Cisplatin- Versus Carboplatin-Based Chemotherapy in First-Line Treatment of Advanced Non–Small-Cell Lung Cancer: An Individual Patient Data Meta-analysis

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Background Because the efficacy of carboplatin and cisplatin in the treatment of advanced non–small-cell lung cancer (NSCLC) has not been proven to be equivalent, an individual patient data meta-analysis comparing the two treatments was performed.

Methods Randomized trials comparing carboplatin to cisplatin in first-line treatment of advanced NSCLC were identified and their electronic databases obtained. A general variance-based method was used to estimate the summary hazard ratios (HRs), odds ratios (ORs), and their 95% confidence intervals (CIs) for mortality, objective response, and toxicity. Cochran's chi-square test (Q test) was used to test for heterogeneity among trials, and the I^2 index, which expresses the proportion of variability of the results due to heterogeneity, was calculated. A random-effects model that takes into account interstudy variation was also applied. All statistical tests were two-sided.

Results Nine trials that included a total of 2968 patients were analyzed; overall median follow-up was 1021 days. The objective response rate was higher for patients treated with cisplatin than for patients treated with carboplatin (30% versus 24%, respectively; OR = 1.37; 95% CI = 1.16 to 1.61; P<.001). Carboplatin treatment was associated with a non–statistically significant increase in the hazard of mortality relative to treatment with cisplatin (HR = 1.07; 95% CI = 0.99 to 1.15; P = .100). In patients with nonsquamous tumors and those treated with third-generation chemotherapy, carboplatin-based chemotherapy was associated with a statistically significant increase in mortality (HR = 1.12; 95% CI = 1.01 to 1.23 and HR = 1.11; 95% CI = 1.01 to 1.21, respectively). Cisplatin-based chemotherapy was associated with more severe nausea and vomiting and nephrotoxicity; severe thrombocytopenia was more frequent during carboplatin-based chemotherapy.

Conclusions Our individual patient data meta-analysis suggests that cisplatin-based chemotherapy is slightly superior to carboplatin-based chemotherapy in terms of response rate and, in certain subgroups, in prolonging survival without being associated with an increase in severe toxic effects. Therefore, cisplatin-based third-generation regimens should remain the standard reference for the treatment of selected patients with advanced-stage NSCLC and of those with earlier-stage disease.

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Approximately one-third of all cancer-related deaths in Western countries are due to lung cancer. Non–small-cell lung cancer (NSCLC) represents 75%–80% of lung cancer cases and accounts for approximately 1.2 million new cases worldwide each year (1).

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CONTEXT AND CAVEATS

Prior knowledge

Platinum-based chemotherapy leads to a small but statistically significant improvement in survival in patients with advanced non–small-cell lung cancer. Carboplatin had largely replaced cisplatin as the platinum-containing drug used to treat this disease because it was associated with a lower incidence of serious side effects. However, it was unclear whether the two drugs had similar clinical efficacy in the treatment of non–small-cell lung cancer.

Study design

A meta-analysis of individual patient data from randomized controlled clinical trials that compared chemotherapy regimens containing either cisplatin or carboplatin.

Contribution

This study presented evidence that cisplatin was more effective than carboplatin in patients treated with newer chemotherapy regimens and in patients with nonsquamous tumors. The side effects associated with the two drugs in non–small-cell lung cancer patients were clarified.

Limitations

The conclusions are based on a somewhat heterogeneous group of clinical trials, some of which were small.

Implications

Cisplatin may well be preferable to carboplatin in non–small-cell lung cancer patients whose disease is at an early stage and in those patients who have advanced disease with a relatively good prognosis.

Disappointingly, the 5-year survival rate is only about 15%, due to the high rate of unresectable disease at diagnosis and to the inability of chemotherapy to cure metastatic disease.

The majority of patients with NSCLC have advanced disease at diagnosis and are therefore potential candidates for systemic therapy. Several prospective trials and meta-analyses were required to prove convincingly that chemotherapy leads to a small but statistically significant improvement in survival when compared with best supportive care only. In the meta-analysis by the Non–Small-Cell Lung Cancer Collaborative Group, a reduction in mortality (hazard ratio [HR] = 0.73) was observed with an absolute improvement of 10% in 1-year survival when platinum-based chemotherapy was compared with best supportive care (2). Furthermore, randomized studies of chemotherapy versus best supportive care have shown that chemotherapy reduces cancer-related symptoms and does not compromise quality of life (3).

A number of recent randomized studies have demonstrated that the addition of platinum to any one of a number of other single agents resulted in an improved outcome compared with the single agent alone and that the introduction of third-generation drugs, such as gemcitabine, taxanes, and vinorelbine, in conjunction with platinum further improved chemotherapy results in advanced NSCLC (4). On the basis of these data, recent American (5), Canadian (6), and European (7) guidelines for the treatment of advanced NSCLC recommend platinum-based third-generation chemotherapy doublets as standard of care for first-line treatment.

Despite its pivotal role in NSCLC management, treatment with cisplatin is associated with a number of serious and unpleasant side effects, including nausea and vomiting, myelosuppression, neurotoxicity, and renal function impairment, and it is burdened by delivery problems, such as the need for prolonged hydration and hospitalization (8). To overcome these limitations, most clinicians now use the cisplatin analog carboplatin, which is associated with a lower incidence of neurotoxicity, nephrotoxicity, and nausea and vomiting compared with cisplatin and does not require prolonged hydration (9).

Although carboplatin and cisplatin have similar mechanisms of action and preclinical activity spectra, it is unclear whether their clinical efficacy is the same for all tumor types. Although for some tumors, such as ovarian cancer, equivalent efficacy has been convincingly proven, for others, such as germ cell and head–neck tumors, there is evidence for the inferiority of carboplatin compared with cisplatin (10).

Nearly 3000 NSCLC patients were enrolled in several randomized trials to determine whether carboplatin or cisplatin is more effective in treating NSCLC. The results from these trials were conflicting, and therefore, it is still debated whether it is justified to replace cisplatin with carboplatin in standard practice (11–13). The use of carboplatin-based regimens is considered to be standard of care for NSCLC in the United States (14), whereas cisplatin-based regimens are generally preferred in Europe (15).

To compare efficacy of cisplatin and carboplatin in the first-line chemotherapy treatment of advanced NSCLC with sufficient statistical power, we conducted an individual patient data meta-analysis (CISCA project [CISplatin versus CArboplatin meta-analysis in advanced NSCLC]) on all patients enrolled in randomized studies comparing the effectiveness of these two platinum agents.

Materials and Methods

Search for Trials

We searched all published (as English-language full paper or abstract) and unpublished randomized trials that compared cisplatin with carboplatin in the first-line treatment of advanced NSCLC. Searches were conducted by 1) regular computer-aided searches of MEDLINE or CANCERLIT literature databases; 2) examining reference lists of published trials, review articles, and bibliographies of relevant oncology books; 3) searching meeting abstracts; 4) consulting the US National Cancer Institute (NCI) Physicians Data Query Clinical Protocol; and 5) contacting individual trialists or cooperative research groups. For databases research, the following strategies were used: "Cisplatin [MeSH] AND Carboplatin [MeSH] AND Carcinoma, Non-small-cell lung/drug therapy [MeSH] AND Clinical trial [pt]" and "Cisplatin AND Carboplatin AND Non-small cell lung cancer."

Selection of Trials

Trials had to fulfill the following inclusion criteria: 1) patients were randomly assigned to treatment; 2) cisplatin and carboplatin were compared in first-line chemotherapy without confounding by additional agents or interventions (i.e., in the combination

chemotherapy, the control and experimental arms had to differ only by cisplatin or carboplatin component); and 3) only patients with diagnosis of NSCLC were included.

Individual Patient Data Collection

The computer files containing the individual patients records including study identification acronym, patient identification number, date of birth, sex, performance status, histology, stage at random assignment, date of randomization, treatment arm, total number of administered cycles, best overall response, worst toxicity (hematologic, nausea and vomiting, neurotoxicity, or nephrotoxicity), date of last observation, and status at last observation were requested from the principal investigators. To avoid potential bias, information for all randomly assigned patients, including those who had been excluded from the final analysis, was required.

Data were collected and analyzed at the Trial Office of National Institute for Cancer Research of Genova, Italy. All data received were checked to ensure both the accuracy of the meta-analysis database and the quality of randomization and follow-up. The study coordinator of each trial had to resolve any computer-generated query. The study protocol was approved by the Ethical Committee and Review Board of the coordinating institution.

Statistical Analysis

The primary endpoint in the meta-analysis was overall survival, defined as the time elapsing from random assignment until death from any cause. Living patients were censored at the date of last follow-up. The secondary endpoints were overall response rate, defined as the sum of partial and complete response rates (according to World Health Organization criteria), and toxicity, which was graded according to NCI Common Toxicity Criteria (CTC).

All analyses were conducted on an intention-to-treat basis, and all randomly assigned patients were included in the analyses according to the allocated treatment. A general variance-based method was used to estimate the summary hazard ratios (HRs), odds ratios (ORs), and their 95% confidence intervals (CIs) (16,17). Ratios were uniformly expressed relative to patients who received cisplatin therapy. The global null hypothesis that the treatment difference in all studies is equal to 0 was tested by comparing the U statistic with the chi-square distribution with 1 df (17). Cochran's chi-square test (Q test) was used to test for the presence of heterogeneity among trials (18). Moreover, the I^2 index, which expresses as a percentage the proportion of variability of the results due to heterogeneity as opposed to sampling error, was calculated (19). Based on the statistical significance of the Q test, we applied a random-effects model, which allows the meta-analysis to take into account interstudy variation. In particular, the random-effects survival model was implemented with a frequentist approach fitting a Cox model with a frailty term (20). The variance of the Gaussian random-effects distribution was based on an approximate restricted maximum likelihood estimation (20). Median follow-up time was estimated by the reverse Kaplan–Meier method (21).

The following factors were identified in the protocol of the study to plan the subgroup analyses: age (<65 versus ≥65 years), stage of disease (IIIB versus IV), performance status (0–1 versus 2), and histology (squamous versus nonsquamous). In the analyses, an additional variable (second- versus third-generation chemotherapy regimen) was considered, although it was not previously specified, based on the results of two meta-analyses that used abstracted data (22,23). Before the subgroup analyses, regression models were used to evaluate the statistical significance of the interaction between the treatment and the potential prognostic factors. These models included a Cox model stratified by trials, for time-to-event outcomes, and a logistic regression model with trial indicator variables, for binary outcomes (24).

All statistical analyses were conducted with SAS for Windows version 9.1 (Cary, NC) and R (http://www.r-project.org). All statistical tests were two-sided, and P values of .05 or less were considered to be statistically significant, except for the test for interaction; in this case, due to the explanatory purpose of the analyses, a cutoff equal to .10 was chosen.

Results

Nine eligible trials (25–33) were identified, and the respective electronic data bases were obtained for all of them. The analysis was conducted on the individual data of the 2968 patients with advanced NSCLC (stage IIIB–IV) enrolled in the nine trials and randomly assigned to receive chemotherapy with cisplatin (1489 patients) or with carboplatin (1479 patients), respectively.

Of the nine trials, seven were randomized phase III trials (25,26,28–31,33), and the remaining two were randomized phase II trials (27,32). None was a placebo-controlled, double-blind trial. Three trials included second-generation chemotherapy regimens: etoposide (25), mitomycin and vindesine (26), and mitomycin and vinblastine (33). Five investigated third-generation chemotherapy doublets: cisplatin or carboplatin with paclitaxel (28,29), docetaxel (31), or gemcitabine (30,32). One trial compared cisplatin and carboplatin when they were used in combination with tirapazamine (27). Two of the nine trials included other treatment arms, in addition to the two arms considered for the meta-analysis (29,31). In the Eastern Cooperative Oncology Group (ECOG) 1594 trial, cisplatin–gemcitabine and cisplatin–docetaxel combinations were also studied (29), and in the TAX326 study, some patients were randomly assigned to a cisplatin–vinorelbine arm (31). Cisplatin dose was 75 mg/m^2 in three trials (27,29,31), 80 mg/m^2 in three others (28,30,32), 100 mg/m^2 in one trial (33), and 120 mg/m^2 in two (25,26). For carboplatin, the dose was expressed in mg/m^2 in three trials; the doses were 325 (25), 500 mg/m^2 (26), and 300 mg/m^2 (33). Carboplatin dose was expressed according to Calvert formula (34) as area under the curve (AUC) in the other six trials; the AUC equaled 6 in four studies (27–29,31), and 5 in the other two trials (30,32).

In the nine trials included in the meta-analysis, patient characteristics were well balanced between the cisplatin and carboplatin treatments (Table 1), such that overall the set of patients treated with cisplatin and those treated with carboplatin had the same median age (60 years), proportion of males (76%), and proportion of patients with performance status between 0 and 1 (86%). The proportions of patients with stage IV disease were 68% and 69% in the cisplatin and carboplatin arms, respectively, and the proportion of patients with squamous histology was slightly more than one-third in both arms. A median of four

Table 1. Characteristics of patients enrolled in the nine trials included in the meta-analysis*

Trial (reference)	No. of patients per regimen	Median age, y (range)	Male (%)	PS, 0–1 (%)	Squamous histology (%)	Stage IV (%)
Klastersky, 1990 (25)	114 (P-E)	61 (36–74)	91	79	53	55
	114 (C-E)	60 (34–74)	88	68	47	54
Jelic, 2001 (26)	112 (P-M-Vd)	57 (24–70)	92	54	100	46
	104 (C-M-Vd)	57 (25–76)	89	67	100	42
Bisset, 2001 (27)	20 (P-TPZ)	60.5 (51–72)	75	95	30	65
	21 (C-TPZ)	64 (50–74)	67	90	52	62
Rosell, 2002 (28)	309 (P-T)	58 (29–78)	82	83	38	64
	309 (C-T)	58 (27–76)	84	83	37	71
Schiller, 2002 (29)	303 (P–T)	61 (25–83)	64	93	20	87
	299 (C-T)	61 (29–84)	62	95	21	87
Zatloukal, 2003 (30)	87 (P-G)	62 (39–75)	77	91	56	59
	89 (C-G)	61 (46–76)	76	90	46	62
Fossella, 2003 (31)	408 (P-D)	60.5 (30–81)	72	96	32	67
	406 (C-D)	59 (23–87)	72	96	34	67
Mazzanti, 2003 (32)	62 (P-G)	59.5 (40–74)	73	79	32	58
	58 (C-G)	64.5 (45–74)	84	86	24	62
Paccagnella, 2004 (33)	74 (P-M-Vb)	59 (37–69)	70	70	23	76
	79 (C-M-Vb)	59.5 (42–74)	78	66	34	73
Total	1489 (P)	60 (24–83)	76	86	39	68
	1479 (C)	60 (23–87)	76	86	38	69

* PS = performance status (according to Eastern Cooperative Oncology Group); P = cisplatin; E = etoposide; C = carboplatin; M = mitomycin; Vd = vindesine; TPZ = tirapazamine; T = paclitaxel; G = gemcitabine; D = docetaxel; Vb = vinblastine.

cycles was administered for both cisplatin (range 0–15) and carboplatin (range 0–22).

Survival

Survival data were available from all nine studies (Table 2). The overall median follow-up was 1021 days. Cisplatin-treated patients had a median survival of 9.1 months and a 1-year survival probability of 37%, while carboplatin-treated patients had a median survival of 8.4 months and a 1-year survival probability of 34% (Fig. 1). The risk of death was higher with carboplatin compared with cisplatin, although the difference was not statistically significant (HR = 1.07, 95% CI = 0.99 to 1.15, P = .100) (Fig. 2). Moreover, there was statistically significant heterogeneity between treatment effects on mortality among the trials (Q test = 17.03,

Table 2. Survival in the nine trials included in the meta-analysis*

Trial (reference)	No. of patients per regimen	ITT	Median survival (mo)	1-year survival (%)	HR† (95% CI)	P‡
Klastersky, 1990 (25)	114 (P-E)	No	7.1	33	1.14 (0.87 to 1.50)	.332
	114 (C-E)		6.9	22		
Jelic, 2001 (26)	112 (P-M-Vd)	No	7.8	21	0.68 (0.51 to 0.91)	.010
	104 (C-M-Vd)		7.9	37		
Bisset, 2001 (27)	20 (P-TPZ)	No	6.3	21	0.55 (0.25 to 1.22)	.143
	21 (C-TPZ)		10.3	33		
Rosell, 2002 (28)	309 (P-T)	Yes	9.7	38	1.22 (1.03 to 1.43)	.019
	309 (C-T)		8.2	32		
Schiller, 2002 (29)	303 (P-T)	No	7.9	32	0.99 (0.84 to 1.16)	.855
	299 (C-T)		8.4	35		
Zatloukal, 2003 (30)	87 (P-G)	Yes	8.8	31	0.98 (0.69 to 1.39)	.902
	89 (C-G)		8	35		
Fossella, 2003 (31)	408 (P-D)	Yes	10.9	45	1.16 (0.99 to 1.35)	.069
	406 (C-D)		9.1	37		
Mazzanti, 2003 (32])	62 (P-G)	No	10.4	43	1.09 (0.75 to 1.59)	.654
	58 (C-G)		11	43		
Paccagnella, 2004 (33)	74 (P-M-Vb)	Yes	10	33	1.18 (0.84 to 1.65)	.348
	79 (C-M-Vb)		7.2	25		
Total	1489 (P)	Yes	9.1	37	1.07 (0.99 to 1.15)	.100
	1479 (C)		8.4	34		

* ITT = intention-to-treat analysis; HR = hazard ratio; CI = confidence interval; P = cisplatin; E = etoposide; C = carboplatin; M = mitomycin; Vd = vindesine; TPZ = tirapazamine; T = paclitaxel; G = gemcitabine; D = docetaxel; Vb = vinblastine.

† Hazard ratio of death in carboplatin-treated patients compared with cisplatin-treated patients.

‡ Two-sided P values were calculated using log-rank test.

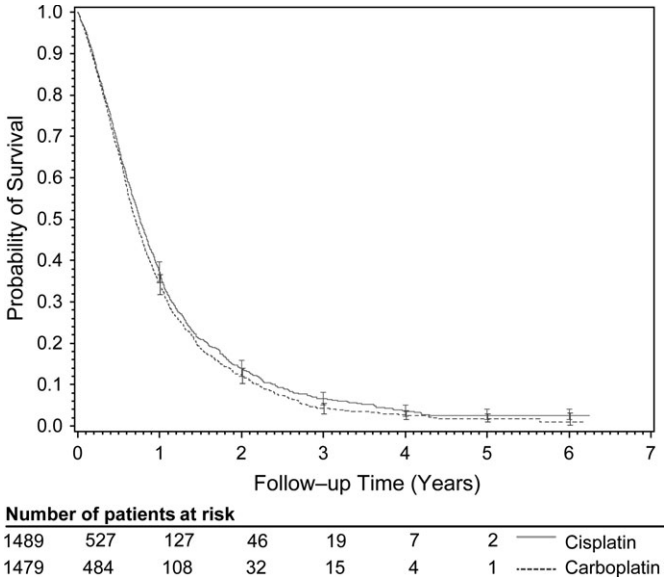

Fig. 1. Kaplan–Meier **curves** and **error bars** showing 95% confidence intervals of overall survival for cisplatin- and carboplatin-based chemotherapies.

P = .030), and the I^2 index indicated that 52% of the variability across trials was due to heterogeneity rather than chance. The random-effects survival model gave an estimated value of the hazard ratio of mortality equal to 1.08 (95% CI = 1.00 to 1.16, P = .063).

The same test for heterogeneity was performed after omitting the study by Jelic at al. (26), the only one showing a statistically significant advantage of carboplatin over cisplatin. With this omission, the result of the Q test was not statistically significant (P = .418), and the value of I^2 index decreased to 1%, indicating that most of heterogeneity in the meta-analysis was related to this single study.

In the subgroup analyses (these included all nine studies) according to age (<65 versus ≥65 years), stage of disease (IIIB versus IV), performance status (0–1 versus 2), histology (squamous versus nonsquamous), and type of chemotherapy regimen (second- versus third-generation), the test for interaction between the treatment and the different variables reached statistical significance for histology and for the type of regimen (P = .098 and P = .093, respectively) (Fig. 3). In the different subgroups, we calculated the hazard ratio for mortality from all causes for patients treated with carboplatin relative to those treated with cisplatin. Based on these analyses, the hazard ratio for mortality in patients with nonsquamous NSCLC was 1.12 (95% CI = 1.01 to 1.23), whereas in the subgroup with squamous histology, it was 0.97 (95% CI = 0.85 to 1.10). The hazard ratios for mortality were 0.94 (95% CI = 0.80 to 1.11) and 1.11 (95% CI = 1.01 to 1.21) in the subgroups of patients treated with second- and third-generation regimens, respectively. Third-generation regimens were administered to 2330 patients, 80% of the total population.

Response Rate

Data about objective response were available for all nine studies (Table 3). Overall, 2669 patients, 1326 treated with cisplatin and 1343 with carboplatin, were assessable for response. (According to

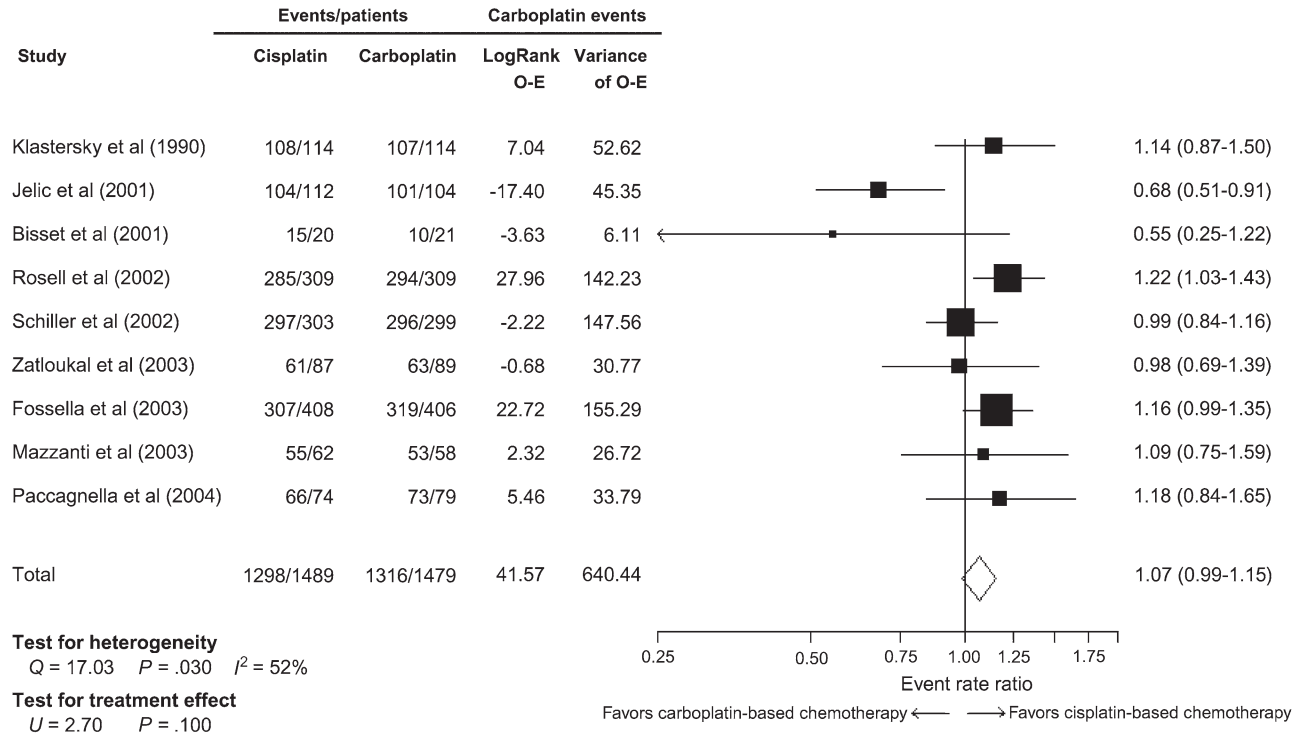

Fig. 2. Overall survival of carboplatin- versus cisplatin-based chemotherapy. To describe the effect of carboplatin on mortality, the log-rank statistic (the observed minus the expected number of deaths) and its variance were computed for each trial. Combining these statistics, the event rate ratios of all trials and their weighted average were calculated with 95% confidence intervals (CIs). The test statistics U and Q were used for hypothesis testing about treatment difference and presence of heterogeneity across studies, respectively. The summary hazard ratio was 1.07 (95% CI = 0.99 to 1.15, P = .100).

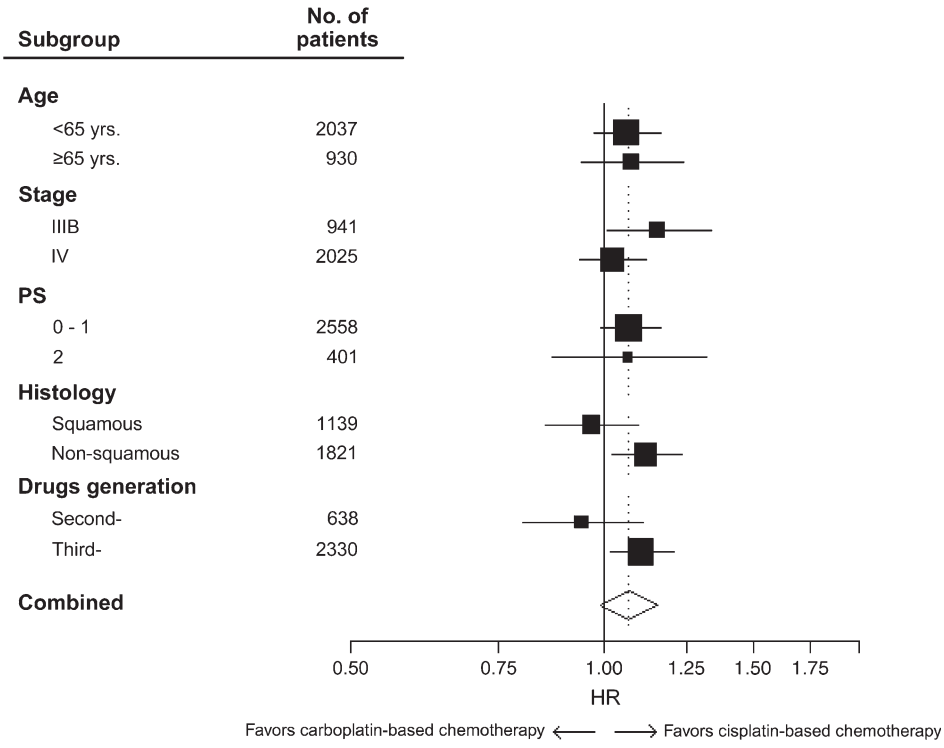

Fig. 3. Hazard ratios for mortality and their 95% confidence intervals of carboplatin- versus cisplatin-based chemotherapy for each of the patient subgroups examined.

the intention-to-treat principle, nonassessable patients were considered as nonresponders.) The response rates (complete plus partial responses according to the World Health Organization criteria) were 30% for cisplatin and 24% for carboplatin, respectively, with an odds ratio for nonresponse (among patients treated with carboplatin versus those treated with cisplatin) of 1.37 (95% CI = 1.16 to 1.61; $P<.001$) (Fig. 4). The result of the test for heterogeneity among the studies was not statistically significant (Q test = 4.13; $P = .845$), and the I^2 index (0%) indicated that variability across trials was due to chance rather than heterogeneity.

In the subgroup analyses (these included all nine studies) according to age (<65 versus ≥65 years), stage of disease (IIIB versus IV), performance status (0–1 versus 2), histology (squamous versus non-squamous), and type of chemotherapy regimen (second- versus third-generation), the result of the interaction test between the treatment and the different variables was statistically significant only

Table 3. Response rate in the nine trials included in the meta-analysis*

Trial (reference)	No. of patients (regimen)	Objective response (%)	OR (95% CI)	P†
Klastersky, 1990 (25)	114 (P-E)	24	1.87 (0.97 to 3.63)	.063
	114 (C-E)	14		
Jelic, 2001 (26)	112 (P-M-Vd)	37	1.09 (0.63 to 1.90)	.761
	104 (C-M-Vd)	35		
Bisset, 2001 (27)	20 (P-TPZ)	25	1.95 (0.42 to 8.95)	.393
	21 (C-TPZ)	14		
Rosell, 2002 (28)	309 (P-T)	27	1.09 (0.76 to 1.56)	.646
	309 (C-T)	25		
Schiller, 2002 (29)	303 (P-T)	21	1.40 (0.93 to 2.11)	.110
	299 (C-T)	16		
Zatloukal, 2003 (30)	87 (P-G)	41	1.70 (0.92 to 3.15)	.092
	89 (C-G)	29		
Fossella, 2003 (31)	408 (P-D)	32	1.47 (1.08 to 2.00)	.014
	406 (C-D)	24		
Mazzanti, 2003 (32)	62 (P-G)	42	1.59 (0.76 to 3.34)	.218
	58 (C-G)	31		
Paccagnella, 2004 (33)	74 (P-M-Vb)	42	1.31 (0.68 to 2.51)	.414
	79 (C-M-Vb)	35		
Total	1489 (P)	30	1.37 (1.16 to 1.61)	<.001
	1479 (C)	24		

* OR = odds ratio for nonresponse in patients treated with carboplatin versus those treated with cisplatin; CI = confidence interval; P = cisplatin; E = etoposide; C = carboplatin; M = mitomycin; Vd = vindesine; TPZ = tirapazamine; T = paclitaxel; G = gemcitabine; D = docetaxel; Vb = vinblastine.

† Two-sided P values were calculated using Pearson chi-square test and U test.

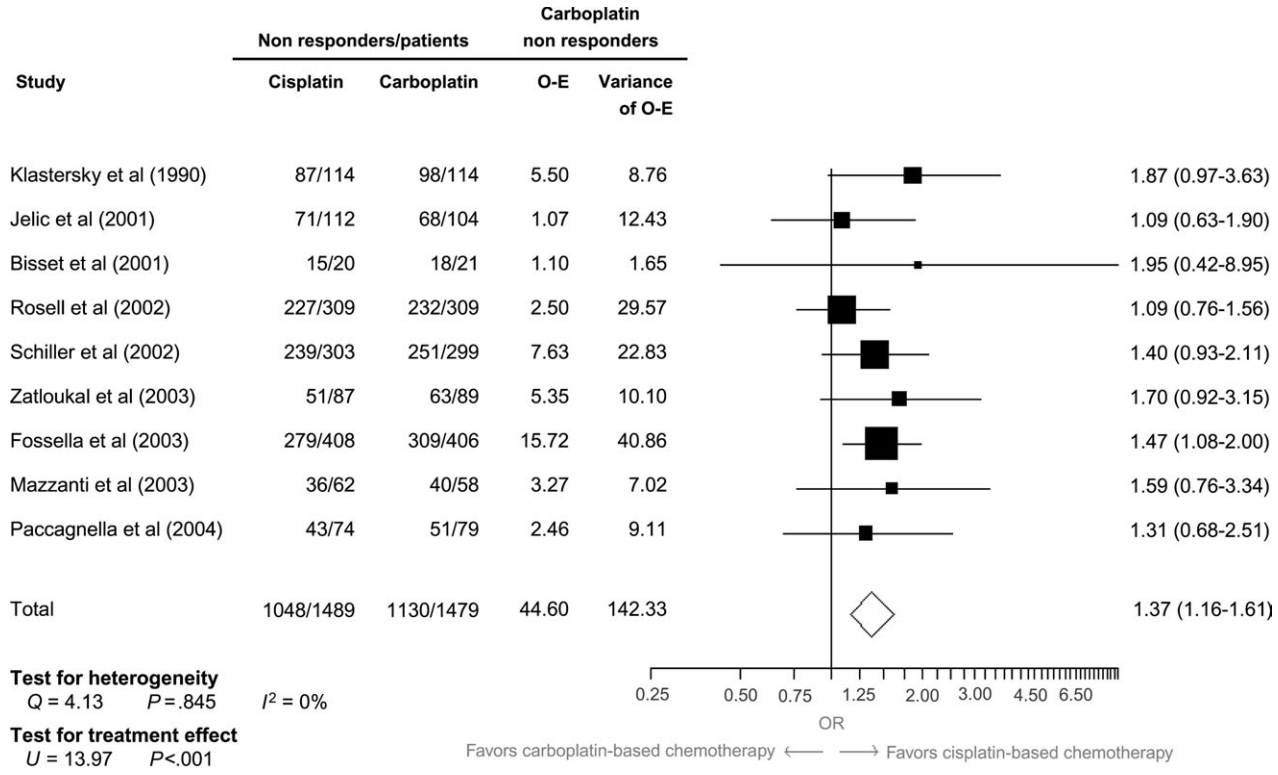

Fig. 4. Response rate of carboplatin- versus cisplatin-based chemotherapy. To describe effect of carboplatin on objective response, the observed minus the expected number of nonresponder patient statistic and its variance was computed for each trial. Combining these statistics, the odds ratios of the trials and their weighted average were calculated with 95% confidence intervals (CIs). The test statistics *U* and *Q* were used for hypothesis testing about treatment difference and presence of heterogeneity across studies, respectively. The summary odds ratio was 1.37 (95% CI = 1.16 to 1.61, *P*<.001).

when patients were categorized according to histology (*P* = .046). The odds ratio was 1.58 (95% CI = 1.27 to 1.97) in the subgroup of the patients with nonsquamous histology, whereas it was 1.10 (95% CI = 0.85 to 1.43) in the subgroup with squamous histology.

Toxicity

Data as to the frequency of NCI-CTC grade 3–4 hematologic and nonhematologic toxic effects were available for eight of the nine studies. Patients treated with carboplatin were more likely to experience thrombocytopenia compared with patients treated with cisplatin (OR = 2.27, 95% CI = 1.71 to 3.01, *P*<.001), whereas the frequencies of leucopenia (OR = 0.96, 95% CI = 0.81 to 1.14, *P* = .644), neutropenia (OR = 0.95, 95% CI = 0.80 to 1.12, *P* = .520), and anemia (OR = 1.10, 95% CI = 0.87 to 1.40, *P* = .424) were the same in those treated with cisplatin compared with those who received carboplatin (Table 4). Cisplatin-based chemotherapy caused more nausea and vomiting than that based on carboplatin (OR = 0.42, 95% CI = 0.33 to 0.53, *P*<.001) and renal toxicity (OR = 0.37, 95% CI = 0.15 to 0.88, *P* = .018). The incidence of neurotoxicity was not different in the two treatments groups (OR = 0.96, 95% CI = 0.75 to 1.23, *P* = .758) (Table 5).

Discussion

The results of this meta-analysis provide evidence that carboplatin-based combination chemotherapy is inferior to therapy based on cisplatin in terms of the rate of objective response (OR for no response = 1.37, 95% CI = 1.16 to 1.61, *P*<.001). Carboplatin-based chemotherapy appeared slightly less effective in prolonging survival, although overall the difference was not statistically significant (HR of death = 1.07, 95% CI = 0.99 to 1.15, *P* = .100). However, when the analysis was restricted to the 2330 patients who were treated with third-generation platinum-based regimens in more recent trials, treatment with cisplatin was associated with a statistically significant improvement in survival compared with treatment based on carboplatin (HR of mortality with carboplatin relative to cisplatin = 1.11, 95% CI = 1.01 to 1.21). Similarly, when the analysis was restricted to patients with nonsquamous histology, treatment with cisplatin was superior, in terms of survival, to treatment with carboplatin (HR = 1.12, 95% CI = 1.01 to 1.23).

The most likely explanation for the achievement of statistical significance in the third-generation chemotherapy and the nonsquamous histology subgroups is that heterogeneity was eliminated in the subgroup analysis. In the analyses of those patients with nonsquamous NSCLC and those who received third-generation chemotherapies, the trial reported by Jelic et al. (26) was not included because it was restricted to patients with squamous histology and it used a second-generation regimen. This study from Serbia, which is the only one that showed statistically significant superiority of carboplatin, was the source of most of the heterogeneity in the meta-analysis; when it was excluded, the test for heterogeneity did not reach statistical significance. Why carboplatin was more effective than cisplatin in the Serbian study, in contrast

Table 4. Grade 3–4 (according to National Cancer Institute Common Toxicity Criteria) hematologic toxicity in eight of the nine trials included in the meta-analysis*

Trial (reference)	No. of patients (regimen)	WBC (% of patients)	OR† (95% CI)	NEU (% of patients)	OR† (95% CI)	HB (% of patients)	OR† (95% CI)	PLT (% of patients)	OR† (95% CI)
Jelic, 2001 (26)	112 (P-M-Vd)	8	2.56‡ (1.10 to 5.95)	8	2.90‡ (1.26 to 6.66)	12	1.93 (0.91 to 4.08)	13	1.47 (0.69 to 3.12)
	104 (C-M-Vd)	18		20		20		17	
Bisset, 2001 (27)	20 (P-TPZ)	0	NA	0	NA	0	NA	0	NA
	21 (C-TPZ)	0		0		0		5	
Rosell, 2002 (28)	309 (P-T)	16	1.61‡ (1.07 to 2.42)	51	1.17 (0.85 to 1.61)	9	0.74 (0.40 to 1.356	2	4.82‡ (1.81 to 12.8)
	309 (C-T)	23		54		7		8	
Schiller, 2002 (29)	303 (P-T)	51	0.42‡ (0.30 to 0.59)	75	0.57‡ (0.40 to 0.81)	14	0.69 (0.41 to 1.14)	6	1.81 (0.97 to 3.36)
	299 (C-T)	30		63		10		10	
Zatloukal, 2003 (30)	87 (P-G)	9	1.65 (0.65 to 4.20)	24	1.42 (0.72 to 2.78)	13	1.47 (0.64 to 3.39)	16	2.45‡ (1.19 to 5.06)
	89 (C-G)	15		30		18		33	
Fossella, 2003 (31)	408 (P-D)	43	1.28 (0.97 to 1.69)	74	0.96 (0.70 to 1.31)	7	1.58 (0.96 to 2.61)	3	2.70‡ (1.33 to 5.51)
	406 (C-D)	49		74		11		7	
Mazzanti, 2003 (32)	62 (P-G)	35	0.75 (0.35 to 1.63)	29	0.93 (0.42 to 2.06)	40	1.48 (0.72 to 3.05)	24	2.06 (0.94 to 4.51)
	58 (C-G)	30		28		50		40	
Paccagnella, 2004 (33)	74 (P-M-Vb)	39	0.61 (0.30 to 1.22)	14	0.52 (0.18 to 1.52)	23	0.79 (0.35 to 1.76)	10	2.10 (0.79 to 5.55)
	79 (C-M-Vb)	28		8		19		19	
Total	1375 (P)	33	0.96 (0.81 to 1.14)	54	0.95 (0.80 to 1.12)	12	1.10 (0.87 to 1.40)	6	2.27‡ (1.71 to 3.01)
	1365 (C)	32		53		13		12	

* WBC = leucopenia; NEU = neutropenia; HB = anemia; PLT = thrombocytopenia; OR = odds ratio; CI = confidence interval; P = cisplatin; E = etoposide; C = carboplatin; Vd = vindesine; M = mitomycin; TPZ = tirapazamine; T = paclitaxel; G = gemcitabine; D = docetaxel; Vb = vinblastine; NA = not applicable.

† Odds ratio of grade 3–4 toxicity in carboplatin-treated patients compared with cisplatin-treated patients.

‡ Statistically significant ($P<.05$); two-sided P values were calculated using U test.

Table 5. Grade 3–4 (according to National Cancer Institute Common Toxicity Criteria) nonhematologic (nausea and vomiting, neurotoxicity, and nephrotoxicity) toxicity in eight of the nine trials included in the meta-analysis*

Trial (reference)	No. of patients (regimen)	N-V (% of patients)	OR† (95% CI)	NEURO (% of patients)	OR† (95% CI)	NEPHRO (% of patients)	OR† (95% CI)
Jelic, 2001 (26)	112 (P-M-Vd)	1	1.08 (0.07 to 17.5)	0	NA	0	NA
	104 (C-M-Vd)	1		0		0	
Bisset, 2001 (27)	20 (P-TPZ)	15	2.27 (0.48 to 10.7)	0	NA	0	NA
	21 (C-TPZ)	15		0		0	
Rosell, 2002 (28)	309 (P-T)	14	0.37‡ (0.21 to 0.67)	7	1.25 (0.70 to 2.25)	1	0.75 (0.17 to 3.37)
	309 (C-T)	6		9		1	
Schiller, 2002 (29)	303 (P-T)	29	0.29‡ (0.18 to 0.45)	28	0.91 (0.63 to 1.30)	3	0.37 (0.10 to 1.42)
	299 (C-T)	10		26		1	
Zatloukal, 2003 (30)	87 (P-G)	18	0.28‡ (0.10 to 0.80)	0	NA	0	NA
	89 (C-G)	6		3		0	
Fossella, 2003 (31)	408 (P-D)	12	0.56‡ (0.34 to 0.90)	11	0.77 (0.49 to 1.23)	1	NA
	406 (C-D)	7		9		0	
Mazzanti, 2003 (32)	62 (P-G)	37	1.38 (0.66 to 2.86)	10	1.49 (0.49 to 4.60)	10	0.16 (0.02 to 1.40)
	58 (C-G)	45		14		2	
Paccagnella, 2004 (33)	74 (P-M-Vb)	27	NA	0	NA	0	NA
	79 (C-M-Vb)	0		0		0	
Total	1375 (P)	18	0.42‡ (0.33 to 0.53)	12	0.96 (0.75 to 1.23)	1.5	0.37‡ (0.15 to 0.88)
	1365 (C)	8		11		0.5	

* N-V = nausea and vomiting; NEURO = neurotoxicity; NEPHRO = nephrotoxicity; OR = odds ratio; CI = confidence interval; P = cisplatin; M = mitomycin; Vd = vindesine; C = carboplatin; TPZ = tirapazamine; T = paclitaxel; G = gemcitabine; D = docetaxel; Vb = vinblastine; NA = not applicable.

† Odds ratio of grade 3–4 toxicity in carboplatin-treated patients compared with cisplatin-treated patients.

‡ Statistically significant ($P<.05$), two-sided P values were calculated using U test.

to the results in most of the other trials, is unknown. However, the patient population (it was younger, had a higher percentage of males and a higher percentage of stage III cancers than the other studies, and was restricted to patients with squamous histology) and the higher carboplatin dose [500 versus 325 (25) or 300 mg/m^2 (33)] used are factors that may account for this discrepancy. In the remaining eight studies, patient characteristics were very similar. Five of the studies (25,28,31–33) showed survival trends in favor of cisplatin, and survival was statistically significantly longer in two of the five (28,31). The small study reported by Bisset et al. (27) showed a survival trend in favor of carboplatin. However, this trial enrolled only 41 patients and combined the platinum agents with a nonclassical anticancer drug, tirapazamine, which by itself is not active against NSCLC.

Most of the evidence for the equivalence of carboplatin and cisplatin in terms of survival comes from the ECOG 1594 study (29). In that four-arm study, 1207 patients were randomly allocated to receive the four most commonly used platinum-based regimens. Among these, 602 patients were randomly assigned to receive cisplatin (75 mg/m^2 on day 2) combined with paclitaxel (135 mg/m^2 administered for a 24-hour period on day 1) every 3 weeks or carboplatin (AUC 6 on day 1) combined with paclitaxel (225 mg/m^2 for 3-hour period on day 1) every 3 weeks. The different doses and schedules of paclitaxel used in this study may represent a possible bias for the comparison between cisplatin and carboplatin. Although the 135 mg/m^2 24-hour infusion and the 225 mg/m^2 3-hour infusion are supposed to have a comparable efficacy, to our knowledge, no formal clinical comparison between the two schedules in patients with NSCLC has been reported. The ECOG 1594 study was designed to detect superiority in median survival of 33% in each of the three experimental arms (including the carboplatin–paclitaxel arm) compared with cisplatin–paclitaxel (the standard reference arm). Based on the results of ECOG 1594, superiority of the carboplatin–paclitaxel arm was excluded; however, because the trial was not designed as a noninferiority trial, no conclusion can be drawn about equivalence of the two regimens.

Another minor bias of this meta-analysis is related to the different doses of cisplatin and carboplatin used in trials that we analyzed. Cisplatin dose ranged from 75 to 120 mg/m^2, and carboplatin dose was either based on body surface (ranging from 300 to 500 mg/m^2) or on AUC (ranging from 5 to 6). However, the platinum dose was always equivalent in the two arms of each study, and it was rather homogenous in those studies in which third-generation treatments were given (cisplatin dose range = 75–80 mg/m^2 and carboplatin dose range = AUC 5–6). No evidence to date exists of a dose–response effect associated with platinum agents within the range of the doses used in these studies. Therefore, it is unlikely that these minor differences in platinum doses affected our findings.

Although the spectrum of toxicity of the two platinum agents was different, the superiority of cisplatin over carboplatin was not achieved at the cost of a statistically significant increase in the incidence of severe side effects. Carboplatin-based regimens were associated with more cases of thrombocytopenia of grade 3–4 (12% versus 6%, $P<.001$). Cisplatin-based therapies were associated with more grade 3–4 nausea and vomiting (18% versus 8%; $P<.001$) and nephrotoxicity (1.5% versus 0.5%, $P = .018$). It is likely that with the recent introduction of newer and more effective antiemetic agents (35), the 10% higher incidence of severe nausea and vomiting associated with intermediate- to high-dose cisplatin can be ameliorated further. There was no difference in the rates of neurotoxicity in patients treated with cisplatin compared to those treated with carboplatin.

Overall, quality of life could not be assessed in our study because only a minority of studies included in the meta-analysis analyzed this endpoint. However, in the three studies where a formal quality of life assessment was prospectively performed, there was no statistically significant difference in quality of life that could be attributed to treatment (28,31,33).

Our results are consistent with those of three other meta-analyses that compared carboplatin and cisplatin in NSCLC treatment and analyzed only published data (22,23,36). In the only meta-analysis reported in full, Hotta et al. (22) found, based on analysis of eight trials, that cisplatin-based chemotherapy was superior in terms of response rate (OR = 1.36, 95% CI = 1.15 to 1.61, $P<.001$) but not in terms of survival (HR = 1.050, 95% CI = 0.907 to 1.216, $P = .515$). In this meta-analysis as well, a statistically significant survival advantage for cisplatin was observed in the subgroup of third-generation regimens (HR = 1.106, 95% CI = 1.005 to 1.218, $P = .039$).

Our meta-analysis was conducted on individual patient data and, therefore, it permits us to draw more definite conclusions than previous analyses, according to the reasons given by Piedbois and Buyse (37). In fact, in contrast to meta-analysis based on abstracted data, individual patient data meta-analysis allows the investigator to evaluate the reliability of the randomization methods, check the trial data, repeat the original analyses (or perform other ones), and update the patients' outcomes.

Given the palliative nature of chemotherapy treatment in advanced NSCLC and the unquestionable practical advantage of carboplatin in terms of ease of administration, it could be argued that the small benefit achieved with cisplatin relative to carboplatin does not justify its preferential use in clinical practice. However, all the progress in the treatment of advanced NSCLC has been made in small increments. Particularly, if one considers that the use of platinum-based combination chemotherapy as opposed to no chemotherapy at all led to only a 27% reduction in the hazard of mortality (2), the benefit from substituting of one platinum agent for another might not be expected to be higher than that observed in this meta-analysis. Other drug substitutions, such as the introduction of third-generation agents, have gained success in clinical practice despite a similarly small benefit (38). If the results of this meta-analysis may still support the use of carboplatin-based regimens in the palliative treatment of patients with very advanced disease and/or poor performance status, cisplatin regimens may well be preferable in patients whose performance status is good and whose disease is less advanced (i.e., oligometastatic stage IV and stage III diseases). Furthermore, the recent results of the Cancer and Leukemia Group B (CALGB) 9633 adjuvant trial, which was performed in patients with completely resected stage IB NSCLC and, unlike other recent adjuvant trials (39), showed no benefit of carboplatin–paclitaxel chemotherapy (40), might be explained by the inferior efficacy of carboplatin observed in our meta-analysis.

In conclusion, based on the results of the randomized trials conducted thus far, our individual patient data meta-analysis, as well as the previous literature-based meta-analyses, cisplatin should remain the reference platinum agent for treatment of NSCLC, at least in advanced disease patients with good prognosis and in those with earlier stage disease.

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Notes

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