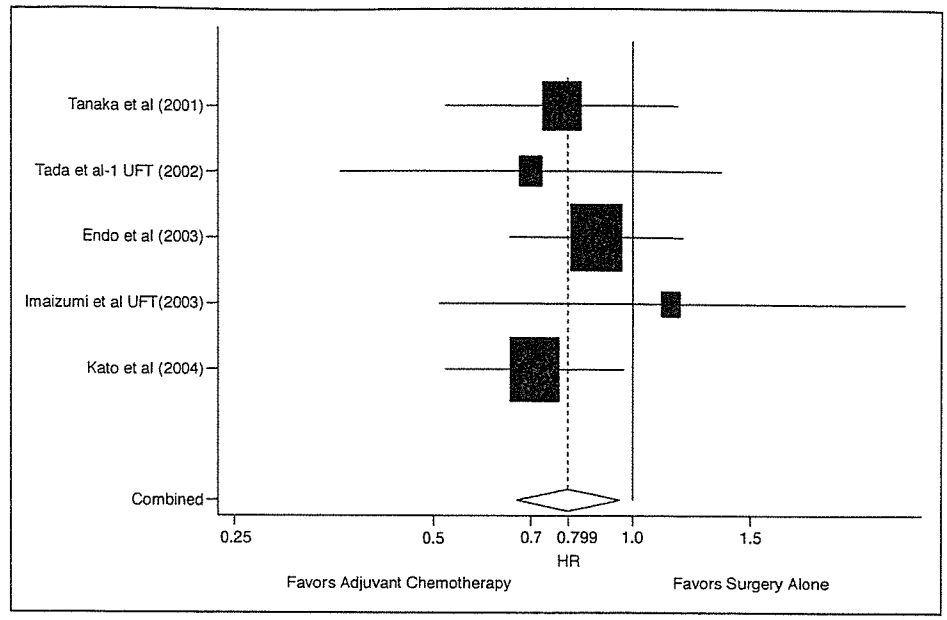

Fig 3. Overall survival with adjuvant tegafur and uracil (UFT) therapy compared with surgery alone. The summary hazard ratio (HR) was 0.799 (95% CI, 0.668 to 0.957; $P = .015$) for adjuvant chemotherapy compared with surgery alone.

nephrotoxicity, and grade 3 or more severe nausea and vomiting were observed in 14%, 2%, 2%, and 10%, respectively, of the patients who received CDDP-based chemotherapy. Grade 3 or more severe nausea and vomiting, diarrhea, and hepatic toxicity were observed in 0.7%, 0.2%, and 0.2% of the patients treated with UFT, respectively. There were 16 treatment-related deaths (0.6%) in 10 trials, including 2,559 assessable patients assigned to adjuvant chemotherapy arms.

DISCUSSION

To our knowledge to date, in the present study, we demonstrated, for the first time, the survival benefit of adjuvant chemotherapy using updated data. Notably, for the case of CDDP-containing regimens, our meta-analysis included data from three times more patients than the previously reported meta-analysis,[4] and the trials employed more effective regimens. As a result, we were able to show that CDDP-based chemotherapy yielded a significant survival benefit, while the previous meta-analysis indicated only a marginal effect of CDDP-based chemotherapy as adjuvant therapy on the overall survival.[4]

We also demonstrated a significant survival advantage of adjuvant UFT therapy in patients with resected NSCLC. However, the objective response rate to single-agent UFT was only 6.3% in patients with advanced NSCLC,[22] indicating the need for clarifying the discordance of UFT activity against early versus advanced NSCLC. Two reports may be helpful in understanding the effect of UFT. First, Tanaka et al reported an antiangiogenic effect of UFT in a preclinical study.[23] Second, Wada et al noted in their adjuvant chemotherapy study that the incidences of death from second primary tumors (SPT) were only 2% and 3%, respectively, in the two UFT arms, which was low compared with 5% in the control arm.[24] In the report by Kato et al also, the SPT incidence was slightly lower in the UFT arm than in the control arm.[15] These results suggest an additional potential benefit of UFT in the prevention of SPT.

Several technical issues have to be mentioned in relation to this meta-analysis. All our analyses were based on abstracted data and not on individual patient data (IPD). The results must therefore be interpreted cautiously, as an IPD-based meta-analysis would give more reliable estimation than one based on abstracted data.[25] Publication bias is a significant threat to the validity of the results of this meta-analysis. Although we found no evidence of publication bias in relation to the graphical or statistical methods, it is difficult to completely rule out this possibility from all aspects of the trials. Heterogeneity among trials may be another limitation of our meta-analysis, even though we applied a random-effect model that takes possible heterogeneity into consideration. We identified the pathological stage of the cancer as a source of heterogeneity. Regarding heterogeneity due to inclusion of stage III patients, subgroup meta-analysis indicated that the effect of adjuvant chemotherapy was stronger in trials without stage III patients. A similar trend was observed for trials with stage II patients. Accordingly, the effects of adjuvant chemotherapy may be greater in stage I patients than in stage II-III patients, though careful interpretation of the heterogeneity detected by metaregression analysis is necessary, as the statistical power was low due to the limited number of trials.

Additionally, inclusion of results presented in the abstract form, which may be only preliminary, might also have biased our final result. However, as we endeavored to obtain the most updated and precise data possible by direct contact with the principal investigators, any bias due to this factor is likely to be small. The accuracy of the HRs estimated from the KM curves is another important issue. We obtained fairly good correlation between the HRs reported in this article and those obtained based on the KM curves, suggesting that curve-based HRs can be substituted in cases where the HRs are not available.

Several other problems also remain unresolved. We analyzed patients with various stages of resected NSCLC who received several types of CDDP-based regimens, as one group. Thus, further clarification of which stage of cancer would be especially benefited by adjuvant chemotherapy, and which drug is best added to CDDP, is essential. It also remains unclear whether new drugs, such as paclitaxel, docetaxel, vinorelbine, and gemcitabine should be combined with platinum agents. Additionally, although the treatment compliance seemed to have improved somewhat in the trials that were included in our study as compared with that reported in the previous meta-analysis[4] (median, 64% *v* 52% of the planned treatment), further efforts to improve chemotherapeutic regimens to minimize toxicities are clearly warranted. Also, neoadjuvant chemotherapy is rapidly becoming one of the most promising modalities for the improvement of the overall survival of operable patients.[26] We have demonstrated the usefulness of adjuvant chemotherapy, but it remains unclear whether adjuvant chemotherapy would be more beneficial for operable patients than neoadjuvant chemotherapy. A Spanish randomized study on 600 patients has been initiated to compare neoadjuvant chemotherapy, surgery alone, and postoperative chemotherapy.[27] The results of this study will hopefully shed light on the most suitable treatment modality in operable patients. Finally, our results should be confirmed by an IPD-based meta-analysis.

In conclusion, this is the first updated meta-analysis to demonstrate the benefit of adjuvant chemotherapy in the treatment of resected NSCLC, though the strength of our main conclusion was limited by the fact that it was based on abstracted data. As for adjuvant therapy using a combination of platinum plus new agents, or molecular-targeted therapy, the results of ongoing and recently completed randomized trials are eagerly awaited.

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Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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Addition of platinum compounds to a new agent in patients with advanced non-small-cell lung cancer: a literature based meta-analysis of randomised trials

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Background: Single new agents reportedly produce promising response and survival effects, but platinum-based doublets remain the standard chemotherapy for advanced non-small-cell lung cancer (NSCLC). The aim of this study was to evaluate the effectiveness of platinum for advanced NSCLC by carrying out a meta-analysis of trials that compared platinum-based doublets with single new agent therapy alone.

Methods: We carried out a literature search to identify trials, conducted between 1994 and 2003, comparing a doublet of platinum plus a new agent with a new agent alone in previously untreated patients with advanced NSCLC. Outcomes analysed were response, survival and toxicity.

Results: Eight trials encompassing 2374 patients were identified. Platinum-based doublets produced an approximately two-fold higher overall (complete and partial) response rate than the new agent alone [odds ratio = 2.32; 95% confidence interval (CI) = 1.68–3.20]. Platinum-based doublet therapy was also associated with a 13% prolongation of survival (hazard ratio = 0.87; 95% CI = 0.80–0.94, $P<0.001$). Despite significant increases in the frequencies of various toxic effects in patients receiving platinum-based doublets, no significant difference in treatment-related mortality was observed.

Conclusion: This is the first published meta-analysis demonstrating the importance of combining platinum with single new agents in the treatment of advanced NSCLC.

Key words: doublets, non-small-cell lung cancer, platinum, single-agent therapy

Introduction

Lung cancer is the leading cause of cancer-related deaths within the United States and throughout the world, with a median survival time of 16.8 months in 2001, and non-small-cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancer cases [1]. A previous meta-analysis showed a 10% absolute improvement in the 1-year survival rate in patients with advanced NSCLC treated with cisplatin (CDDP)-based chemotherapy over best supportive care alone [2].

Recently, new agents with novel mechanisms [paclitaxel (Taxol), docetaxel (Taxotere), irinotecan, gemcitabine and vinorelbine] have been developed and some of them have already been reported to produce a significant survival advantage as a single-agent over the best supportive care alone in patients with advanced NSCLC [3, 4]. Furthermore, doublets consisting of CDDP plus one of these new agents have been shown to improve survival compared to CDDP plus existing agents such as vindesine or etoposide in patients with advanced NSCLC [5, 6].

Several randomised trials have thus compared single new agent treatment with doublets consisting of platinum plus one of the new agents [7–16]. However, these trials have yielded conflicting survival results. Accordingly, we carried out a meta-analysis to compare the effects of platinum plus a single new agent with single new agent therapy alone on overall survival as well as on overall (complete and partial) response rate and toxicity in patients with advanced NSCLC.

Materials and methods

Search for trials

Both published and unpublished trials reported between January 1994 and February 2003 were identified through a computer-based search of the PubMed database and Ichushi, a Japanese journal database, and a manual search of abstracts from the past 10 conferences of the American Society of Clinical Oncology and the past three conferences of the International Association for the Study of Lung Cancer. We searched using the following terms: 'lung cancer', 'chemotherapy' and 'randomised

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