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.

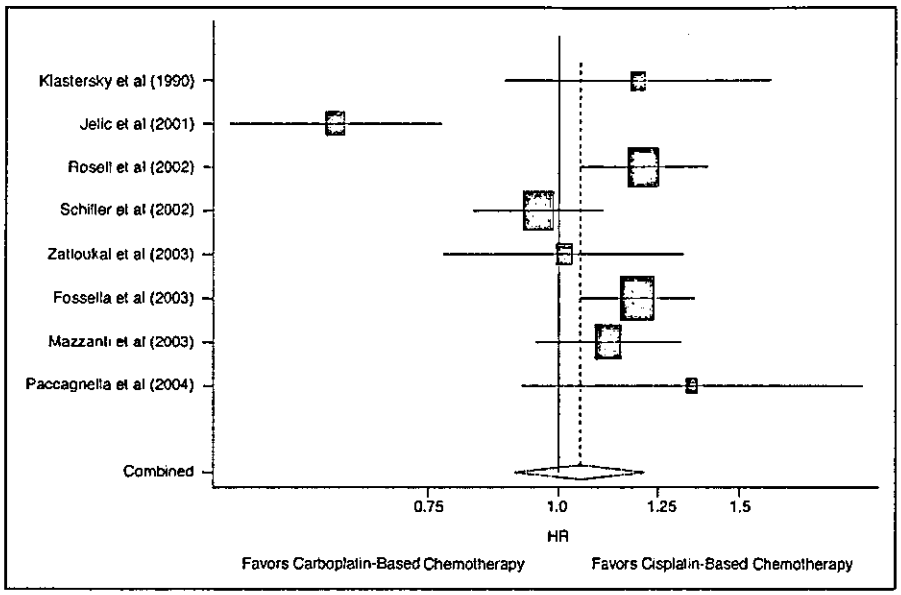

Fig 2. Overall survival with cisplatin-based compared with carboplatin-based chemotherapy. The summary hazard ratio (HR) was 1.050 (95% CI, 0.907 to 1.216; $P = .515$) indicating a 5.0% increase in hazard events in carboplatin-based chemotherapy compared to cisplatin-based therapy.

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.

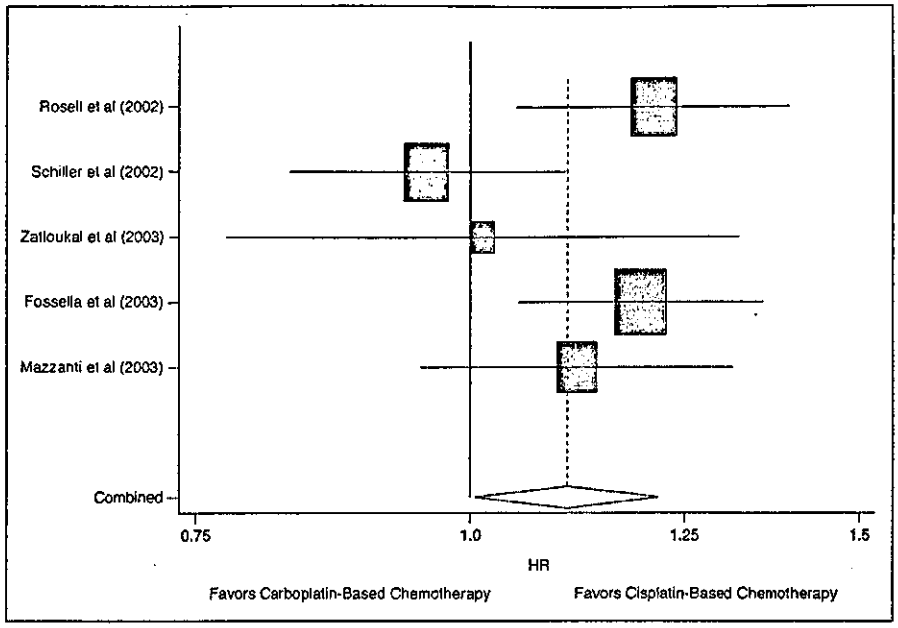

Fig 3. Overall survival with cisplatin plus new agents compared with carboplatin plus new agents. The summary hazard ratio (HR) was 1.106 (95% CI, 1.005 to 1.218; P = .039) indicating a 10.6% increase in hazard events in carboplatin-based chemotherapy compared to cisplatin-based chemotherapy.

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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A B S T R A C T

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/m²); d 1-5 + C (300 mg/m²) + V (1.4 mg/m²) + A (50 mg/m²) + L (50 mg/m²); 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/m²); d 1 + E (120 mg/m²); 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/m²); d 1 + Vd (3 mg/m²); 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/m²); d 1 + Vd (3 mg/m²); 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/m²) + M (8 mg/m²); d 1 + Vd (3 mg/m²); d 1,8	69
Waller et al[12]	2003	1995	192	189	I-IV‡	34	21	2	P (80 mg/m²); d 1 + Vd (3 mg/m²); d 1,8, or P (80 mg/m²); d 1 + Vn (30 mg/m²); d 1,8; or P (50 mg/m²) + M (6 mg/m²); d 1, + I (3 g/m²); d 1, or P (50 mg/m²) + M (6 mg/m²); d 1, + Vb (6 mg/m²); d 1	64
Arriagada et al[11]	2004	1995	932	935	I-III	39	26	2	P (80-120 mg/m²); d 1 + E (100 mg/m²); d 1-3, or + Vn (30 mg/m²), or + Vb (4 mg/m²), or + Vd (3 mg/m²); weekly	74
Kato et al[15]	2004	1994	498	501	I	0	0	2	U (250 mg/m²); 2 years	61
Tada et al[9]	2004	1994	59	60	IIIA	100	100	2	P (80 mg/m²); d 1 + Vd (3 mg/m²); 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.

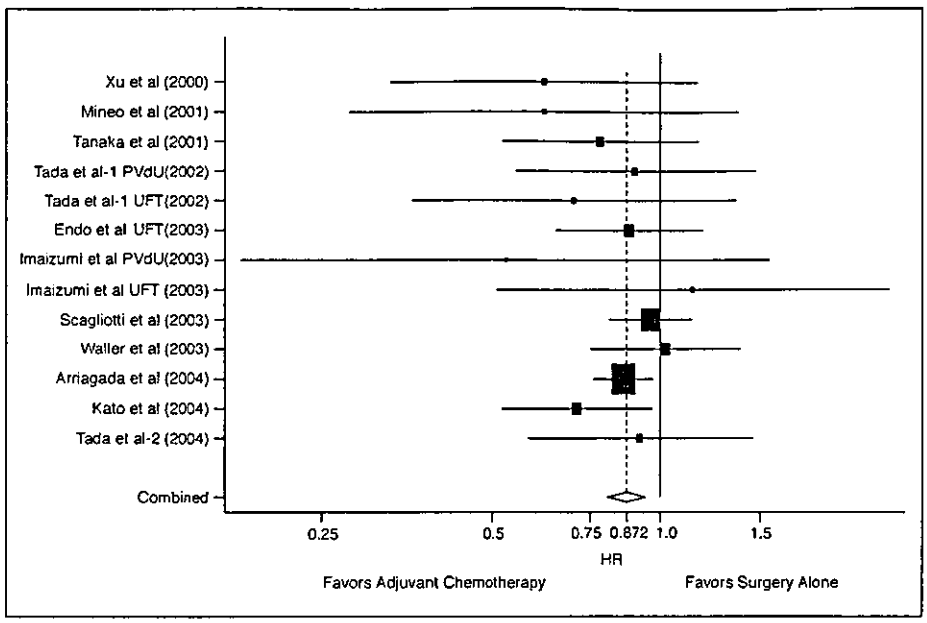

Fig 1. Overall survival with adjuvant chemotherapy compared with surgery alone. The summary hazard ratio (HR) was 0.872 (95% CI, 0.805 to 0.944; $P = .001$) for adjuvant chemotherapy compared with surgery alone. PVdU, cisplatin, vindesine, and tegafur-uracil; UFT, tegafur and uracil.

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

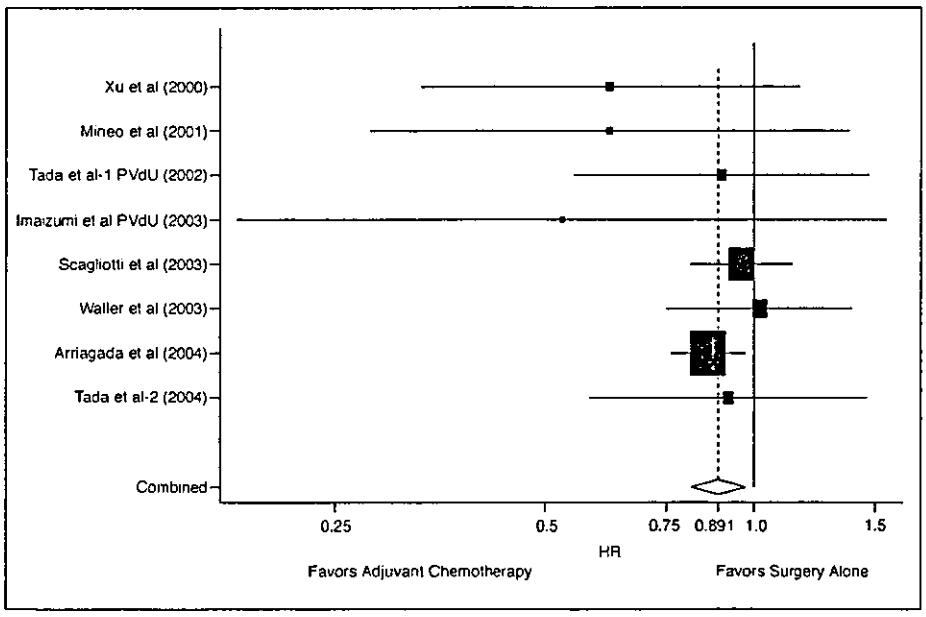

Fig 2. Overall survival with adjuvant cisplatin-based chemotherapy compared with surgery alone. The summary hazard ratio (HR) was 0.891 (95% CI, 0.815 to 0.975; $P = .012$) for adjuvant chemotherapy compared with surgery alone. PVdU, cisplatin, vindesine, and tegafur-uracil.

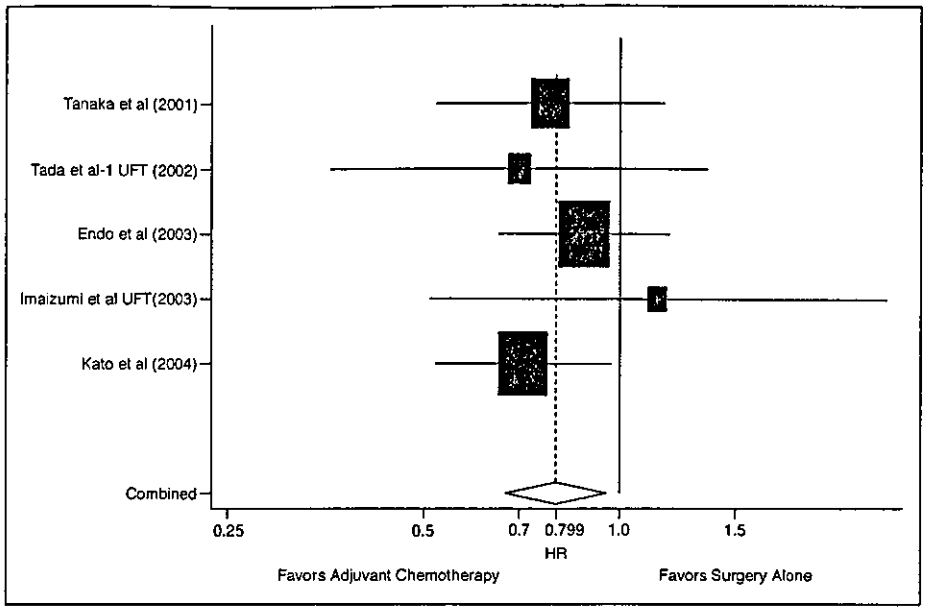

Fig 3. Overall survival with adjuvant tegafur and uracil (UFT) therapy compared with surgery alone. The summary hazard ratio (HR) was 0.799 (95% CI, 0.668 to 0.957; $P = .015$) for adjuvant chemotherapy compared with surgery alone.

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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Original article

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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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controlled trial'. We also examined reference lists of original articles, review articles, relevant books and the Physician Data Query registry of clinical trials.

Selection of trials

If at least one platinum-based doublet and one single new agent therapy were included in a randomised trial, it was considered to be eligible. A platinum-based doublet included one platinum agent and one new agent (paclitaxel, docetaxel, irinotecan, gemcitabine, or vinorelbine), and the single agent had to be one of these new agents. Trials were excluded from our analysis if the new agents used in the platinum-based doublet were different from the single-agent therapies. Patients with pathologically confirmed advanced NSCLC who had not previously received chemotherapy were enrolled in these trials.

Validity assessment

We carried out an open assessment of the trials and used the instrument reported by Jadad et al. [17]. However, no evident differences were observed among the trials. Therefore, the result of the validity assessment was not considered in the meta-analysis.

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 subsequently compared the results. All data were checked for internal consistency, and disagreements were resolved by discussion among the investigators. We tried to contact principal investigators of the trials to confirm or update both published and unpublished data.

Quantitative data synthesis

We applied odds ratios (ORs) to assess objective response rate and toxic events. We constructed 2×2 tables from abstracted data for responses and for each toxic event. ORs and their variances for the subjects who received a platinum-based doublet relative to those receiving single new agent therapy alone were calculated from the tables. For OR calculations, we excluded ineligible subjects from each evaluation.

Hazard ratios (HR) were applied to assess the survival advantage of platinum-based doublets compared with that of single-agent therapy alone. Crude log HR and its variance for each trial were calculated using the abstracted survival probabilities at each time point 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 a constant hazard for the two types of therapy within an individual trial, all of 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 represent how many times

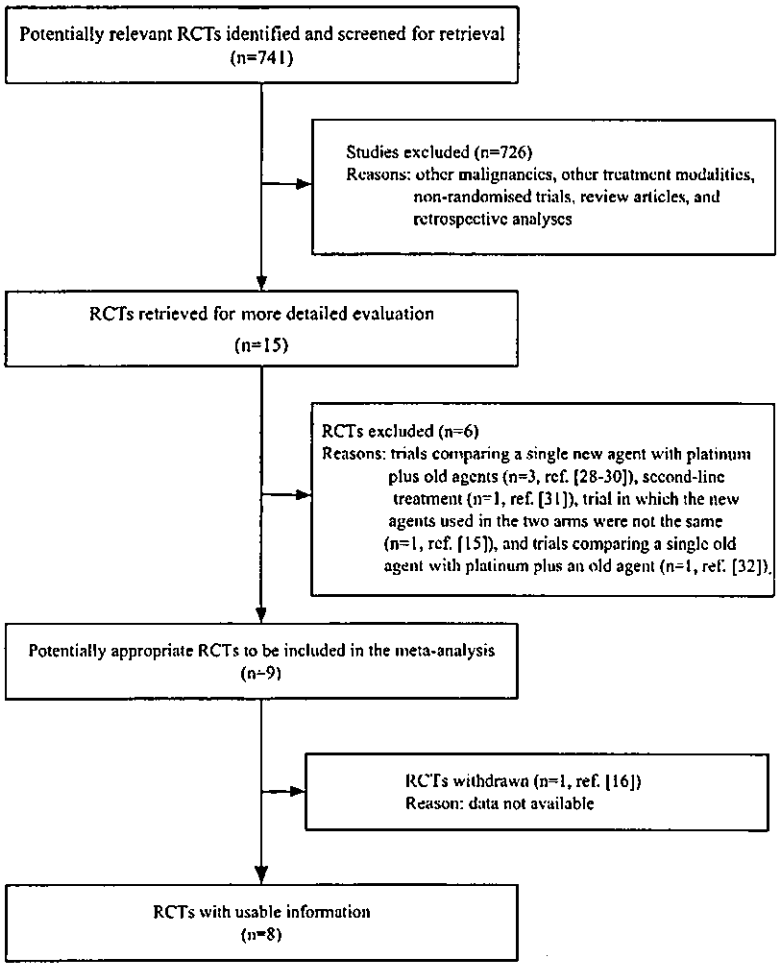

Figure 1. A flow chart showing the progress of trials through the review. RCT, randomised controlled trials.

higher the probability of death was from any cause in patients receiving a platinum-based doublet compared with those receiving single-agent therapy. Therefore, a HR below unity indicates that the platinum-based doublet is better than single-agent therapy.

A general variance-based method was used to estimate the summary HR, ORs and their 95% confidence intervals (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]. Regardless of the statistical significance of the Q test, we applied a random effect model which allows meta-analyses to take between-study variation into consideration. 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 survival analysis. The factors examined in meta-regression analysis were study quality score [17], starting year of the trial, proportion of patients with performance status (PS) 0–1, using the World Health Organization criteria or others proportion of stage IV patients, proportion of male patients, and inclusion of carboplatin. A cumulative meta-analysis was planned in order to take trial quality into consideration when the trial showed quality score heterogeneity [17].

All statistical analyses were conducted with STATA ver. 8 software (College Station, TX, USA). We defined a statistical test with a P value less than 0.05 as significant.

Results

Trial flow

The flow chart of our study is shown in Figure 1. Ultimately, eight trials involving 2374 patients with advanced NSCLC were analysed in this meta-analysis [7–14]. There were no trials that were excluded from our study only because they were published in languages other than English. One of the remaining 10 potentially appropriate trials that compared CDDP and gemcitabine with gemcitabine alone in 72 patients was excluded from our analysis because we were unable to obtain the relevant data [16].

Characteristics of the eight trials

Baseline characteristics of the eight trials are listed in Table 1. In total, 2351 patients were randomised to a platinum-based doublet (1191 patients) or a single new agent therapy (1160 patients); 23 patients enrolled in one trial were excluded before randomisation [12]. Further information about one published trial [8] and three unpublished trials [11–13] were obtained by contacting the principal authors. Other potential sources of heterogeneity, including platinum type (CDDP versus carboplatin), were examined by meta-regression analysis. However, none of these factors were associated with significant differences in outcomes with a few exceptions as described below.

Response rate and overall survival

Data on objective response rates were available for all eight trials (Table 2). Based on intention-to-treat analysis using all randomised patients, the objective response rate to a platinum-based doublet was more than two-fold higher than to single-agent therapy (OR = 2.32; 95% CI = 1.68–3.20 Figure 2). Neither a funnel plot nor a rank correlation test regarding response rate indicated the existence of publication bias ($Z = 1.24$, $P = 0.22$). The heterogeneity test yielded a significant result ($P = 0.017$). Meta-regression analysis showed

Table 1. Characteristics of the eight trials included in this meta-analysis

Author	Year	Publication form	No. of randomised patients	Chemotherapy regimen	Sex (male, %)	PS 0–1 (%)	Stage IV (%)
Depierre	1994	F	121	P 80 mg/m^2, d1, q3ws + V 30 mg/m^2, weekly	91	72	53
			119	V 30 mg/m^2, weekly	82	70	56
Le Chevalier	1994	F	206	P 120 mg/m^2, d1, q4ws + V 30 mg/m^2, weekly	88	80	50
			206	V 30 mg/m^2, weekly	91	77	47
Lorusso	1995	F	34	P 80 mg/m^2, d1 + V 25 mg/m^2, d1,8, q3–4ws	94	52	32
			35	V 25 mg/m^2, weekly	100	55	39
Deza	1996	A	89	P 100 mg/m^2, d1 + V 30 mg/m^2, d1,8,15, q4ws	82	78	75
			73	V 30 mg/m^2 weekly	90	81	71
Georgoulias	2002	A	160	P 80 mg/m^2, d2 + D 100 mg/m^2, d1, q3ws	94	93	64
			148	D 100 mg/m^2, d1, q3ws	90	89	65
Lilenbaum	2002	A	284	C AUC = 6, d1 + PTX 225 mg/m^2, d1, 3 h, q3ws	68	83	71
			277	PTX 225 mg/m^2, d1, 3 h, q3ws	69	82	73
Sederholm	2002	A	164	C AUC = 5, d1 + G 1250 mg/m^2, d1,8, q3ws	60	82	54
			170	G 1250 mg/m^2, d1,8, q3ws	52	88	63
Negoro	2003	F	133	P 80 mg/m^2, d1 + I 60 mg/m^2, d1,8,15, q4ws	76	94	62
			132	I 100 mg/m^2, d1,8,15, q4ws	74	94	66

All trials were randomised phase III trials except for Lorusso's trial that was designed as a randomised phase II trial.
PS, performance status; F, full text; A, abstract form; P, cisplatin; V, vinorelbine; D, docetaxel; C, carboplatin; AUC, area under the plasma concentration–time curve; PTX, paclitaxel; G, gemcitabine; I, irinotecan; d, day; ws, weeks.

that a higher percentage of stage IV patients had a reduced response ($P = 0.01$).

Data on overall survival were available for all eight trials (2331 patients, Table 3). Survival analyses were carried out based on intention-to-treat analysis in five trials and seven, six and seven patients in the trials reported by Lorusso et al. [9], Deza et al. [11] and Negoro et al. [10], respectively, were excluded from the survival analysis after randomisation. Since none of the trials gave the HR required for meta-analysis, we applied HRs calculated from KM curves in all trials, based on

Table 2. Responses in the eight trials

Author	Chemotherapy regimen	No. of responding patients	No. of randomised patients	Objective response (%)
Depierre	CDDP + VNR	50	121	41
	VNR	18	119	15
Le Chevalier	CDDP + VNR	57	206	28
	VNR	28	206	14
Lorusso	CDDP + VNR	13	34	38
	VNR	4	35	11
Deza	CDDP + VNR	31	89	35
	VNR	30	73	41
Georgoulias	CDDP + DOC	57	160	36
	DOC	29	148	20
Lilenbaum	CBDCA + PTX	82	284	29
	PTX	47	277	17
Sederholm	CBDCA + GEM	40	164	24
	GEM	18	170	11
Negoro	CDDP + CPT	55	133	41
	CPT	26	132	20

CDDP, cisplatin; VNR, vinorelbine; DOC, docetaxel; CBDCA, carboplatin; PTX, paclitaxel; GEM, gemcitabine; CPT, irinotecan.

Table 3. Survival in the eight trials

Author	Chemotherapy regimen	Intention-to-treat analysis	No. of assessable patients	Median survival time (weeks)	1-year survival (%)	*P* value
Depierre	CDDP + VNR	Yes	121	33	28	0.48
	VNR		119	32	21	
Le Chevalier	CDDP + VNR	Yes	206	40	38	0.05
	VNR		206	31	34	
Lorusso	CDDP + VNR	No	31	38	NR	NS
	VNR		31	30	NR	
Deza	CDDP + VNR	No	83	41	NR	0.23
	VNR		73	33	NR	
Georgoulias	CDDP + DOC	Yes	160	43	45	NS
	DOC		148	34	40	
Lilenbaum	CBDCA + PTX	Yes	284	38	37	0.20
	PTX		277	29	33	
Sederholm	CBDCA + GEM	Yes	164	43	41	0.02
	GEM		170	39	32	
Negoro	CDDP + CPT	No	129	50	47	NR
	CPT		129	46	42	

All *P* values were extracted from original papers.
CDDP, cisplatin; VNR, vinorelbine; DOC, docetaxel; CBDCA, carboplatin; PTX, paclitaxel; GEM, gemcitabine; CPT, irinotecan; NR, not recorded; NS, not significant.

the method of Parmar et al. [18]. Platinum-based doublet therapy was associated with a 13% improvement in overall survival compared with single-agent therapy (HR = 0.87; 95% CI = 0.80–0.94, $P<0.001$, Figure 3). Similarly, a funnel plot and rank correlation test regarding survival confirmed the absence of publication bias ($Z=0.83$, $P=0.40$).

Toxicity

Eight trials encompassing 2251 patients provided toxicity profile results (Table 4). Complete data for neutropenia were not obtained in three trials [9, 11, 13]; data for thrombocytopenia and nausea/vomiting were not available in two trials each [9, 11]; and data for nephrotoxicity were not available in one trial [11]. The heterogeneity test was statistically significant for neutropenia and nausea/vomiting. Further meta-regression analysis failed to show any significant source of heterogeneity from examined factors for neutropenia. Regarding nausea/vomiting, male subjects had an increased chance of experiencing a nausea/vomiting event and use of carboplatin reduced it. Platinum-based doublet therapy significantly increased the frequency of all toxic effects over single-agent therapy, whereas no significant difference in treatment-related mortality was observed between the two treatment modalities (1.4% versus 1.2%, OR = 0.97; 95% CI = 0.41–2.26, $P=0.94$).

Discussion

Lilenbaum et al. [12] previously carried out a meta-analysis to compare the effect of combination chemotherapy with that of single-agent chemotherapy on overall survival in patients with advanced NSCLC [23]. They concluded that overall survival was modestly improved with combination chemotherapy. However, in the majority of trials analysed, outdated chemotherapy regimens were used, and only small numbers of patients were included. Thus, the impact of platinum plus one of the new agents on the survival of advanced NSCLC patients compared with that of single new agent therapy remained undetermined.

In this study, we used data from trials comparing platinum plus one of the new agents with the new agent alone; three trials evaluated in our study were also included in Lilenbaum's study [7, 8, 11]. Our results indicate that the addition of platinum to single new agents is important, if they have adequate organ function and good performance status. However, it remains unclear which new drug should be combined with platinum in a platinum-based doublet and further investigation is necessary.

Two meta-analyses on the addition of a second drug for recently advanced NSCLC have been presented [24, 25]. Both were based on literature data. Using 33 trials with 7872 patients, Delbaldo et al. [24] demonstrated a significant increase in response rate and survival in favour of two drugs (OR = 0.39; 95% CI = 0.35–0.45, $P<0.001$ and HR = 0.79; 95%CI = 0.75–0.83, $P<0.001$). Baggstrom et al. [25] identified 17 trials randomising 4421 patients with advanced NSCLC to one drug or two drugs, and demonstrated that the doublet chemotherapy is superior in terms of overall survival as well as response. Although the eligible trials and patient populations were different among the studies, all three studies including our study indicate that a one-drug regimen is inferior in terms of response and survival.

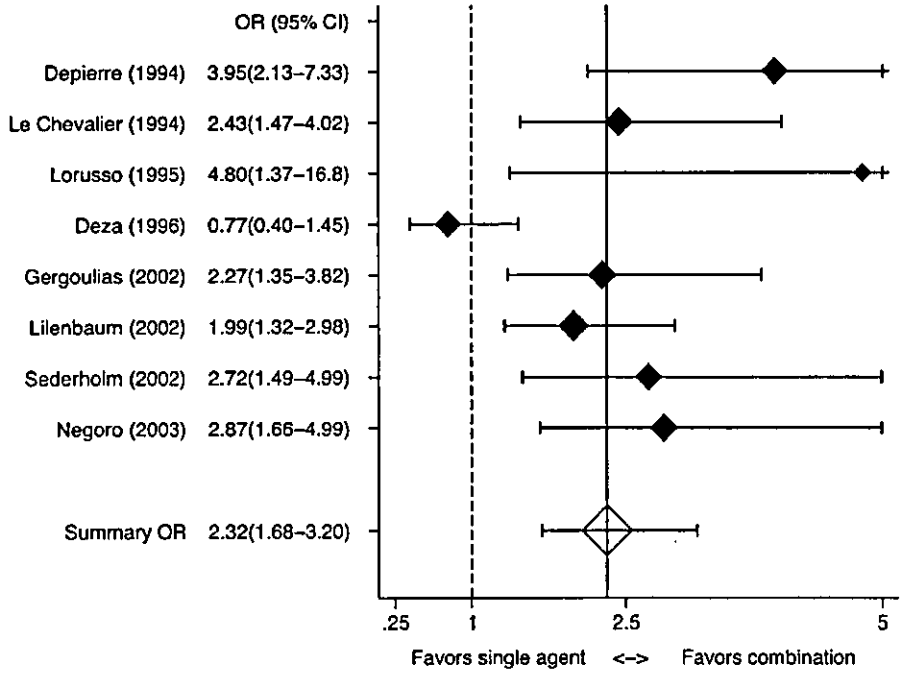

Figure 2. Response to a platinum-based doublet compared with a single new agent alone. The heterogeneity test yielded a significant result ($P=0.017$). Meta-regression analysis showed that an increased percentage of stage IV patients had a reduced response ($P=0.01$).

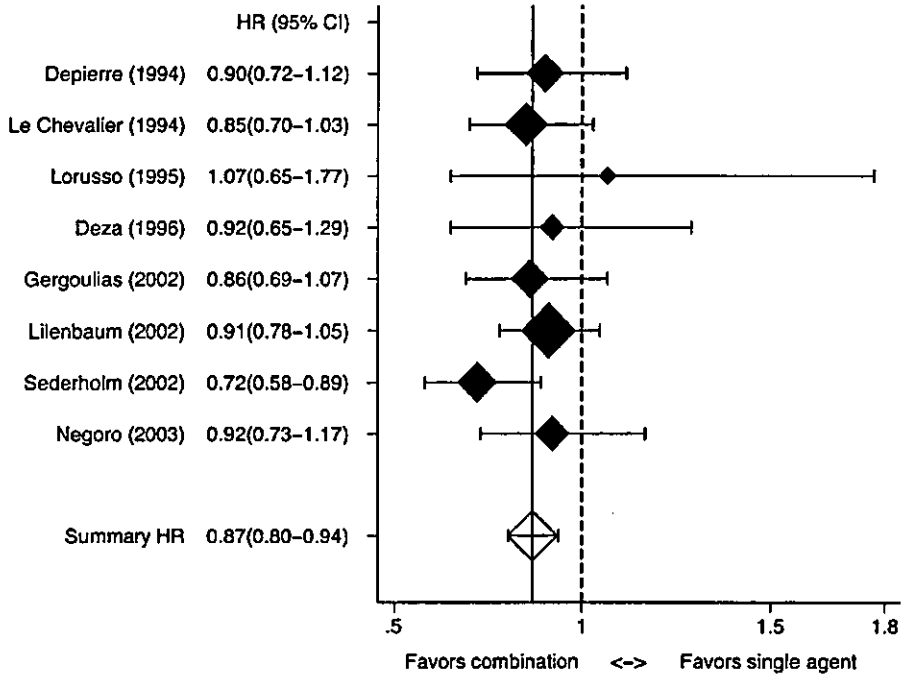

Figure 3. Overall survival with a platinum-based doublet compared with a single new agent alone. The summary hazard range indicated a 13% hazard event reduction in those receiving a platinum-containing regimen compared to those given single new agent therapy. The heterogeneity test yielded no significant result ($P = 0.704$).

Table 4. Toxic effects in trials comparing platinum-containing regimen with single new agent alone (grades 3 and 4)

Toxicity	No. of evaluable trials	Combination chemotherapy		Single-agent therapy		OR (95% CI)	*P* value for *Q* test
		No. of patients with toxicity (%)	No. of evaluable patients	No. of patients with toxicity (%)	No. of evaluable patients		
Neutropenia	5	507 (56.5)	897	281 (32.2)	872	3.12 (1.98–4.91)	0.002
Thrombocytopenia	6	90 (8.5)	1054	6 (0.6)	1041	14.4 (6.75–30.5)	0.992
Nephrotoxicity	7	62 (5.7)	1085	9 (0.8)	1072	6.44 (2.95–14.0)	0.376
Nausea/vomiting	6	223 (21.2)	1054	60 (5.8)	1041	4.01 (1.94–8.30)	0.001

Heterogeneity tests showed significant results for neutropenia and nausea/vomiting. We failed to find any source of heterogeneity in the factors using the meta-regression analysis. Regarding nausea/vomiting, male subjects had an increased chance of experiencing a nausea/vomiting event and use of carboplatin reduced it.

OR, odds ratio; CI, confidence interval.

We included the two trials in which the effect of carboplatin was investigated [12, 13]. Recently, we carried out another meta-analysis of the trials that compared CDDP-based chemotherapy with carboplatin-based chemotherapy, which revealed that combination chemotherapy consisting of CDDP plus a new agent yields a substantial survival advantage compared with carboplatin plus a new agent in patients with advanced NSCLC [26]. Thus, inclusion of trials using carboplatin will give conservative *P* values for summary statistics. However, the highly significant association found in the current analysis indicates that CDDP is important in the treatment of advanced NSCLC. In addition, meta-regression analysis in this study showed that inclusion of trials using carboplatin did not change the results in our study, which suggests that the inclusion of the two trials using carboplatin did not alter our main conclusion. Further investigation will be needed to clarify the role of carboplatin in the treatment of advanced NSCLC.

Our study has several limitations. First, one major problem is that our analyses were based on abstracted data, since an individual patient data based meta-analysis would give a more robust estimate of the association [27]. Therefore, physicians should interpret our results carefully. Second, some of the trials we identified were reported in abstract form only, which made it difficult to extract complete data for our meta-analysis. However, additional updated data fully adequate for this meta-analysis were obtained in several cases by contacting the principal investigators. Third, as is often the case with

meta-analysis, one must still be cautious in interpreting our results because of the substantial effect of heterogeneity, although we applied a random-effect model to obtain summary statistics. The significant results from the heterogeneity tests for response rate, neutropenia and nausea/vomiting represent potential heterogeneity and may modify the association we found in our study. Possible publication bias is also a potential harm in our study, though we did not detect it statistically. Finally, the dose of new agent used in the platinum-based doublet was different from that in the single-agent therapy in Negoro's trial [10]. Irinotecan was administered at a dose of 100 mg/m^2 in the single-agent therapy, whereas 60 mg/m^2 of irinotecan was combined with cisplatin in the combination arm. It might be problematic to analyse the importance of platinum in our study. However, we considered that the effect would be very small, if any, because it occurred in only one of the eight trials and because the same administration schedule for irinotecan was used in both arms.

In conclusion, this is the first published meta-analysis, to our knowledge, of randomised trials of platinum-based doublet versus single new agent therapy alone. Although modest, the survival improvement obtained with the platinum-based doublet in comparison to a single new agent therapy indicates the importance of platinum in the treatment of advanced NSCLC.

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