Cisplatin versus carboplatin in combination with third-generation drugs for advanced non-small cell lung cancer (Review)

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[Intervention Review]

Cisplatin versus carboplatin in combination with third-generation drugs for advanced non-small cell lung cancer

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ABSTRACT

Background

An estimated 220,000 new cases of non-small cell lung cancer (NSCLC) and 160,000 deaths are expected to occur in the US in 2013, representing about 28% of cancer-related mortality. Approximately 75% of these people will have locally advanced or metastatic disease and will be treated in a palliative setting. Platinum-based combination chemotherapy has benefits in terms of survival and symptom control when compared with best supportive care.

Objectives

To assess the efficacy and safety of carboplatin-based chemotherapy when compared with cisplatin-based chemotherapy, both in combination with a third-generation drug, in people with advanced NSCLC. To compare quality of life in people with advanced NSCLC receiving chemotherapy with cisplatin and carboplatin combined with a third-generation drug.

Search methods

We searched the following electronic databases: MEDLINE (via PubMed) (1966 to 6 March 2013), EMBASE (via Ovid) (1974 to 6 March 2013), Cochrane Central Register of Controlled Trials (CENTRAL; Issue 2, 2013), and LILACS (1982 to 6 March 2013). In addition, we handsearched the proceedings of the American Society of Clinical Oncology Meetings (January 1990 to March 2013), reference lists from relevant resources and the Clinical Trial.gov database.

Selection criteria

Randomised clinical trials comparing regimens with carboplatin or cisplatin combined with a third-generation drug in people with locally advanced or metastatic NSCLC. We accepted any regimen and number of cycles that included these drugs, since there is no widely accepted standard regimen.

Data collection and analysis

Two review authors independently assessed search results and a third review author resolved any disagreements. We analysed the following endpoints: overall survival, one-year survival, quality of life, toxicity and response rate.

Main results

We included 10 trials with 5017 people, 3973 of whom were available for meta-analysis. There was no difference between carboplatin-based and cisplatin-based chemotherapy in overall survival (hazard ratio (HR) 1.00; 95% confidence interval (CI) 0.51 to 1.97, I^2 = 0%) and one-year survival rate (risk ratio (RR) 0.98; 95% CI 0.88 to 1.09, I^2 = 24%). Cisplatin had higher response rates when we performed an overall analysis (RR 0.88; 95% CI 0.79 to 0.99, I^2 = 3%), but trials using paclitaxel or gemcitabine plus a platin in both arms had equivalent response rates (paclitaxel: RR 0.89; 95% CI 0.74 to 1.07, I^2 = 0%; gemcitabine: RR 0.92; 95% CI 0.73 to 1.16, I^2 = 34%). Cisplatin caused more nausea or vomiting, or both (RR 0.46; 95% CI 0.32 to 0.67, I^2 = 53%) and carboplatin caused more thrombocytopenia (RR 2.00; 95% CI 1.37 to 2.91, I^2 = 21%) and neurotoxicity (RR 1.55; 95% CI 1.06 to 2.27, I^2 = 0%). There was no difference in the incidence of grade III/IV anaemia (RR 1.06; 95% CI 0.79 to 1.43, I^2 = 20%), neutropenia (RR 0.96; 95% CI 0.85 to 1.08, I^2 = 49%), alopecia (RR 1.11; 95% CI 0.73 to 1.68, I^2 = 0%) or renal toxicity (RR 0.52; 95% CI 0.19 to 1.45, I^2 = 3%). Two trials performed a quality of life analysis; however, they used different methods of measurement so we could not perform a meta-analysis.

Authors' conclusions

The initial treatment of people with advanced NSCLC is palliative, and carboplatin can be a treatment option. It has a similar effect on survival but a different toxicity profile when compared with cisplatin. Therefore, the choice of the platin compound should take into account the expected toxicity profile and the person's comorbidities. In addition, when used with either paclitaxel or gemcitabine, the drugs had an equivalent response rate.

PLAIN LANGUAGE SUMMARY

Comparing chemotherapy with cisplatin or carboplatin in the treatment of people with advanced lung cancer

Lung cancer is the leading cause of cancer death and almost 75% of people are incurable at diagnosis. Non-small cell is the most common type of lung cancer (almost 90% of all lung cancer cases). For many of these people, chemotherapy is a good treatment option and it is associated with longer survival and better quality of life. However, treatment for people with advanced non-small cell lung cancer is palliative, in that it provides relief from pain and other distressing symptoms. Treatments that include cisplatin or carboplatin plus another drug are the most widely used drug combinations, but they can be associated with undesirable toxicity. Thus, it would be desirable to have a treatment that is just as effective but with less toxicity.

We found 10 trials (including 5017 people) that compared cisplatin with carboplatin, both combined with another modern drug, called a third-generation drug. The drugs were equally effective at prolonging survival, but the toxicity profile was different. Cisplatin caused more nausea or vomiting or both and carboplatin caused more numbness and tingling in hands and feet and greater decrease in the number of platelets (which control clotting) in the blood.

Unfortunately, we could not analyse quality of life in our review because only two trials studied this and they used different methods to measure the effects.

BACKGROUND

Description of the condition

Lung cancer is currently the second most common malignant tumour and is the leading cause of cancer-related mortality in the US (American Cancer Society 2010). About 85% of lung cancers are of the non-small cell type and approximately 75% of people present with locally advanced or metastatic disease (Govindan 2006).

Description of the intervention

Chemotherapy in advanced non-small cell lung cancer (NSCLC)

has been under investigation for several decades. In the 1990s, a meta-analysis of 52 randomised clinical trials (RCTs) showed that cisplatin-based chemotherapy had increased median survival by six weeks compared with best supportive care in people with NSCLC (NSCLC Collaborative Group 1995). Since then, cisplatin has been the mainstay component of chemotherapy for any stage of NSCLC. However, cisplatin causes a number of significant side effects, including nausea and vomiting, alopecia, neutropenia, neurotoxicity and renal function impairment (Reed 2005).

Several newer anticancer drugs with different mechanisms of action are available, such as irinotecan, paclitaxel, docetaxel, gemcitabine and vinorelbine; these are known as third-generation drugs. These drugs, combined with cisplatin, are considered the standard chemotherapy regimen for advanced NSCLC (Azzoli 2009).

Since 1990, at least 20 trials have compared cisplatin versus carboplatin in this setting, but a small number of these studies compared regimens containing a third-generation drug. In 2002, Schiller et al published a trial that compared cisplatin plus paclitaxel versus carboplatin plus paclitaxel. They found similar survival and response rates but less toxicity with carboplatin plus paclitaxel, although quality of life (QoL) was not assessed (Schiller 2002).

In 2004, Hotta et al published a meta-analysis that found no differences between cisplatin and carboplatin in survival of people with advanced NSCLC (Hotta 2004). In 2007, another two meta-analyses showed similar findings, but the cisplatin-based regimen had a higher overall response rate (Ardizzoni 2007; Jiang 2007). Moreover, these meta-analyses also showed similar results in terms of toxicity profile. However, these three meta-analyses included studies that used old traditional drugs in combination with a platin and did not assess a combination with third-generation drugs, which seem to be more effective (Baggstrom 2007). QoL assessment has also become extremely important, given the small survival advantage and the toxicity of chemotherapy, but only three of the included trials had used an acceptable QoL analysis (Fossella 2003; Paccagnella 2004; Rosell 2002).

In the modern approach, newly diagnosed advanced NSCLC should be tested for mutation in epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) translocation, which predicts better response to small molecule inhibitors (erlotinib, gefinitib, crizotinib). Chemotherapy is the only option to those patients with EGFR and ALK wild type tumours.

Why it is important to do this review

Given that people with advanced NSCLC are treated primarily in a palliative setting, the requirement to use drugs with low toxicity seems clear. Carboplatin-based chemotherapy a better toxicity profile than cisplatin-based chemotherapy (Reed 2005). In this review, we analysed treatment for advanced NSCLC using carboplatin or cisplatin plus a third-generation drug.

OBJECTIVES

To assess the efficacy and safety of carboplatin-based chemotherapy when compared with cisplatin-based chemotherapy, both in combination with a third-generation drug, in people with advanced NSCLC. To compare QoL in people with advanced NSCLC receiving chemotherapy with cisplatin and carboplatin combined with a third-generation drug.

METHODS

Criteria for considering studies for this review

Types of studies

RCTs that compared regimens with cisplatin or carboplatin in combination with a third-generation drug (i.e. docetaxel, paclitaxel, vinorelbine, gemcitabine or irinotecan) in people with advanced NSCLC. We excluded non-randomised and quasi-randomised studies.

Types of participants

People with pathologically confirmed NSCLC, with metastatic disease, or pleural or pericardial effusion (stage IIIB or IV; Sobin 2002).

Types of interventions

- Cisplatin plus gemcitabine versus carboplatin plus gemcitabine.
- Cisplatin plus docetaxel versus carboplatin plus docetaxel.
- Cisplatin plus paclitaxel versus carboplatin plus paclitaxel.
- Cisplatin plus vinorelbine versus carboplatin plus vinorelbine.
- Cisplatin plus irinotecan versus carboplatin plus irinotecan.

We included trials comparing these compounds for any number of cycles or treatment schedules.

Types of outcome measures

Primary outcomes

- Overall survival.
- One-year survival rate.
- QoL.
- Drug toxicities (according to the National Cancer Institute Common Toxicity Criteria v2.0) (NCI Common Toxicity Criteria).

Secondary outcomes

- Objective response rate, classified according to the Response Evaluation Criteria in Solid Tumors (RECIST) (Eisenhauer 2009).

Search methods for identification of studies

We performed the search for trials in accordance with the Cochrane Lung Cancer Review Group recommendations and there were no limits regarding study publication date or language.

Electronic searches

We performed electronic searches of the following databases:

1. The Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 2, 2013);
2. MEDLINE (via PubMed) (1966 to 6 March 2013);
3. EMBASE (via Ovid) (1974 to 6 March 2013); and
4. LILACS (1982 to 6 March 2013).

The search strategies used for each database are presented in Appendix 1.

Searching other resources

We carried out a manual search of the Proceedings of the American Society of Clinical Oncology Meetings (1990 to 2012). We searched the reference lists from relevant studies and contacted authors to obtain information about ongoing or non-published studies. We also searched Clinical Trials.gov.

Data collection and analysis

Selection of studies

Two review authors (TBC and AFTG) independently examined the abstracts of studies found in the search. From this initial assessment, we obtained full-text versions of all potentially relevant articles. A third review author (RR) resolved any disagreements.

Data extraction and management

We extracted and recorded data on data extraction forms. Two review authors (TBC and AFTG) independently developed and piloted the forms. These two review authors independently conducted full data extraction. A third review author (RR) resolved any disagreements. We included the following information from individual studies on the data extraction forms:

- publication details;
- study design, setting, inclusion/exclusion criteria, method of allocation, allocation concealment, blinding, risk of bias;
- participant population (e.g. age, type of surgical procedure, type of tumour);
- details of intervention: doses, regimen, scheme, duration;
- outcome measures;
- withdrawals, duration and method of follow-up, proportion of follow-up;
- type of analyses (e.g. intention-to-treat, modified intention-to-treat).

Assessment of risk of bias in included studies

Two review authors (TBC and AFTG) independently performed an assessment of risk of bias for each study using the 'Risk of bias' tool created by The Cochrane Collaboration (Higgins 2011). For each 'Risk of bias' domain we assigned 'low risk of bias', 'high risk of bias' or 'unclear risk of bias' using the specific questions detailed below. We then classified the studies as 'low', 'moderate' or 'high' risk of bias (Figure 1; Figure 2).

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

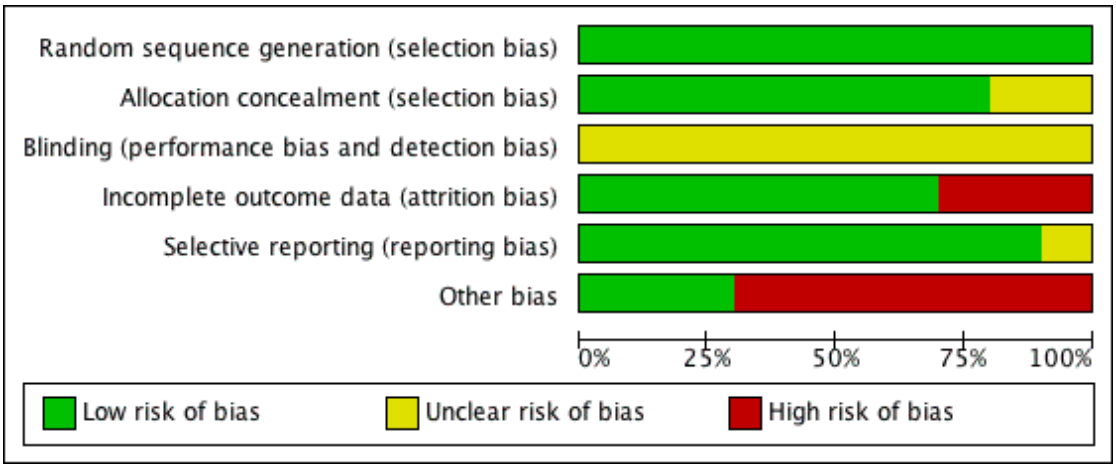
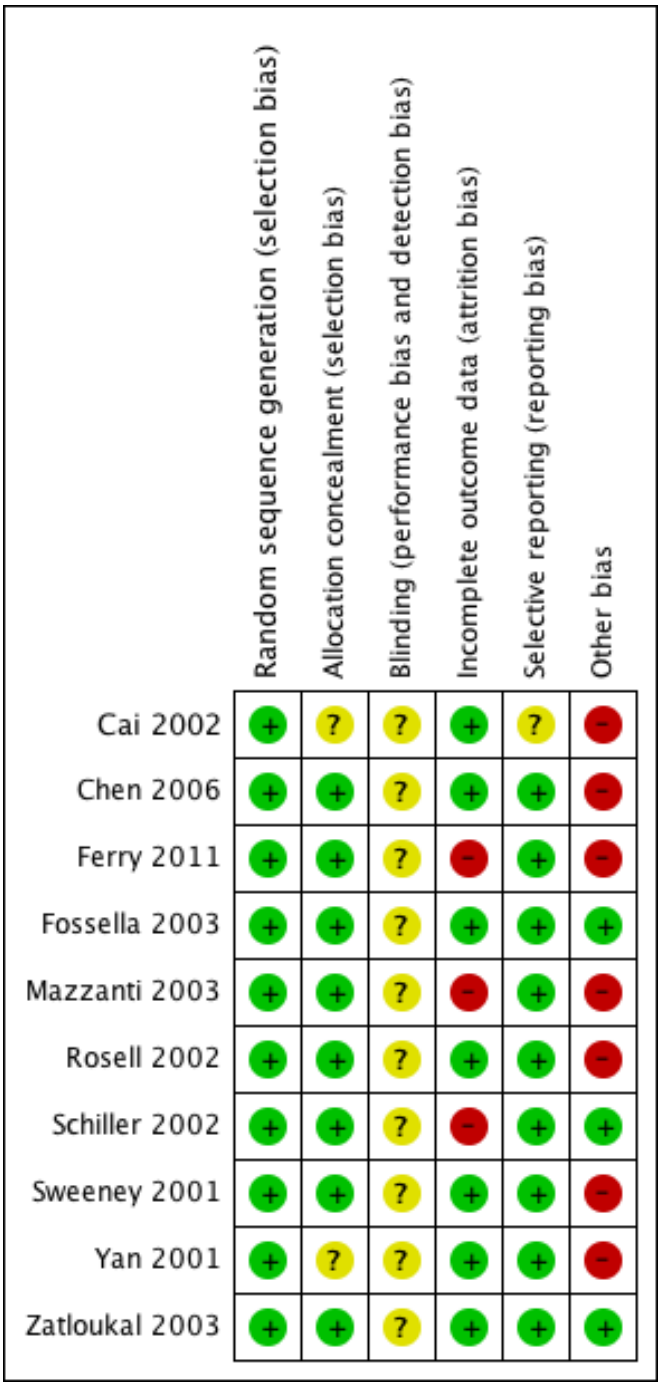


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



- Sequence generation: was the allocation sequence adequately generated?
- Allocation concealment: was allocation adequately concealed?
- Blinding of participants, personnel and outcome assessors: was knowledge of the allocated interventions adequately prevented during the study?
- Incomplete outcome data: were outcome data adequately assessed and accounted for?
- Selective outcome reporting: were reports of the study free of suggestion of selective outcome reporting?
- Other potential threats to validity: was the study apparently free from other problems that could put it at risk of bias?

Measures of treatment effect

We calculated risk ratios (RRs) and 95% confidence intervals (CI) for dichotomous outcomes. When focusing on grade III or IV toxic events (NCI Common Toxicity Criteria), an RR value greater than one indicated that the carboplatin-based regimen was more toxic than the cisplatin-based regimen.
For time-to-event outcomes, we presented hazard ratio (HR) with 95% CIs when appropriate.

Unit of analysis issues

We included only RCTs in this review. We found no cross-over or cluster randomised trials.

Dealing with missing data

If the data were missing to the extent that we could not add the study to the meta-analysis and we could not retrieve the data, we presented the findings and discussed them in the main text of the review. We contacted the authors by e-mail to request more information about methods or results data.

Assessment of heterogeneity

We evaluated heterogeneity between studies using the I^2 statistic and considered an I^2 value greater than 50% to indicate substantial heterogeneity.

Assessment of reporting biases

We contacted study authors to request full data sets or to establish the reasons for the non-reporting of some data outcomes. We performed searches for the protocols of included trials.

Data synthesis

We summarised data through the forest plot graphics produced by Review Manager, using a random-effects model (RevMan 2011). We presented a narrative summary of the results of individual studies and discussed the results where data aggregation was not possible.

Subgroup analysis and investigation of heterogeneity

If we found an I^2 value greater than 50%, we considered there to be substantial heterogeneity and we performed a subsequent analysis excluding trials that would be responsible for the heterogeneity based on clinical or methodological factors. We reported these results separately in the text.
We compared the effectiveness and toxicity of carboplatin with that of cisplatin when both were combined with any third-generation drug. We then analysed carboplatin or cisplatin combined with each of the following drugs: gemcitabine, paclitaxel and docetaxel. In terms of toxicity, we analysed trials reporting toxicity data as events per cycle or events per participant mode.
Since the dose of cisplatin varied in the trials, which would affect effectiveness and toxicity, we also performed an analysis comparing different dose ranges of cisplatin: lower (40 to 80 mg/m^2) and higher (80 to 100 mg/m^2). These subgroups and dose limits had been proposed by the authors before the search and were based on the most used dose of cisplatin in current trials (75-80 mg/mL).

Sensitivity analysis

We performed several sensitivity analyses to assess the robustness of the overall results. We explored the following factors:

- restriction to published data: given the difficulties in evaluating potential biases and the real effect of therapies, we performed a sensitivity analysis excluding unpublished trials, as suggested by Hopewell 2007 (Cochrane 2007), and revealed results in an individual table;

- statistical model: since included trials had different sample sizes and, therefore, statistical power, we also performed a fixed-effect analysis.

- only phase III trials: since response to therapy use to be overestimated in phase II trials, analysis of efficacy (response rate and survival data) should be considered exploratory in such trials (Green 2003). We carried out a sensitivity analysis excluding phase II trials.

RESULTS

Description of studies

Results of the search

Our initial search strategy found 1718 manuscripts: 19 in CENTRAL, 1172 in MEDLINE, 527 in EMBASE and none in LILACS. We considered 33 to be potentially eligible for our systematic review. After full-text analysis of these, we excluded a further 23 (17 trials) because they were reported in other publications.

Included studies

We included 10 trials with 5017 people, 3973 of whom were available for meta-analysis.

All 10 trials were conducted with people with locally advanced or metastatic NSCLC and no important comorbidities. Trials used gemcitabine (Cai 2002; Ferry 2011; Mazzanti 2003; Zatloukal 2003), paclitaxel (Chen 2006; Rosell 2002; Schiller 2002; Sweeney 2001; Yan 2001), or docetaxel (Fossella 2003), in combination with a platin compound.

All of the authors specified inclusion criteria but exclusion criteria were not cited in two Chinese trials (Cai 2002; Yan 2001). Among exclusion criteria were pregnancy, current organ dysfunction and symptomatic central nervous system metastases (asymptomatic was allowed in some trials). Details of those RCTs are available in the Characteristics of included studies table.

In a phase II trials, Cai 2002 randomised 40 people to receive gemcitabine (1000 mg/m^2) on days one and eight and carboplatin (area under the curve (AUC) 4 to 6 mg/mL X min) on day one or gemcitabine (1000 mg/m^2) on days one and eight and cisplatin (30 to 40 mg/m^2) on days one to three. Treatments were repeated every three weeks. The study authors included people with a Karnofsky performance status (PS) of 40 or higher.

Chen 2006 studied 81 people aged 70 years or older, PS 0 to 2 on the World Health Organization (WHO) scale and with no signs or symptoms of brain metastases. People were randomised to paclitaxel (160 mg/m^2) on day one and carboplatin (AUC 6 mg/mL X min) on day one or paclitaxel (160 mg/m^2) on day one and cisplatin (60 mg/m^2) on day one. Treatments were repeated every three weeks.

Ferry 2011 randomised 1363 people to receive gemcitabine (1250 mg/m^2) on days one and eight and cisplatin (80 mg/m^2) on day one, every 3 weeks or gemcitabine (1250 mg/m^2) and cisplatin (50 mg/m^2) on day one, every 3 weeks or gemcitabine (1250 mg/m^2) and carboplatin (AUC 6 mg/mL X min) on day one, every 3 weeks. The results of this trial have yet to be published.

Fossella 2003 published results of a phase III trial with 1218 people comparing regimens of chemotherapy for people with locally advanced or metastatic NSCLC who had a Karnofsky PS of 70 or higher and no significant comorbidities. Participants were randomised to receive docetaxel (75 mg/m^2) on day one and cisplatin (75 mg/m^2) on day one or docetaxel (75 mg/m^2) on day one and intravenous carboplatin (AUC 6 mg/mL X min) on day one. Treatments were repeated every three weeks. We did not use a third treatment arm (vinorelbine plus cisplatin) in the analysis because there was no parallel arm with vinorelbine and carboplatin.

In Mazzanti 2003, 120 people with Eastern Cooperative Oncology Group (ECOG) PS 0 to 2 and life expectancy greater than 12 weeks were eligible for gemcitabine (1200 mg/m^2) on days one and eight and cisplatin (80 mg/m^2) on day two or gemcitabine (1200 mg/m^2) on days one and eight and carboplatin (AUC 5 mg/mL X min) on day two. Treatments were repeated every three weeks. People with symptomatic central nervous system metastases were excluded.

Rosell 2002 published the results of a phase III trial with 618 people with a ECOG PS 0 to 2 and able to understand the European Organisation for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire Core 30 (EORTC QLC-C30). People received paclitaxel (200 mg/m^2) and cisplatin (80 mg/m^2) or paclitaxel (200 mg/m^2) and carboplatin (AUC 6 mg/mL X min). Treatments were repeated every three weeks. The primary outcome was response rate and among other secondary outcomes, the authors analysed QLC-C30 and Quality of Life Lung Cancer supplement 13 (QOL-LC13).

Schiller 2002 published the results of a phase III trial with 1207 people. Initially people with an ECOG PS 0 to 2 were eligible for enrolment, but after 66 people with PS of 2 had been enrolled, the study design was amended to exclude those participants because of the high rate of serious adverse events. Participants were randomised to receive paclitaxel (135 mg/m^2 infusion over 24 hours) on day one and cisplatin (75 mg/m^2) on day two or paclitaxel (225 mg/m^2 infusion over three hours) on day one and carboplatin (AUC 6 mg/mL X min) on day one. Treatments were repeated every three weeks. We did not analyse arms two and three of the study in this review because they used regimens that did not fulfil the inclusion criteria. A total of 1155 people were analysed.

Sweeney 2001 performed a phase II trial with 68 people, all of whom had a ECOG PS 2, and randomised them to paclitaxel (135 mg/m^2 infusion over 24 hours) on day one and cisplatin (75 mg/m^2) on day two or paclitaxel (225 mg/m^2 infusion over three hours) on day one and carboplatin (AUC 6 mg/mL X min) on day one. Treatments were repeated every three weeks. We excluded arms two and three of this trial because they used regimens that did not fulfil the inclusion criteria of this review. The primary outcomes of this trial were toxicity and adverse events.

Yan 2001 randomised 126 people with Karnofsky PS of 60 or higher to receive paclitaxel (175 mg/m^2) on day one and carboplatin (350 mg/m^2) on day one or paclitaxel (175 mg/m^2) on days one and eight and cisplatin (100 mg/m^2) on day one. Treatments were repeated every four weeks.

Zatloukal 2003 randomised 176 people with Karnofsky PS of 70 or higher to receive gemcitabine (1200 mg/m^2) on days one and eight and intravenous cisplatin (80 mg/m^2) on day one, or

gemcitabine (1200 mg/m^2) and carboplatin (AUC 5 mg/mL X min) on day one. Treatments were repeated every three weeks. The primary outcome of the trial was toxicity.

Excluded studies

We excluded 23 publications (17 trials) from the first selection after a full-text analysis because they had been published in more than one database, were related to the same trial, or they had presented a preliminary or subset analysis of another trial (Characteristics of excluded studies).

Risk of bias in included studies

Allocation

Of the 10 trials of cisplatin-based versus carboplatin-based chemotherapy, allocation was adequately concealed in seven trials (Chen 2006; Fossella 2003; Mazzanti 2003; Rosell 2002; Schiller 2002; Sweeney 2001; Zatloukal 2003). We obtained the allocation method of Ferry 2011 by e-mail. Two Chinese trials did not provide clear information about allocation concealment and we could not contact the authors(Cai 2002; Yan 2001).

Blinding

None of the 10 RCTs reported complete information about the blinding processes (Cai 2002; Chen 2006; Ferry 2011; Fossella 2003; Mazzanti 2003; Rosell 2002; Schiller 2002; Sweeney 2001; Yan 2001; Zatloukal 2003). After contacting the authors and obtaining more information, we obtained no more details about blinding (the process and which elements were blinded). Therefore, we judged all trials as 'unclear' for blinding.

Incomplete outcome data

Of the 1218 people in the Fossella 2003 study, 15 people did not receive treatment (nine were ineligible, four withdrew consent and two died of malignant disease before the first drug infusion); thus, we excluded these from the safety analysis.

In Schiller 2002, the study design was amended to include only people with a ECOG 0 or 1 after 66 people with a ECOG 2 had been enrolled. These participants were not included in the final analysis and this could have affected results since people with a ECOG 2 have a poorer prognosis and the numbers of them in each arm were not reported.

Of the 618 people randomised in Rosell 2002, 10 (2%) did not receive a study drug (three in the carboplatin arm and seven in cisplatin arm), but we considered it unlikely that this would result in a significant bias.

Selective reporting

Cai 2002 reported no survival data and was excluded from the analysis of overall survival and one-year survival rate. In Ferry 2011, the response rate could not be evaluated for 160 people in the gemcitabine plus cisplatin (80 mg/m^2) arm, 152 people in the gemcitabine plus cisplatin (50 mg/m^2) arm and 151 people in the gemcitabine plus carboplatin arm. This might have affected the final analysis of this endpoint.

Yan 2001 reported no overall survival data but did provide one-year survival rate.

The remainder of the studies reported overall survival data only as median and confidence intervals (CIs). Therefore, we converted them to HRs, according to the method proposed by Parmar 1998.

In the analysis of adverse effects that were measured as number of events per cycle, alopecia was not mentioned in Mazzanti 2003 and renal toxicity analysis was not performed by Ferry 2011.

In the analysis of adverse effects that were measured as events per participant, nausea, vomiting, or both were not evaluated by Cai 2002, which was the only trial to describe the incidence of skin rash. Incidence of alopecia was analysed only by Yan 2001 and Zatloukal 2003. Neurotoxicity was evaluated by Chen 2006, Rosell 2002, Schiller 2002, Sweeney 2001 and Zatloukal 2003.

Other potential sources of bias

Data from Ferry 2011 were only presented at a conference, and so we could not exclude the occurrence of other biases. Therefore, we performed a sensitivity analysis excluding this trial and have presented results in an additional table. It is also important to note that the Wright formula was used for calculation of creatinine clearance, which usually results in about 10% higher doses of carboplatin than with the use of the Cockcroft-Gault formula (Wright 2001).

Cai 2002, Chen 2006, Mazzanti 2003, Sweeney 2001 and Yan 2001 were planned as randomised phase II studies. Therefore, the findings obtained from the treatment-arm comparisons should be considered exploratory.

In Rosell 2002, a reduction of carboplatin dose was necessary for 96 of 279 (34%) people randomised to the drug, and the mean dose AUC for them was 4.9 mg/mL X min. This dose could be associated with a lower effectiveness.

In Schiller 2002, paclitaxel dose (135 mg/m^{2}and 225 mg/m^2) and length of infusion (24 and 3 hours) were different. These differences may have compromised the comparison in efficacy and toxicity.

Effects of interventions

Carboplatin-based versus cisplatin-based chemotherapy

Overall survival (Analysis 1.1)

Overall survival was evaluated in eight trials (4851 participants; 3807 pooled for meta-analysis). Meta-analysis of these trials showed that there was no difference in overall survival between cisplatin-based and carboplatin-based chemotherapy (HR 1.00; 95% CI 0.51 to 1.97, I^2 = 0%) (Analysis 1.1). There was no significant heterogeneity among trials.

Subgroup analysis

In a subgroup analysis with three trials in which cisplatin or carboplatin were added to gemcitabine, we obtained a similar overall survival among trials including 1659 people (HR 0.99; 95% CI 0.34 to 2.90, I^2 = 0%). Considering trials with paclitaxel, four trials and 1334 people were analysed and there was no difference in overall survival (HR 1.00; 95% CI 0.37 to 2.73, I^2 = 0%). Finally, when combined with docetaxel, one trial with 814 people found no significant difference between cisplatin plus docetaxel and carboplatin plus docetaxel (HR 1.01; 95% CI 0.16 to 6.37).

One-year survival (Analysis 1.2)

One-year survival rate was evaluated in nine RCTs (4977 people; 3933 pooled for meta-analysis). There was no difference in one-year survival rate between cisplatin-based and carboplatin-based chemotherapy (RR 0.98; 95% CI 0.88 to 1.09, I^2 = 24%) (Analysis 1.2), and no significant heterogeneity was detected among trials.

Subgroup analysis

A subgroup analysis showed comparable results in three trials (1659 people) with gemcitabine (RR 1.10; 95% CI 0.97 to 1.26, I^2 = 0%) or in five trials (1334 people) with paclitaxel (RR 0.97; 95% CI 0.84 to 1.12, I^2 = 0%). However, one trial with 814 participants analysing cisplatin plus docetaxel versus carboplatin plus docetaxel found benefit with the cisplatin-based regimen (RR 0.82; 95% CI 0.70 to 0.97) (Fossella 2003).

Quality of life analysis

Only two trials performed a QoL analysis. Fossella 2003 evaluated QoL using the EORTC LC-13 and the Lung Cancer Symptom Scale (LCSS) questionnaires but did not compare cisplatin and carboplatin arms directly. Rosell 2002 applied the QLQ-C30 and QOL-LC13 questionnaires to compare the two drugs and found no significant differences in global health status or in functional scales. Because of this paucity of QoL data, we could not perform a meta-analysis.

Grade III or IV toxicity by cycle (Analysis 1.3)

Adverse effects data were available for all 10 RCTs. The rates of adverse effects were reported as number of events per participant or events per cycle. Since eight trials reported data as per participant and two trials as per treatment cycle, we analysed them separately and only grade III and IV toxicities were considered (Analysis 1.3). Performing a meta-analysis of two trials that evaluated toxicity as events per cycle, we found a higher incidence of anaemia (RR 3.93; 95% CI 1.83 to 8.42, I^2 = 34%) in the carboplatin arm. There was no difference in the incidence of nausea or vomiting or both (RR 0.70; 95% CI 0.48 to 1.02, I^2 = 0%), renal toxicity (RR 0.33; 95% CI 0.01 to 7.99), neurotoxicity (RR 1.85; 95% CI 0.40 to 8.61, I^2 = 0%), skin rash (RR 1.97; 95% CI 0.57 to 6.80), alopecia (RR 0.49; 95% CI 0.06 to 4.40) or neutropenia (RR 2.31; 95% CI 0.77 to 6.95, I^2 = 76%). The heterogeneity evident in the neutropenia analysis can be explained by the difference in the risk of neutropenia and the large differences in sample sizes.

Subgroup analysis

We found similar rates of neutropenia with significant heterogeneity in the trials with gemcitabine (RR 2.31; 95% CI 0.77 to 6.95, I^2 = 76%). However, only two trials were included in this analysis and we could not perform a sensitivity analysis.

Grade III or IV toxicity by participant (Analysis 1.4)

We performed a meta-analysis of eight RCTs that evaluated toxicity as events per participant and we found a higher incidence of nausea or vomiting or both in the cisplatin arm (RR 0.46; 95% CI 0.32 to 0.67, I^2 = 53%) (Analysis 1.4). However, carboplatin-based chemotherapy caused more neurotoxicity (RR 1.55; 95% CI 1.06 to 2.27, I^2 = 0%) and thrombocytopenia (RR 2.00; 95% CI 1.37 to 2.91, I^2 = 21%). Heterogeneity in nausea or vomiting or both was mainly due to the trial of Yan 2001, the only trial that had a superior incidence of nausea or vomiting or both in the carboplatin arm. We performed a sensitivity analysis excluding that trial and obtained a similar estimate of effect but with lower heterogeneity (RR 0.42; 95% CI 0.31 to 0.55, I^2 = 31%). Historically, cisplatin has been associated with a higher rate of nausea and vomiting when compared with carboplatin, but, in Yan 2001, carboplatin cause more nausea or vomiting or both. There was no specific reason for this but one hypothesis is the use of carboplatin in a fixed dose (300 mg/m^2) rather than an AUC dose.

There was no significant difference in renal toxicity (RR 0.52; 95% CI 0.19 to 1.45, I^2 = 3%), skin rash (RR 3.00; 95% CI 0.13 to 69.52), alopecia (RR 1.11; 95% CI 0.73 to 1.68, I^2 = 0%), anaemia (RR 1.06; 95% CI 0.79 to 1.43, I^2 = 20%) and neutropenia (RR 0.96; 95% CI 0.85 to 1.08, I^2 = 49%) between cisplatin-based chemotherapy and carboplatin-based chemotherapy.

Subgroup analysis

When considering only trials using gemcitabine, we found a similar incidence of thrombocytopenia with significant heterogeneity (RR 1.43; 95% CI 0.63 to 3.25, I^2 = 53%). However, only two trials were included in this analysis and we could not perform a sensitivity analysis.

Subgroup analysis including trials with paclitaxel showed no difference in neutropenia (RR 0.91; 95% CI 0.73 to 1.15, I^2 = 62%). The significant heterogeneity may be explained by the fact that the two larger trials had opposite estimates of effect. After excluding only Rosell 2002, we found a similar incidence in neutropenia (RR 0.83; 95% CI 0.58 to 1.18, I^2 = 30%, 4 trials included) as well as after removing only Schiller 2002 from the analysis (RR 0.94; 95% CI 0.60 to 1.46, I^2 = 43%, 4 trials included).

Response rate (Analysis 1.5)

Response rate was evaluated in all 10 RCTs (5017 people; 3486 pooled for meta-analysis). Meta-analysis showed that cisplatin had a superior response rate when compared to carboplatin, with no significant heterogeneity among trials (RR 0.88; 95% CI 0.79 to 0.99, I^2 = 3%) (Analysis 1.5).

Subgroup analysis

Subgroup analyses according to different third-generation drugs used in combination with platin showed a superiority of cisplatin plus docetaxel over carboplatin plus docetaxel (RR 0.76; 95% CI 0.60 to 0.95) in the only trial with 814 people that used docetaxel (Fossella 2003). The response rate in five trials (1436 people) with cisplatin or carboplatin combined with paclitaxel (RR 0.89; 95% CI 0.74 to 1.07, I^2 = 0%) or in four trials (1236 people available) combined with gemcitabine (RR 0.92; 95% CI 0.73 to 1.16, I^2 = 34%) were equivalent.

Subgroup analysis (cisplatin dose)

Overall survival (Analysis 2.1)

Carboplatin versus cisplatin (40-80 mg/m^2)

Meta-analysis of five RCTs (3937 people; 2437 available for pooling) showed no statistically significant difference between carboplatin and lower dose of cisplatin (40-80 mg/m^2) in terms of overall survival (HR 0.98; 95% CI 0.41 to 2.33, I^2 = 0%) (Analysis 2.1).

Carboplatin versus cisplatin (80-100 mg/m^2)

Similarly, when we analysed four trials (2277 people; 1823 available for pooling) comparing carboplatin and higher dose of cisplatin (80-100 mg/m^2), we detected no difference in overall survival (HR 0.98; 95% CI 0.44 to 2.20, I^2 = 0%) (Analysis 2.1).

One-year survival (Analysis 2.2)

Carboplatin versus cisplatin (40 to 80 mg/m^2)

Meta-analysis of five RCTs (3937 people; 2437 available for pooling) showed no statistically significant differences between carboplatin and lower dose of cisplatin in one-year survival rate (RR 1.04; 95% CI 0.84 to 1.29, I^2 = 67%) (Analysis 2.2). Since Fossella 2003 was the only trial with superior one-year survival rate in the cisplatin arm and the only trial using docetaxel in doublet, we performed an analysis excluding this trial and obtained a higher one-year survival in the carboplatin arm without heterogeneity (RR 1.18; 95% CI 1.03 to 1.35, I^2 = 0%).

Carboplatin versus cisplatin (80 to 100 mg/m^2)

A meta-analysis of five RCTs (2403 people; 1949 available for pooling) found no statistically significant differences between carboplatin and higher dose of cisplatin in one-year survival rate (RR 0.96; 95% CI 0.85 to 1.08, I^2 = 0%) (Analysis 2.2).

Response rate (Analysis 2.3)

Carboplatin versus cisplatin (40 to 80 mg/m^2)

Meta-analysis of six RCTs (3977 people; 2150 available for pooling) showed no statistically significant differences between carboplatin and lower dose of cisplatin in response rate (RR 0.95; 95% CI 0.74 to 1.23, I^2 = 58%) (Analysis 2.3).

Carboplatin versus cisplatin (80 to 100 mg/m^2)

Similarly, we carried out a meta-analysis of five trials (2403 people and 1638 available for pooling) comparing carboplatin to higher dose cisplatin (80 to 100 mg/m^2) and found no difference in response rate (RR 0.86; 95% CI 0.74 to 1.00, I^2 = 0%) (Analysis 2.3).

Sensitivity analysis

Only published trials (Analysis 3.1; Analysis 3.2; Analysis 3.3)

We performed a sensitivity analysis excluding Ferry 2011, the only unpublished trial in this meta-analysis, to avoid potential biases

and incomplete data from grey literature (Cochrane 2007). This analysis revealed similar overall survival (HR 1.00; 95% CI 0.47 to 2.10, I^2 = 0%) (Analysis 3.1), one-year survival (RR 0.92; 95% CI 0.83 to 1.02, I^2 = 0%) (Analysis 3.2) and response rate (RR 0.83; 95% CI 0.73 to 0.94, I^2 = 0%) (Analysis 3.3).
We did not perform an analysis of adverse effects in this section because, after excluding Ferry 2011, only Mazzanti 2003 had performed this analysis using the number of events per cycle model.

Fixed-effect model (Analysis 4.1; Analysis 4.2; Analysis 4.3)

There were no significant changes in overall survival (HR 1.00; 95% CI 0.51 to 1.97) (Analysis 4.1), one-year survival rate (RR 0.98; 95% CI 0.90 to 1.06) (Analysis 4.2) or response rate (RR 0.88; 95% CI 0.79 to 0.98) (Analysis 4.3) when fixed-effect analyses were performed.

Phase III trials (Analysis 5.1; Analysis 5.2; Analysis 5.3)

When we limited the analysis to phase III trials, there were minimal changes in the results (overall survival: HR 0.99; 95% CI 0.49 to 2.02 (Analysis 5.1); one-year survival rate: RR 0.97; 95% CI 0.84 to 1.13 (Analysis 5.2); response rate: RR 0.85; 95% CI 0.72 to 1.00 (Analysis 5.3)).

DISCUSSION

Since the 1990s, many trials have been published comparing chemotherapy with best supportive care in people with advanced NSCLC and the effectiveness of platin-based chemotherapy on overall survival and control of symptoms is clear (NSCLC Collaborative Group 1995).

The modern approach for these people depends on the presence of a somatic mutation in the EGFR and in the ALK fusion oncogene. For people who have no EGFR or ALK mutations, cytotoxic chemotherapy based on a platin doublet remains the primary treatment. Furthermore, since these people are treated with a palliative intent, the current challenge is to find a treatment with greater effectiveness and a better toxicity profile.

We performed a meta-analysis of trials comparing regimens including cisplatin plus a third-generation drug versus regimens including carboplatin plus a third-generation drug. We found that cisplatin-based regimens were slightly more effective in terms of response rate, as in previous meta-analyses, but there was no significant difference in survival data (Ardizzoni 2007; Hotta 2004; Jiang 2007). This improved response rate could be attributed to one trial, which was the only trial with a significantly higher response rate for cisplatin (Fossella 2003). In this trial, docetaxel was used in both arms, even though paclitaxel and gemcitabine are generally preferred due to their better tolerability and are used in almost all modern trials.

Since only two RCTs evaluated QoL, we could not perform a meta-analysis (Fossella 2003; Rosell 2002). This was also a challenge to the authors of previous meta-analyses (Ardizzoni 2007; Hotta 2004; Jiang 2007), because different scores were used, and some questionnaires could be used only in the countries in which a translated version of the QoL tool with validation was available. Moreover, no one trial compared QoL with cisplatin and carboplatin directly.

Different criteria were applied (RECIST), Southwest Oncology Group (SWOG), WHO and ECOG criteria) to evaluate response rate. Furthermore, different doses of drugs were used in these trials and this could modify the assessment of effect.

Nowadays, the importance of histology as a predictive of response to some therapies is understood (non-epidermoid and pemetrexed; epidermoid and gemcitabine) (Scagliotti 2008). Unfortunately, we were unable to consider histology in our analysis because this criterion was not evaluated in the included trials.

In this review, carboplatin-based chemotherapy was associated with a higher incidence of neurotoxicity. However, only one trial had a significantly higher incidence of neurotoxicity in the carboplatin arm (Schiller 2002). This may be explained by the fact that participants in the carboplatin arm received 225 mg/m^2 of paclitaxel whereas participants in the cisplatin arm received only 135 mg/m^2 of paclitaxel. Since paclitaxel may cause neurotoxicity, this drug could be a confounding factor in the final analysis.

Although we did not obtain data on second-line chemotherapy, it is possible that some of included participants crossed over to another therapy when the disease progressed. The effect of such a cross-over on the results of this systematic review is unknown and might have affected survival results.

Two trials evaluated the benefit of bevacizumab, a recombinant humanised monoclonal antibody that binds vascular endothelial growth factor (VEGF), in chemotherapy for advanced NSCLC. One trial combined bevacizumab with carboplatin plus paclitaxel (Sandler 2006), while the other trial combined bevacizumab with cisplatin plus gemcitabine (Reck 2010); both showed higher overall survival, response rate and progression-free survival. On that basis, new trials are needed to investigate if there is difference between cisplatin and carboplatin when combined with bevacizumab and a third-generation drug.

Summary of main results

We obtained data on 3973 participants in 10 RCTs. These trials had at least one treatment arm with cisplatin and one treatment arm with carboplatin, both combined with paclitaxel (five trials), gemcitabine (four trials) or docetaxel (one trial).

There was no difference in overall survival (HR 1.00; 95% CI 0.51 to 1.97, I^2 = 0%) or one-year survival rate (RR 0.98; 95% CI 0.88 to 1.09, I^2 = 24%).

With grade III-IV toxicity measured by the participants, we detected a higher incidence of nausea or vomiting or both in the cisplatin arm (RR 0.46; 95% CI 0.32 to 0.67, I^2 = 53%). Carboplatin-based chemotherapy was associated with more neurotoxicity (RR 1.55; 95% CI 1.06 to 2.27, I^2 = 0%) and thrombocytopenia (RR 2.00; 95% CI 1.37 to 2.91, I^2 = 21%).

Considering the response rate in the 10 RCTs analysed, cisplatin was slightly more effective than carboplatin (RR 0.88; 95% CI 0.79 to 0.99, I^2 = 3%).

We also performed a subgroup analysis comparing carboplatin with different doses of cisplatin: 'lower dose' (40 to 80 mg/m^2) and 'higher dose' (80 to 100 mg/m^2). We found no statistically significant difference in terms of overall survival, 1-year survival rate or response rate between carboplatin and both doses of cisplatin.

We could not perform an analysis of QoL in our review, because data were provided by only two trials (Fossella 2003; Rosell 2002).

Overall completeness and applicability of evidence

With regards to external validation, the doses of drugs were variable among analysed trials and that should be considered while selecting the treatment.

It is also important to note that the trials analysed in our review did not take into account the status of the EGFR and ALK mutations, which are critical in deciding the initial approach in advanced disease.

Quality of the evidence

The categorisation of the quality of the evidence (into high, moderate, low or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest.

Our review included 10 RCTs. Since none of these trials described allocation concealment and blinding process adequately, we considered available data to have moderate quality of evidence for response rate, one-year survival rate and overall survival. However, because different doses of drugs were used and some adverse effects were omitted from analysis in the original trials, we also considered data to have moderate quality of evidence for adverse effects and note that this information has to be considered cautiously.

Potential biases in the review process

We performed an electronic search of the main databases and extended our search to include meetings of the American Society of Clinical Oncology. We found one unpublished trial with our search strategy (Ferry 2011), but it is not known whether there are other reports of unpublished trials in different languages or presented at different meetings.

We found two Chinese trials (Cai 2002; Yan 2001). For Cai 2002, we could not obtain data for overall survival or one-year survival rate and for Yan 2001 there was no information about overall survival. Since both trials recruited a small number of participants, we concluded that they did not cause a significant bias in survival analysis.

We identified no more significant potential biases.

Agreements and disagreements with other studies or reviews

In 2004, Hotta et al published a meta-analysis that included eight trials comparing doublets of cisplatin or carboplatin plus another drug (Hotta 2004). Only five of these trials were included in our analysis because the other three studies used older agents combined with platin. The study author had found results that were comparable to those presented in this review: cisplatin was related to higher response rate but this superiority did not translate into survival benefit. However, a subset analysis of trials consisting of a platin plus a third-generation drug found superior survival in the cisplatin arm.

Jiang 2007 and Ardizzoni 2007 performed two meta-analyses that revealed benefits of cisplatin in response rate and equivalent survival when compared to carboplatin. In a subgroup analyses containing only doublets of platin plus a third-generation drug, Ardizzoni et al yielded a superior HR for mortality in the carboplatin arm.

AUTHORS' CONCLUSIONS

Implications for practice

Our findings suggest several implications for practice. In our meta-analysis, carboplatin and cisplatin had equivalent overall survival and one-year survival. As with others authors, we found a higher response rate in the cisplatin arm, but this result appeared to be mainly due to one trial that combined cisplatin with docetaxel. When combined with gemcitabine or paclitaxel, carboplatin had the same response rate.

With respect to toxicity, carboplatin caused more thrombocytopenia and cisplatin caused more gastrointestinal toxicity, as found in previous meta-analyses. Since quality of life (QoL) was not directly compared between cisplatin and carboplatin treatment, the approach for these people has to be individualised.

Implications for research

As previous reviewers have found, we could not perform a meta-analysis of QoL data. Many trials have evaluated QoL and the European Organisation for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire Core 30 (EORTC QLC-C30) score has been the most popular score in some of these trials. It is crucial to consider QoL in future RCTs.

Finally, although our review has shown that carboplatin has at least equivalent efficacy when compared with cisplatin, it is important to define the role of both combined with a third-generation drug plus new drugs, such as monoclonal antibodies.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Cai 2002

Methods	Inclusion: eligible participants had to meet the following criteria: pathology- and cytology-confirmed stage IIIB or IV stage NSCLC; Karnofsky score $\geq$ 40; expected life span > 3 months; adequate haematological, hepatic and renal function Exclusion: there were no exclusion criteria specified for this study
Participants	20 people in arm I and 20 people in treatment arm iv
Interventions	Arm I: gemcitabine (1000 mg/m^2) iv on day 1 and 8 and carboplatin (AUC 4-6 mg/mL X minutes) on day 1, every 3 weeks Arm II: gemcitabine (1000 mg/m^2) iv on day 1 and 8 and cisplatin (30-40 mg/m^2) on days 1-3, every 3 weeks
Outcomes	Primary outcome: response rate Secondary outcome: toxicity
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were stratified according to staging, sex and histology
Allocation concealment (selection bias)	Unclear risk	Not clearly reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information about blinding of the assessor
Incomplete outcome data (attrition bias) All outcomes	Low risk	There was no evidence of incomplete outcome
Selective reporting (reporting bias)	Unclear risk	Incidence of overall survival and 1-year survival rate were not reported. The authors had not specified which efficacy outcomes would be analysed, so we judged this trial with unclear risk of selective reporting bias

Cai 2002 (*Continued*)

Other bias	High risk	Participants received carboplatin AUC 4-6 mg/mL X minute and that was inferior to the doses in almost all others trials (AUC 6 mg/mL X minute). On addition, analysis should be considered exploratory because this is a phase II trial

Chen 2006

Methods	Inclusion: eligible participants had to meet following criteria: cytological or histological diagnosis of stage IIIb with malignant effusion, or stage IV NSCLC; 70 years or older; no prior chemotherapy or immunotherapy; PS of 0 to 2 on the WHO scale; bi-dimensionally measurable disease; adequate bone marrow reserve Exclusion: participants were ineligible if they had: signs or symptoms of brain metastases; inadequate liver function (serum bilirubin > 1.5 times and alanine aminotransferase/ aspartate transaminase > 3 times upper limit of normal); inadequate renal function (serum creatinine > 1.5 times upper limit of normal)
Participants	Arm I: 40 people Arm II: 41 people
Interventions	Arm I: paclitaxel (160 mg/m^2) iv over 3 hours on day 1 and carboplatin (AUC 6 mg/mL X minutes) iv over 1 hour on day 1, every 3 weeks Arm II: paclitaxel (160 mg/m^2) iv over 3 hours on day 1 and cisplatin (60 mg/m^2) iv over 1 hour on day 1, every 3 weeks
Outcomes	Primary outcome: response rate Secondary outcomes: time to progression; toxicity; overall survival
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants were stratified according staging and PS

Chen 2006 (*Continued*)

Allocation concealment (selection bias)	Low risk	Participants were randomised into the paclitaxel plus carboplatin or paclitaxel plus cisplatin treatment arm by an outside centre not involved in the study
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information about blinding process
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence of incomplete outcome
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting bias
Other bias	High risk	Phase II trial and a study of elderly people so could be associated with higher response rate

Ferry 2011

Methods	Inclusion: eligible participants met criteria for histologically confirmed NSCLC, PS 0-2, life expectancy >12 weeks, stage IIIB/IV disease and had a GFR of > 60 mL/minute calculated using the Wright equation Participant compliance and geographic proximity that allowed adequate follow-up was required Exclusion: participants were ineligible if they had: mixed histologies of small cell lung cancer and NSCLC; clinically apparent brain metastases; had prior chemotherapy, including neoadjuvant or adjuvant chemotherapy; other concurrent cytotoxic chemotherapy; had prior radiotherapy (prior surgical resection for NSCLC allowed); other malignancy that would preclude study treatment or study comparisons; pre-existing neuropathy grade > 2; psychiatric disorder making reliable informed consent impossible or that might prevent completion of treatment or follow-up; evidence of severe or uncontrolled systemic disease, significant clinical disorder or laboratory finding that would preclude study participation
Participants	Arm I: 456 people Arm II: 454 people Arm III: 453 people
Interventions	Arm I (GC80): gemcitabine (1250 mg/m^2) iv over 30 minutes on days 1 and 8 and cisplatin (80 mg/m^2) iv over 1 hour on day 1 (total time of infusion: 6 hours), every 3 weeks Arm II (GC50): gemcitabine (1250 mg/m^2) iv over 30 minutes on days 1 and 8 and

	cisplatin (50 mg/m^2) iv over 1 hour on day 1 (total time of infusion: 6 hours), every 3 weeks Arm III (GCb): gemcitabine (1250 mg/m^2) iv over 30 minutes on days 1 and 8 and carboplatin (AUC 6 mg/mL X minutes) iv over 1 hour on day 1 (total time of infusion: 1.5 hours), every 3 weeks
Outcomes	Primary outcome: overall survival Secondary outcomes: symptom control and QoL as measured by the EORTC QLQ-C30 and QoL-LC13 together with EuroQol-5 domain questionnaire; treatment response as measured by RECIST criteria; dose intensity of chemotherapy; ratio of treatment courses given as inpatient vs. outpatient; toxicity as measured by CTCAE v3.0
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation was stratified by PS (0, 1 and 2), stage (IIIB and IV) and centre to ensure that there is a balance between treatments within the strata defined by these key prognostic factors
Allocation concealment (selection bias)	Low risk	Random assignment to treatment was conducted by a computer, based at the BTOG2 Study Office
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Since times to infusion were different (extra fluid administration in cisplatin arm), participants were not blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Response rate could not be evaluated in several people (160 people in GC80, 152 people in GC50 and 151 people in GCb) and that could be affect the final analysis of this endpoint
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting bias
Other bias	High risk	It is important to note that the Wright formula was used for calculation of creatinine clearance, which usually results in about 10% higher doses of carboplatin than with the use of the Cockcroft-Gault formula

Fossella 2003

Methods	Inclusion: participants with histological or cytological diagnosis of locally advanced or recurrent (stage IIIB) or metastatic (stage IV) NSCLC who had met the following criteria: $\geq$ 18 years of age; Karnofsky PS $\geq$ 70; at least 1 measurable or assessable lesion; adequate bone marrow, hepatic and renal function Exclusion: participants were ineligible if they had: prior treatment with a biological response modifier or chemotherapeutic agent; previous or concurrent malignant disease (except cone-biopsied carcinoma in-situ of the cervix or adequately treated basal or squamous cell carcinoma of the skin); history of brain or leptomeningeal metastases (except if adequately treated and radiologically stable for at least 4 weeks); peripheral neuropathy of National Cancer Institute common toxicity criteria grade II or above; major surgery within 2 weeks of study entry; radiotherapy within 4 weeks of study entry; other serious concomitant illness
Participants	Arm I: 408 people Arm II: 406 people
Interventions	Arm I: docetaxel (75 mg/m^2) iv over 1 hour on day 1 and cisplatin (75 mg/m^2) iv over 1 hour on day 1, every 3 weeks Arm II: docetaxel (75 mg/m^2) iv over 1 hour on day 1 and carboplatin (AUC 6 mg/mL X minutes) iv on day 1, every 3 weeks Arm III (vinorelbine and cisplatin) was not be used in analysis
Outcomes	Primary outcome: overall survival Secondary outcomes: response rate; toxicity; QoL (LCSS and the global QoL scale (EuroQol)
Notes	Arm III (vinorelbine and cisplatin) was not be used in analysis Arm III: vinorelbine (25 mg/m^2) iv on day 1,8,15 and 22, plus cisplatin (100 mg/m^2) iv on day 1, every 4 weeks

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Before random assignment to treatment, participants were stratified according to disease stage (IIIB vs. IV) and geographic region (North America vs. South Africa, New Zealand and Australia vs. Europe, Lebanon and Israel vs. South America)

Fossella 2003 (*Continued*)

Allocation concealment (selection bias)	Low risk	Random assignment to treatment was conducted by an independent research organisation using computer-generated lists
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information about blinding process
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of the 1218 participants, 15 did not receive treatment (9 were ineligible, 4 withdrew consent, and 2 died of malignant disease before the first drug infusion) and were excluded from the safety analysis
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting bias
Other bias	Low risk	No other bias

Mazzanti 2003

Methods	Inclusion: eligible participants had to meet the following criteria: histologically or cytologically confirmed NSCLC; stage IIIB or IV NSCLC (according to the American Joint Committee on Cancer staging system, 1992); PS 0-2 on the ECOG scale; aged 18-75 years; at least 1 measurable lesion; life expectancy > 12 weeks; adequate bone marrow, hepatic, cardiac and renal function. Participants who had received previous radiotherapy were included if their assessable disease was outside of the radiation field Exclusion: participants were ineligible if they had: symptomatic central nervous system metastases; second primary malignancy; serious systemic disorders
Participants	Arm I: 58 people Arm II: 62 people
Interventions	Arm I: gemcitabine (1200 mg/m^2) iv over 30 minutes on days 1 and 8 and cisplatin (80 mg/m^2) iv over 45 minutes on day 2, every 3 weeks Arm II: gemcitabine (1200 mg/m^2) iv over 30 minutes on days 1 and 8 and carboplatin (AUC 5 mg/mL X minutes) iv over 1 hour on day 2, every 3 weeks
Outcomes	Primary outcome: response rate Secondary outcomes: duration of response; toxicity; time to progression; overall survival;

	1-year survival	
Notes	-	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The randomisation algorithm, based on the Pocock and Simon method (Pocock 1975), included ECOG PS (0/1 vs. 2) and disease stage (IIIB vs. IV) as stratification factors
Allocation concealment (selection bias)	Low risk	Eligible participants were randomised to 1 of 2 arms, GCb or GC, using a concealed list of random numbers. The randomisation algorithm was based on the Pocock and Simon method
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information about blinding process
Incomplete outcome data (attrition bias) All outcomes	High risk	5 of the participants were randomly assigned to the GC arm, but were ineligible to receive treatment (3 with an ECOG PS of 3 at baseline, 1 pretreated with chemotherapy and 1 affected by a serious cardiac disease)
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting bias
Other bias	High risk	The trial was planned as a randomised phase II study to obtain information for further development in a controlled randomised phase III setting. Thus, the findings obtained from the treatment-arm comparisons of this phase II study should be considered to be exploratory

Rosell 2002

Methods	Inclusion: eligible participants were required to meet all of the following criteria: histological or cytological diagnosis of NSCLC; stage IIIB or IV; ≥ 18 years; PS of 0, 1 or 2 in ECOG scale with a predicted life expectancy of at least 12 weeks; no prior chemotherapy; any radiotherapy completed > 3 weeks before enrolment and the person recovered from any adverse effects; adequate baseline bone marrow, liver and kidney functions; participants had to be able to understand the EORTC QLQ-C30 Exclusion: participants were ineligible if they had: history of prior or concomitant malignancy (except for curatively treated non-melanoma skin cancer or carcinoma in situ of the cervix or other cancer for which the participant had been disease-free for 5 years); active or uncontrolled infection; symptomatic brain metastases; pregnancy, lactation or refusal to use contraception; peripheral neuropathy; uncontrolled diabetes mellitus; significant cardiovascular disease or other serious medical condition
Participants	Arm I; 309 people Arm II: 309 people
Interventions	Arm I: paclitaxel (200 mg/m^2) iv over 3 hours and cisplatin (80 mg/m^2) iv over 30 minutes every 3 weeks Arm II: paclitaxel (200 mg/m^2) iv over 3 hours and carboplatin (AUC 6 mg/mL X minutes) iv over 30 minutes every 3 weeks
Outcomes	Primary outcome: response rate, according to WHO criteria Secondary outcomes: median survival; progression-free survival; toxicity; QoL measured by the EORTC QLC-C30 and QoL-LC13
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	This procedure minimised imbalance in treatment assignment with respect to the following parameters: centre, PS (ECOG 0 or 1 vs. 2), disease stage (IIIB vs. IV) and histology (squamous cell vs. non-squamous cell carcinoma)
Allocation concealment (selection bias)	Low risk	Randomisation was performed centrally by Bristol-Myers Squibb Inc., Waterloo, Belgium, using a dynamic balancing algorithm of the Pocock-Simon type

Rosell 2002 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information about blinding process
Incomplete outcome data (attrition bias) All outcomes	Low risk	10 (2%) people never received a study drug (3 in carboplatin arm and 7 in cisplatin arm). We considered it unlikely that this could result in a significant bias
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting bias
Other bias	High risk	The only bias was that dose reduction of carboplatin was necessary for 96 of the 279 (34%) evaluable participants; this reduction occurred mainly during course 1, due to a miscalculation of AUC. The mean AUC for these 96 participants was 4.9 mg/mL X minutes

Schiller 2002

Methods	Inclusion: eligible participants had confirmed NSCLC, measurable or non-measurable, stage IIIB/IV or recurrent disease. Initially people with an ECOG PS 0-2 were eligible for enrolment, but after 66 people with PS of 2 had been enrolled, the study design was amended to exclude them because of the high rate of serious adverse events Eligible participants had also met the following criteria: aged $\geq$ 18 years; adequate haematological function (as indicated by a white cell count of at least 4000/mm^3 and a platelet count of at least 100,000/mm^3); hepatic function (as indicated by a bilirubin level that did not exceed 1.5 mg/dL (25.6 μmol/L); renal function (as indicated by a creatinine level that did not exceed 1.5 mg/dL (132.6 μmol/L); people with stable brain metastases were eligible; radiotherapy at symptomatic sites was permitted Exclusion: 52 people were ineligible because of following reasons (number of people): incorrect stage (18); histological findings that were inconsistent with the diagnosis of NSCLC (7); prior chemotherapy (5); inadequate information on laboratory tests, x-rays, or PS for documentation of eligibility (5); diagnosis of a second cancer (3); treatment that was not included in the protocol (3); coexisting conditions (3); poor PS (3); progression of disease before treatment (2); withdrawal of consent (1); other (2)
Participants	Arm I: 299 people Arm IV: 303 people
Interventions	Arm I: paclitaxel 135 mg/m^2 over 24-hour period on day 1 and cisplatin, 75 mg/m^2 on day 2 (3-week cycle) Arm IV: paclitaxel 225 mg/m^2 over 3-hour period on day 1 and carboplatin, AUC 6.0 mg/mL x minute on day 1 (3-week cycle)

Schiller 2002 (*Continued*)

Outcomes	Primary outcome: overall survival Secondary outcomes: overall response rate; median time to progression; survival rate at 1 and 2 years; toxicity
Notes	Arms II and III were not used in analysis. Arm II: gemcitabine (1000 mg/m^2) on days 1, 8, and 15 and cisplatin (100 mg/m^2) on day 1, every 4 weeks Arm III: docetaxel (75 mg/m^2) on day 1 and cisplatin (75 mg/m^2) on day 1, every 3 weeks

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were stratified according to ECOG PS (0 or 1 vs. 2, with higher scores indicating greater impairment), weight loss in the previous 6 months (< 5% vs. > 5%), stage of disease (IIIB vs. IV or recurrent disease), and the presence or absence of brain metastases
Allocation concealment (selection bias)	Low risk	Participants were allocated using a computer-generated random list into 1 of 4 arms
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information about blinding process
Incomplete outcome data (attrition bias) All outcomes	High risk	"After 66 patients with a performance status of 2 had been enrolled, the study design was amended to include only patients with a performance status of 0 or 1 because of the high rate of serious adverse events in the patients with a performance status of 2" In final analysis, the authors considered only people with a PS of 0 or 1
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting bias
Other bias	Low risk	No evidence of other bias

Sweeney 2001

Methods	Inclusion: Eligible participants had to meet the following criteria: Confirmed stage IIIB (pleural effusion) or stage IV NSCLC; ECOG PS 2; no prior chemotherapy; adequate haematological, hepatic and renal function Participants with clinically stable brain metastases managed by surgery or radiotherapy, or both were eligible Exclusion: participants were ineligible if they had: pregnancy or were breastfeeding; other active malignancy; clinically significant neuropathy by history or physical examination; prior radiotherapy to site of indicator lesion unless subsequent disease progression; small cell anaplastic elements; diagnosis based on sputum cytology alone; prior treatment with a biological response modifier or chemotherapeutic agent; serious active uncontrolled infection; significant cardiovascular disease or other serious medical condition
Participants	Arm I: 18 people Arm IV: 15 people
Interventions	Arm I: paclitaxel (135 mg/m^2) iv over 24 hours on day 1 and cisplatin (75 mg/m^2) on day 2, every 3 weeks Arm IV: paclitaxel (225 mg/m^2) over 3 hours on day 1 and carboplatin (AUC 6 mg/mL X minutes) on day 1, every 3 weeks
Outcomes	Primary outcome: toxicity and adverse events Secondary outcomes: response rate; time to progression; overall survival
Notes	Arms II and III were not used in analysis. Arm II: gemcitabine (1 g/m^2) on days 1, 8 and 15 and cisplatin (100 mg/m^2) on day 1, every 4 weeks Arm III: docetaxel (75 mg/m^2) on day 1 and cisplatin (75 mg/m^2) on day 1, every 3 weeks

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants are stratified by weight loss within the past 6 months, disease stage and presence of brain metastases
Allocation concealment (selection bias)	Low risk	Participants were allocated using a computer-generated random list into 1 of 4 arms

Sweeney 2001 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information about blinding process
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence of incomplete outcome data
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting bias
Other bias	High risk	This report represents a final analysis of a subgroup of people with a PS of 2 who seem to have a poorer prognosis compared with people with PS 0 or 1

Yan 2001

Methods	Inclusion: eligible participants had to meet the following criteria: pathology- and cytology-confirmed locally advanced or metastatic NSCLC (stage IIIA-IV); Karnofsky score $\geq$ 60; life expectancy > 3 months; adequate haematological, hepatic and renal function Exclusion: no exclusion criteria specified for this study
Participants	Arm I: 61 people Arm II: 65 people
Interventions	Arm I: paclitaxel (175 mg/m^2) iv on day 1 and carboplatin (350 mg/m^2) on day 1, every 4 weeks Arm II: paclitaxel (175 mg/m^2) iv on days 1 and 8 and cisplatin (100 mg/m^2) on day 1, every 4 weeks
Outcomes	Primary outcome: response rate; toxicity Secondary outcomes: 1-year survival; overall survival
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants were stratified according to sex and staging

Yan 2001 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	No clear description about randomisation in the publication
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information about blinding process
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence of incomplete outcome data
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting bias
Other bias	High risk	The dose of carboplatin was 350 mg/m^2 iv on day 1, which is different from doses used in almost all others trials (AUC 4-6 mg/mL X minutes)

Zatloukal 2003

Methods	Inclusion: chemo-naive participants with histological or cytological diagnosis of stage IIIb or IV NSCLC who were not eligible for curative surgery or radiotherapy were enrolled. Participants had to meet following criteria: aged 18-75 years; bi-dimensionally measurable lesions at least 1 cm by 1 cm (or 2 cm by 2 cm by physical examination); estimated life expectancy of at least 12 weeks; prior radiotherapy (up to 60 Gy) was permitted as long as the irradiated area was not the only source of measurable disease; Karnofsky PS of $\geq$ 70; adequate bone marrow reserve Exclusion: participants were ineligible if they had: active infection; symptomatic central nervous system metastases; pregnancy; second primary malignancy; serious concomitant systemic disorders incompatible with the study; inadequate liver or renal function
Participants	Arm I: 87 people Arm II: 89 people
Interventions	Arm I: gemcitabine (1200 mg/m^2) iv over 30 minutes on days 1 and 8 and cisplatin (80 mg/m^2) iv on day 1 Arm II: gemcitabine (1200 mg/m^2) iv over 30 minutes and carboplatin (AUC 5 mg/mL X minutes) iv on day 1 2 weeks of treatment followed by 1 week of rest, a 21-day period, defined a cycle of therapy for both arms

Zatloukal 2003 (*Continued*)

Outcomes	Primary outcome: toxicity Secondary outcomes: response rate; duration of response; time to progressive disease; overall survival	
Notes	-	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation was stratified by 4 factors: gender (male/female), disease stage (stage IIIb/stage IV), PS ($\leq$ 80 and > 80) and investigational site (1 stratum per centre)
Allocation concealment (selection bias)	Low risk	Participants were balanced with respect to study treatment in each stratum and for each factor using the algorithm described by Pocock and Simon
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information about blinding process
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence of incomplete outcome data
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting bias
Other bias	Low risk	No evidence of other bias

AUC: area under the curve; BTOG2: British Thoracic Oncology Group Trial; CTCAE: common terminology criteria for adverse events; ECOG: Eastern Cooperative Oncology Group; EORTC: European Organisation for Research and Treatment of Cancer; GC: gemcitabine plus cisplatin; GC80: gemcitabine plus cisplatin (80 mg/m^2); GC50: gemcitabine plus cisplatin (50 mg/m^2); GCb: gemcitabine plus carboplatin; GFR: glomerular filtration rate; iv: intravenous; LCSS: Lung Cancer Symptom Scale; NSCLC: non-small cell lung cancer; PS: performance status; QLQ-C30: Quality of Life Questionnaire Core 30 Items; QoL: quality of life; QoL-LC13: Quality of Life Lung Cancer supplement 13; RECIST: Response Evaluation Criteria in Solid Tumors; WHO: World Health Organization.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Belani 2001	Data from this paper were included in the Fossella 2003 study.
Belani 2002	Data from this paper were included in the Fossella 2003 study.
Belani 2006	Data from this paper were included in the Fossella 2003 study.
Fossella 2001	Data from this paper were included in the Fossella 2003 study.
Gatzemeier 1999	Data from this paper were included in the Rosell 2002 study.
Macha 1998	Data from this paper were included in the Rosell 2002 study.
Mazzanti 2000	Data from this paper were included in the Mazzanti 2003 study.
Mazzanti 2001	Data from this paper were included in the Mazzanti 2003 study.
Novakova 2002	Data from this paper were included in the Mazzanti 2003 study.
Ramlau 2007	Data from this paper were included in the Fossella 2003 study.
Rodriguez 2001	Data from this paper were the preliminary results of the Fossella 2003 study.

All of the following publications are among included trials. However, they had been found in more than one database:
Zatloukal 2003 has been found in Pubmed, Cochrane and EMBASE database and we excluded two of them.
Chen 2006 has been found in Pubmed and Cochrane database and we excluded one of them.
Fossella 2003 has been found in Pubmed and Cochrane database and we excluded one of them.
Cai 2002 has been found in Pubmed and Cochrane database and we excluded one of them.
Yan 2001 has been found in Pubmed and Cochrane database and we excluded one of them.
Schiller 2002 has been found in Pubmed and Cochrane database and we excluded one of them.
Rosell 2002 has been found in Pubmed and EMBASE database and we excluded one of them.

DATA AND ANALYSES

Comparison 1. Carboplatin-based versus cisplatin-based chemotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	8	3807	Hazard Ratio (Random, 95% CI)	1.00 [0.51, 1.97]
1.1 Carboplatin vs. cisplatin plus gemcitabine	3	1659	Hazard Ratio (Random, 95% CI)	0.99 [0.34, 2.90]
1.2 Carboplatin vs. cisplatin plus paclitaxel	4	1334	Hazard Ratio (Random, 95% CI)	1.00 [0.37, 2.73]
1.3 Carboplatin vs. cisplatin plus docetaxel	1	814	Hazard Ratio (Random, 95% CI)	1.01 [0.16, 6.37]
2 1-year survival rate	9	3933	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.88, 1.09]
2.1 Carboplatin vs. cisplatin plus gemcitabine	3	1659	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.97, 1.26]
2.2 Carboplatin vs. cisplatin plus paclitaxel	5	1460	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.84, 1.12]
2.3 Carboplatin vs. cisplatin plus docetaxel	1	814	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.70, 0.97]
3 Grade III or IV toxicity by cycle	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Nausea, vomiting or both	2	4817	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.48, 1.02]
3.2 Renal toxicity	1	533	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.99]
3.3 Neurotoxicity	2	4817	Risk Ratio (M-H, Random, 95% CI)	1.85 [0.40, 8.61]
3.4 Skin rash	1	4284	Risk Ratio (M-H, Random, 95% CI)	1.97 [0.57, 6.80]
3.5 Alopecia	1	4284	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.06, 4.40]
3.6 Anaemia	2	4817	Risk Ratio (M-H, Random, 95% CI)	3.93 [1.83, 8.42]
3.7 Neutropenia	2	4817	Risk Ratio (M-H, Random, 95% CI)	2.31 [0.77, 6.95]
4 Grade III or IV toxicity by participant	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Nausea, vomiting or both	7	2422	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.32, 0.67]
4.2 Renal toxicity	2	1201	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.19, 1.45]
4.3 Neurotoxicity	5	1489	Risk Ratio (M-H, Random, 95% CI)	1.55 [1.06, 2.27]
4.4 Skin rash	1	40	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.13, 69.52]
4.5 Alopecia	2	300	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.73, 1.68]
4.6 Anaemia	8	2462	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.79, 1.43]
4.7 Thrombocytopenia	8	2462	Risk Ratio (M-H, Random, 95% CI)	2.00 [1.37, 2.91]
4.8 Neutropenia	8	2462	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.85, 1.08]
5 Response rate	10	3486	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.79, 0.99]
5.1 Carboplatin vs. cisplatin plus gemcitabine	4	1236	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.73, 1.16]
5.2 Carboplatin vs. cisplatin plus paclitaxel	5	1436	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.74, 1.07]
5.3 Carboplatin vs. cisplatin plus docetaxel	1	814	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.60, 0.95]

Comparison 2. Subgroup analysis (cisplatin dose: 40 to 80 mg/m^2 versus 80 to 100 mg/m^2)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	8		Hazard Ratio (Random, 95% CI)	Subtotals only
1.1 40-80 mg/m^2	5	2437	Hazard Ratio (Random, 95% CI)	0.98 [0.41, 2.33]
1.2 80-100 mg/m^2	4	1823	Hazard Ratio (Random, 95% CI)	0.98 [0.44, 2.20]
2 1-year survival rate	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 40-80 mg/m^2	5	2437	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.84, 1.29]
2.2 80-100 mg/m^2	5	1949	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.85, 1.08]
3 Response rate	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 40-80 mg/m^2	6	2150	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.74, 1.23]
3.2 80-100 mg/m^2	5	1638	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.74, 1.00]

Comparison 3. Sensitivity analysis (only published trials)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	7	2444	Hazard Ratio (Random, 95% CI)	1.00 [0.47, 2.10]
2 1-year survival rate	8	2570	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.83, 1.02]
3 Response rate	9	2586	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.73, 0.94]

Comparison 4. Sensitivity analysis (fixed-effect model)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	8	3807	Hazard Ratio (Fixed, 95% CI)	1.00 [0.51, 1.97]
2 1-year survival rate	9	3933	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.90, 1.06]
3 Response rate	10	3486	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.79, 0.98]

Comparison 5. Sensitivity analysis (phase III trials)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	5	3573	Hazard Ratio (Random, 95% CI)	0.99 [0.49, 2.02]
2 1-year survival rate	5	3573	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.84, 1.13]
3 Response rate	5	3086	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.72, 1.00]

Analysis 1.1. Comparison 1 Carboplatin-based versus cisplatin-based chemotherapy, Outcome 1 Overall survival.

Review: Cisplatin versus carboplatin in combination with third-generation drugs for advanced non-small cell lung cancer

Comparison: 1 Carboplatin-based versus cisplatin-based chemotherapy

Outcome: 1 Overall survival

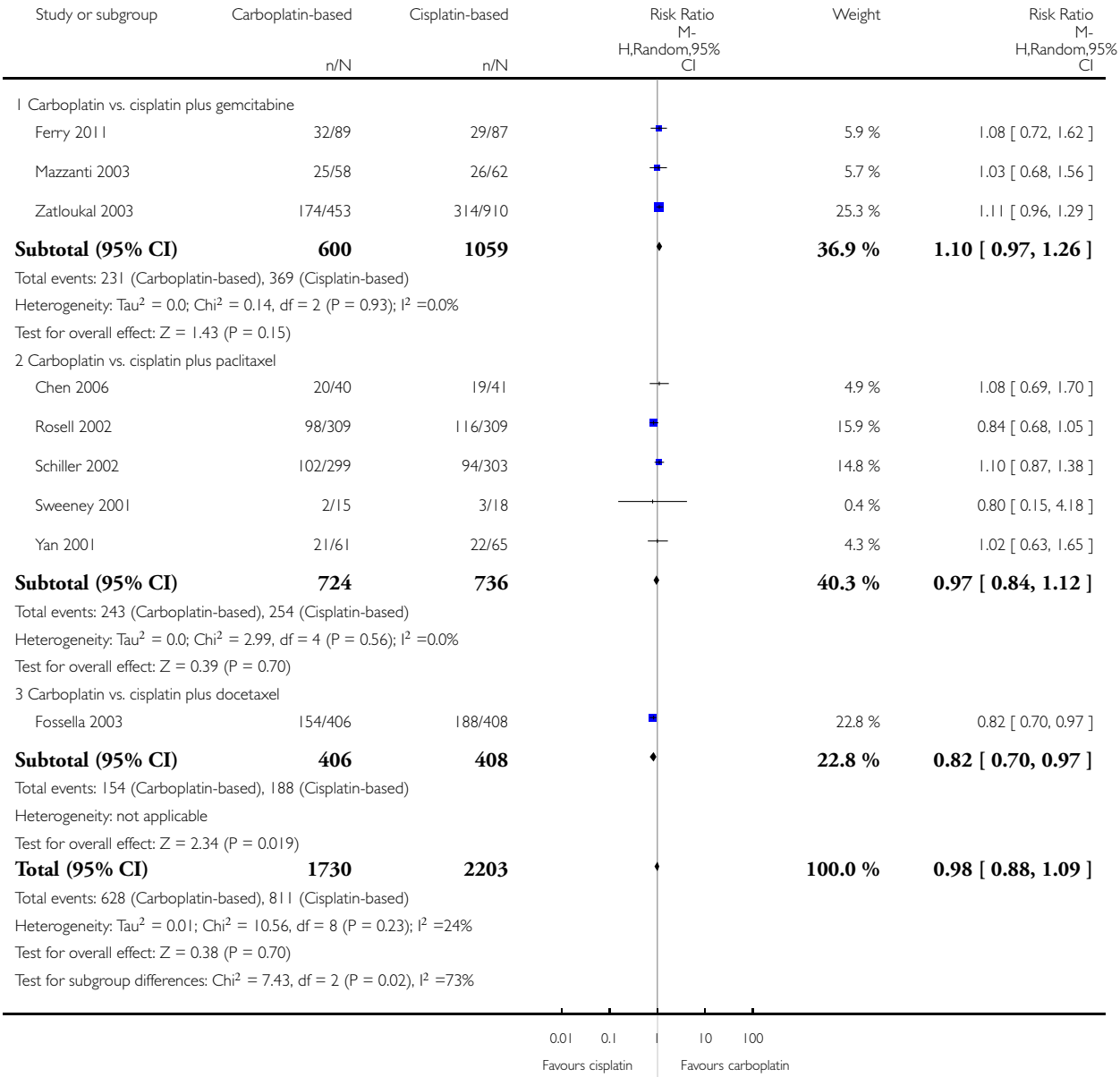
Study or subgroup	Carboplatin-based N	Cisplatin-based N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Weight	Hazard Ratio IV,Random,95% CI
1 Carboplatin vs. cisplatin plus gemcitabine						
Ferry 2011	89	87	0.008 (0.86)		16.3 %	1.01 [0.19, 5.44]
Mazzanti 2003	58	62	0.11 (1.25)		7.7 %	1.12 [0.10, 12.94]
Zatloukal 2003	453	910	-0.08 (0.86)		16.3 %	0.92 [0.17, 4.98]
Subtotal (95% CI)					**40.3 %**	**0.99 [0.34, 2.90]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.02$, df = 2 (P = 0.99); $I^2 = 0.0\%$						
Test for overall effect: Z = 0.01 (P = 0.99)						
2 Carboplatin vs. cisplatin plus paclitaxel						
Chen 2006	40	41	-0.16 (3.67)		0.9 %	0.85 [0.00, 1133.50]
Rosell 2002	309	309	-0.09 (0.91)		14.6 %	0.91 [0.15, 5.44]
Schiller 2002	299	303	0.05 (0.63)		30.4 %	1.05 [0.31, 3.61]
Sweeney 2001	15	18	-0.34 (7.85)		0.2 %	0.71 [0.00, 3421936.85]
Subtotal (95% CI)					**46.0 %**	**1.00 [0.37, 2.73]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.02$, df = 3 (P = 1.00); $I^2 = 0.0\%$						
Test for overall effect: Z = 0.00 (P = 1.0)						
3 Carboplatin vs. cisplatin plus docetaxel						
Fossella 2003	406	408	0.01 (0.94)		13.6 %	1.01 [0.16, 6.37]
Subtotal (95% CI)					**13.6 %**	**1.01 [0.16, 6.37]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.01 (P = 0.99)						
Total (95% CI)					**100.0 %**	**1.00 [0.51, 1.97]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.04$, df = 7 (P = 1.00); $I^2 = 0.0\%$						
Test for overall effect: Z = 0.01 (P = 1.0)						
Test for subgroup differences: $Chi^2 = 0.00$, df = 2 (P = 1.00), $I^2 = 0.0\%$						

Analysis 1.2. Comparison 1 Carboplatin-based versus cisplatin-based chemotherapy, Outcome 2 1-year survival rate.

Review: Cisplatin versus carboplatin in combination with third-generation drugs for advanced non-small cell lung cancer

Comparison: 1 Carboplatin-based versus cisplatin-based chemotherapy

Outcome: 2 1-year survival rate

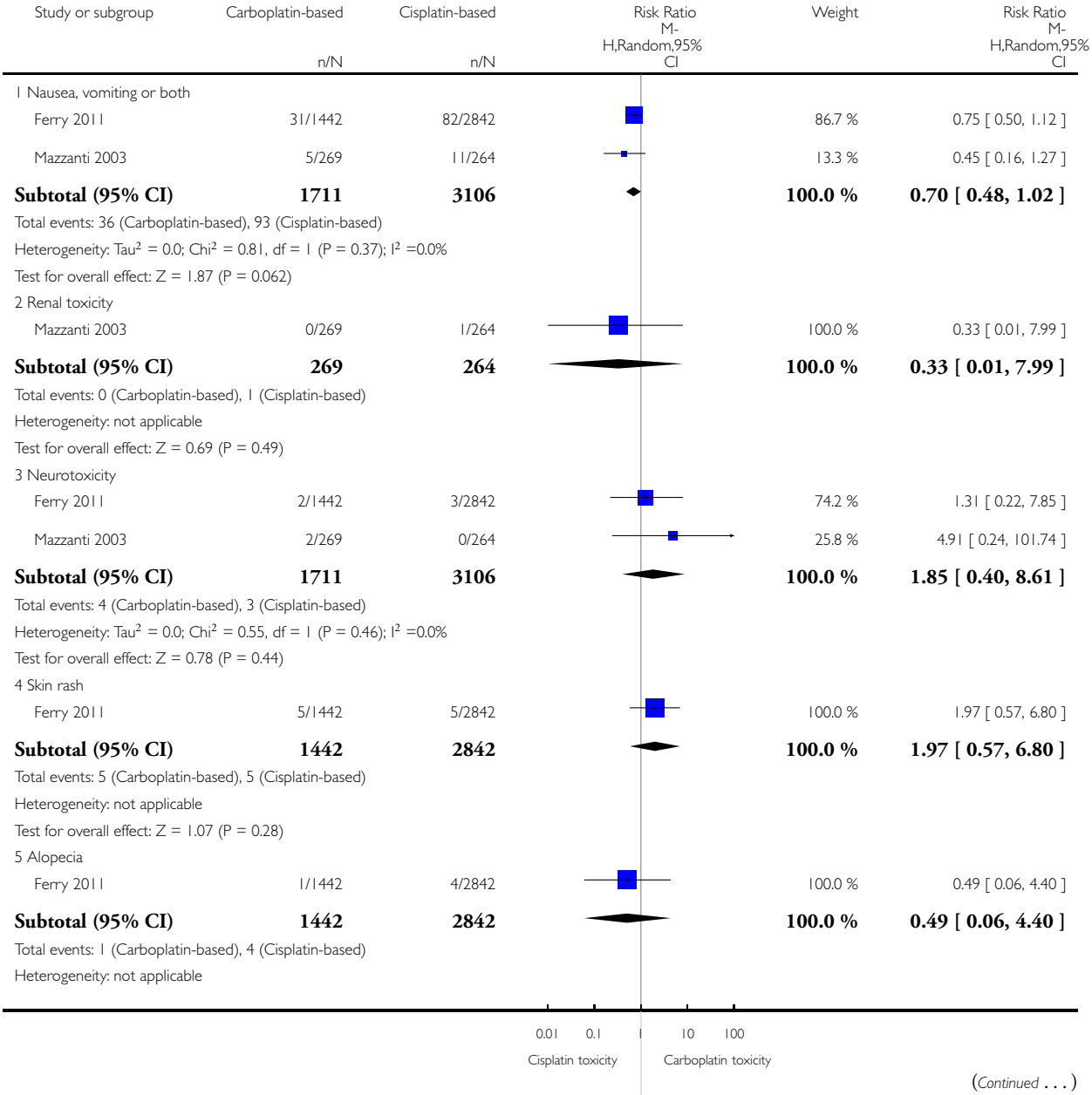


Analysis 1.3. Comparison 1 Carboplatin-based versus cisplatin-based chemotherapy, Outcome 3 Grade III or IV toxicity by cycle.

Review: Cisplatin versus carboplatin in combination with third-generation drugs for advanced non-small cell lung cancer

Comparison: 1 Carboplatin-based versus cisplatin-based chemotherapy

Outcome: 3 Grade III or IV toxicity by cycle



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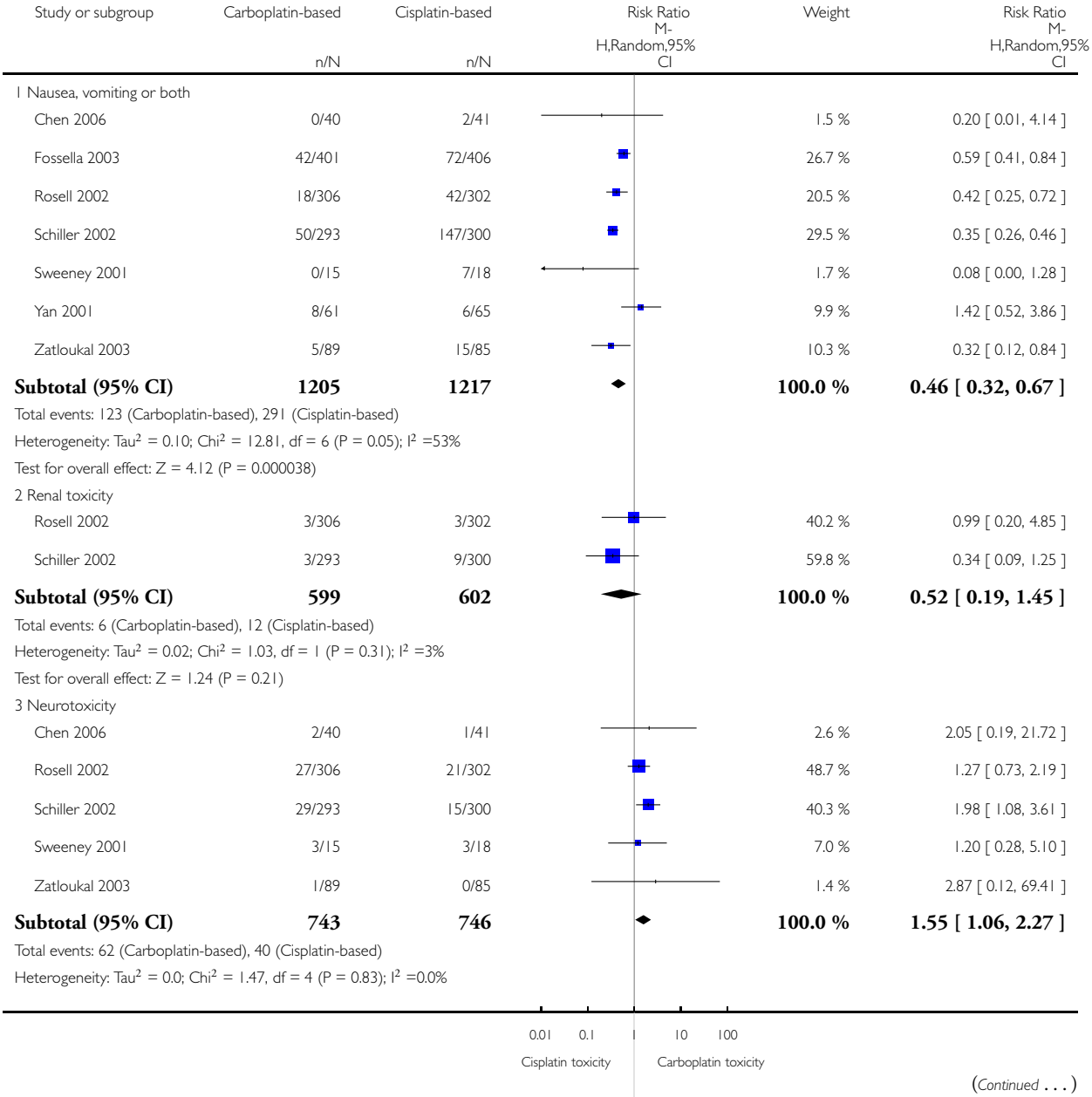
Study or subgroup	Carboplatin-based n/N	Cisplatin-based n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Test for overall effect: Z = 0.63 (P = 0.53)					
6 Anaemia					
Ferry 2011	57/1442	23/2842		76.0 %	4.88 [3.02, 7.89]
Mazzanti 2003	6/269	3/264		24.0 %	1.96 [0.50, 7.77]
Subtotal (95% CI)	**1711**	**3106**		**100.0 %**	**3.93 [1.83, 8.42]**
Total events: 63 (Carboplatin-based), 26 (Cisplatin-based)					
Heterogeneity: Tau^2 = 0.14; Chi^2 = 1.50, df = 1 (P = 0.22); I^2 =34%					
Test for overall effect: Z = 3.51 (P = 0.00044)					
7 Neutropenia					
Ferry 2011	226/1442	123/2842		60.9 %	3.62 [2.93, 4.47]
Mazzanti 2003	7/269	6/264		39.1 %	1.14 [0.39, 3.36]
Subtotal (95% CI)	**1711**	**3106**		**100.0 %**	**2.31 [0.77, 6.95]**
Total events: 233 (Carboplatin-based), 129 (Cisplatin-based)					
Heterogeneity: Tau^2 = 0.51; Chi^2 = 4.23, df = 1 (P = 0.04); I^2 =76%					
Test for overall effect: Z = 1.49 (P = 0.14)					

Analysis 1.4. Comparison 1 Carboplatin-based versus cisplatin-based chemotherapy, Outcome 4 Grade III or IV toxicity by participant.

Review: Cisplatin versus carboplatin in combination with third-generation drugs for advanced non-small cell lung cancer

Comparison: 1 Carboplatin-based versus cisplatin-based chemotherapy

Outcome: 4 Grade III or IV toxicity by participant



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Study or subgroup	Carboplatin-based n/N	Cisplatin-based n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Test for overall effect: Z = 2.24 (P = 0.025)					
4 Skin rash					
Cai 2002	1/20	0/20		100.0 %	3.00 [0.13, 69.52]
Subtotal (95% CI)	**20**	**20**		**100.0 %**	**3.00 [0.13, 69.52]**
Total events: 1 (Carboplatin-based), 0 (Cisplatin-based)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.69 (P = 0.49)					
5 Alopecia					
Yan 2001	25/61	22/65		83.3 %	1.21 [0.77, 1.91]
Zatloukal 2003	6/89	8/85		16.7 %	0.72 [0.26, 1.98]
Subtotal (95% CI)	**150**	**150**		**100.0 %**	**1.11 [0.73, 1.68]**
Total events: 31 (Carboplatin-based), 30 (Cisplatin-based)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.88, df = 1 (P = 0.35); I^2 =0.0%					
Test for overall effect: Z = 0.49 (P = 0.62)					
6 Anaemia					
Cai 2002	2/20	2/20		2.5 %	1.00 [0.16, 6.42]
Chen 2006	5/40	4/41		5.3 %	1.28 [0.37, 4.43]
Fossella 2003	42/401	28/406		25.9 %	1.52 [0.96, 2.40]
Rosell 2002	21/306	27/302		20.5 %	0.77 [0.44, 1.33]
Schiller 2002	29/293	39/300		26.2 %	0.76 [0.48, 1.20]
Sweeney 2001	3/15	4/18		4.6 %	0.90 [0.24, 3.41]
Yan 2001	4/61	0/65		1.0 %	9.58 [0.53, 174.31]
Zatloukal 2003	16/89	11/85		14.0 %	1.39 [0.68, 2.82]
Subtotal (95% CI)	**1225**	**1237**		**100.0 %**	**1.06 [0.79, 1.43]**
Total events: 122 (Carboplatin-based), 115 (Cisplatin-based)					
Heterogeneity: Tau^2 = 0.03; Chi^2 = 8.70, df = 7 (P = 0.27); I^2 =20%					
Test for overall effect: Z = 0.40 (P = 0.69)					
7 Thrombocytopenia					
Cai 2002	5/20	6/20		11.2 %	0.83 [0.30, 2.29]
Chen 2006	3/40	1/41		2.7 %	3.08 [0.33, 28.34]
Fossella 2003	28/401	11/406		20.2 %	2.58 [1.30, 5.11]
Rosell 2002	24/306	6/302		14.0 %	3.95 [1.64, 9.52]
Schiller 2002	29/293	18/300		25.5 %	1.65 [0.94, 2.90]
Sweeney 2001	1/15	0/18		1.4 %	3.56 [0.16, 81.55]
Yan 2001	9/61	2/65		5.7 %	4.80 [1.08, 21.31]
Zatloukal 2003	16/89	11/85		19.2 %	1.39 [0.68, 2.82]

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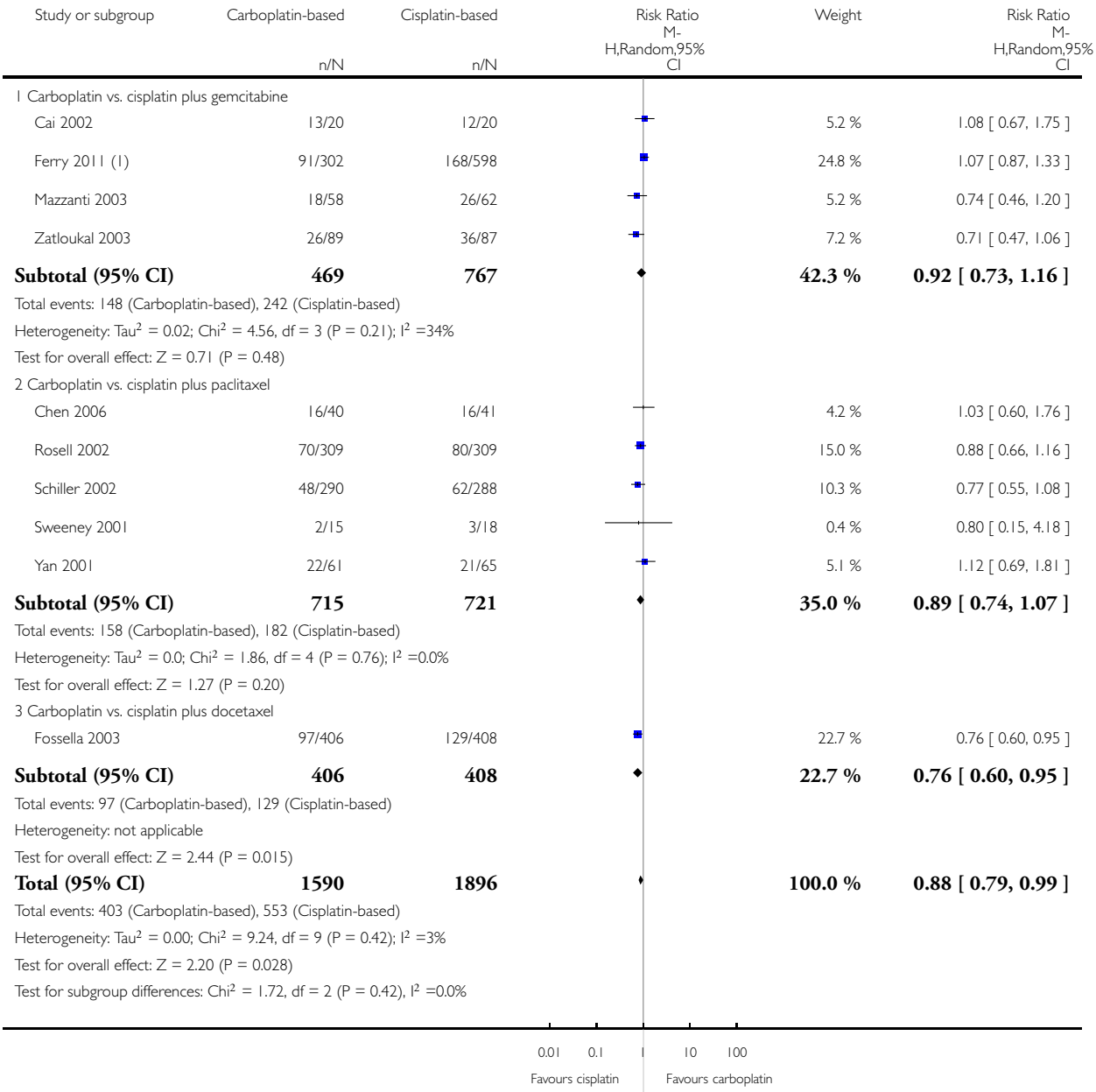
Study or subgroup	Carboplatin-based n/N	Cisplatin-based n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Subtotal (95% CI)	**1225**	**1237**		**100.0 %**	**2.00 [1.37, 2.91]**
Total events: 115 (Carboplatin-based), 55 (Cisplatin-based)					
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 8.91$, df = 7 (P = 0.26); $I^2 = 21\%$					
Test for overall effect: Z = 3.61 (P = 0.00031)					
8 Neutropenia					
Cai 2002	5/20	6/20		1.4 %	0.83 [0.30, 2.29]
Chen 2006	6/40	2/41		0.6 %	3.08 [0.66, 14.34]
Fossella 2003	294/401	302/406		33.6 %	0.99 [0.91, 1.07]
Rosell 2002	165/306	154/302		24.6 %	1.06 [0.91, 1.23]
Schiller 2002	185/293	225/300		30.1 %	0.84 [0.75, 0.94]
Sweeney 2001	7/15	11/18		3.2 %	0.76 [0.40, 1.47]
Yan 2001	4/61	10/65		1.2 %	0.43 [0.14, 1.29]
Zatloukal 2003	27/89	20/85		5.3 %	1.29 [0.79, 2.12]
Subtotal (95% CI)	**1225**	**1237**		**100.0 %**	**0.96 [0.85, 1.08]**
Total events: 693 (Carboplatin-based), 730 (Cisplatin-based)					
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 13.67$, df = 7 (P = 0.06); $I^2 = 49\%$					
Test for overall effect: Z = 0.70 (P = 0.48)					

Analysis 1.5. Comparison 1 Carboplatin-based versus cisplatin-based chemotherapy, Outcome 5 Response rate.

Review: Cisplatin versus carboplatin in combination with third-generation drugs for advanced non-small cell lung cancer

Comparison: 1 Carboplatin-based versus cisplatin-based chemotherapy

Outcome: 5 Response rate



(1) oth arms using cisplatin-based regimens were grouped in the same analysis

Analysis 2.1. Comparison 2 Subgroup analysis (cisplatin dose: 40 to 80 mg/m2 versus 80 to 100 mg/m2), Outcome 1 Overall survival.

Review: Cisplatin versus carboplatin in combination with third-generation drugs for advanced non-small cell lung cancer

Comparison: 2 Subgroup analysis (cisplatin dose: 40 to 80 mg/m^2 versus 80 to 100 mg/m^2)

Outcome: 1 Overall survival

Study or subgroup	Carboplatin-based N	Cisplatin-based N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Weight	Hazard Ratio IV,Random,95% CI
1 40-80 mg/m^2						
Chen 2006	40	41	-0.16 (3.67)		1.5 %	0.85 [0.00, 1133.50]
Ferry 2011 (1)	453	454	-0.17 (0.86)		26.5 %	0.84 [0.16, 4.55]
Fossella 2003	406	408	0.01 (0.94)		22.2 %	1.01 [0.16, 6.37]
Schiller 2002	299	303	0.05 (0.63)		49.5 %	1.05 [0.31, 3.61]
Sweeney 2001	15	18	-0.34 (7.85)		0.3 %	0.71 [0.00, 3421936.85]
Subtotal (95% CI)					**100.0 %**	**0.98 [0.41, 2.33]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.05, df = 4 (P = 1.00); I^2 =0.0%						
Test for overall effect: Z = 0.05 (P = 0.96)						
2 80-100 mg/m^2						
Ferry 2011 (2)	453	456	0.01 (0.61)		45.6 %	1.01 [0.31, 3.34]
Mazzanti 2003	58	62	0.11 (1.25)		10.9 %	1.12 [0.10, 12.94]
Rosell 2002	309	309	-0.09 (0.91)		20.5 %	0.91 [0.15, 5.44]
Zatloukal 2003	89	87	-0.08 (0.86)		23.0 %	0.92 [0.17, 4.98]
Subtotal (95% CI)					**100.0 %**	**0.98 [0.44, 2.20]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.02, df = 3 (P = 1.00); I^2 =0.0%						
Test for overall effect: Z = 0.05 (P = 0.96)						
Test for subgroup differences: Chi^2 = 0.00, df = 1 (P = 1.00), I^2 =0.0%						

(1) Only patients using 50 mg/m2 were included

(2) Only patients using 80 mg/m2 were included

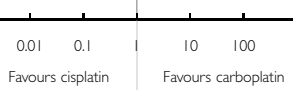
Analysis 2.2. Comparison 2 Subgroup analysis (cisplatin dose: 40 to 80 mg/m2 versus 80 to 100 mg/m2), Outcome 2 1-year survival rate.

Review: Cisplatin versus carboplatin in combination with third-generation drugs for advanced non-small cell lung cancer

Comparison: 2 Subgroup analysis (cisplatin dose: 40 to 80 mg/m^2 versus 80 to 100 mg/m^2)

Outcome: 2 1-year survival rate

Study or subgroup	Carboplatin-based n/N	Cisplatin-based n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 40-80 mg/m^2					
Chen 2006	20/40	19/41		14.1 %	1.08 [0.69, 1.70]
Ferry 2011 (1)	174/453	139/454		28.8 %	1.25 [1.05, 1.50]
Fossella 2003	154/406	188/408		29.9 %	0.82 [0.70, 0.97]
Schiller 2002	102/299	94/303		25.6 %	1.10 [0.87, 1.38]
Sweeney 2001	2/15	3/18		1.7 %	0.80 [0.15, 4.18]
Subtotal (95% CI)	**1213**	**1224**		**100.0 %**	**1.04 [0.84, 1.29]**
Total events: 452 (Carboplatin-based), 443 (Cisplatin-based)					
Heterogeneity: Tau^2 = 0.03; Chi^2 = 12.27, df = 4 (P = 0.02); I^2 =67%					
Test for overall effect: Z = 0.35 (P = 0.73)					
2 80-100 mg/m^2					
Ferry 2011 (2)	174/453	176/456		49.9 %	1.00 [0.84, 1.17]
Mazzanti 2003	25/58	26/62		7.8 %	1.03 [0.68, 1.56]
Rosell 2002	98/309	116/309		28.4 %	0.84 [0.68, 1.05]
Yan 2001	21/61	22/65		5.7 %	1.02 [0.63, 1.65]
Zatloukal 2003	32/89	29/87		8.2 %	1.08 [0.72, 1.62]
Subtotal (95% CI)	**970**	**979**		**100.0 %**	**0.96 [0.85, 1.08]**
Total events: 350 (Carboplatin-based), 369 (Cisplatin-based)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.98, df = 4 (P = 0.74); I^2 =0.0%					
Test for overall effect: Z = 0.69 (P = 0.49)					
Test for subgroup differences: Chi^2 = 0.40, df = 1 (P = 0.53), I^2 =0.0%					



(1) Only patients using 50 mg/m2 were included

(2) Only patients using 80 mg/m2 were included

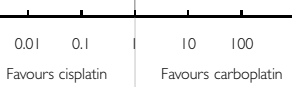
Analysis 2.3. Comparison 2 Subgroup analysis (cisplatin dose: 40 to 80 mg/m2 versus 80 to 100 mg/m2), Outcome 3 Response rate.

Review: Cisplatin versus carboplatin in combination with third-generation drugs for advanced non-small cell lung cancer

Comparison: 2 Subgroup analysis (cisplatin dose: 40 to 80 mg/m^2 versus 80 to 100 mg/m^2)

Outcome: 3 Response rate

Study or subgroup	Carboplatin-based n/N	Cisplatin-based n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 40-80 mg/m^2					
Cai 2002	13/20	12/20		14.8 %	1.08 [0.67, 1.75]
Chen 2006	16/40	16/41		13.0 %	1.03 [0.60, 1.76]
Ferry 2011 (1)	91/302	68/302		23.7 %	1.34 [1.02, 1.75]
Fossella 2003	97/406	129/408		25.9 %	0.76 [0.60, 0.95]
Schiller 2002	48/290	62/288		20.4 %	0.77 [0.55, 1.08]
Sweeney 2001	2/15	3/18		2.1 %	0.80 [0.15, 4.18]
Subtotal (95% CI)	**1073**	**1077**		**100.0 %**	**0.95 [0.74, 1.23]**
Total events: 267 (Carboplatin-based), 290 (Cisplatin-based)					
Heterogeneity: Tau^2 = 0.05; Chi^2 = 11.99, df = 5 (P = 0.03); I^2 =58%					
Test for overall effect: Z = 0.37 (P = 0.71)					
2 80-100 mg/m^2					
Ferry 2011 (2)	91/302	100/296		40.0 %	0.89 [0.71, 1.13]
Mazzanti 2003	18/58	26/62		9.4 %	0.74 [0.46, 1.20]
Rosell 2002	70/309	80/309		28.1 %	0.88 [0.66, 1.16]
Yan 2001	22/61	21/65		9.3 %	1.12 [0.69, 1.81]
Zatloukal 2003	26/89	36/87		13.1 %	0.71 [0.47, 1.06]
Subtotal (95% CI)	**819**	**819**		**100.0 %**	**0.86 [0.74, 1.00]**
Total events: 227 (Carboplatin-based), 263 (Cisplatin-based)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.48, df = 4 (P = 0.65); I^2 =0.0%					
Test for overall effect: Z = 1.95 (P = 0.052)					
Test for subgroup differences: Chi^2 = 0.46, df = 1 (P = 0.50), I^2 =0.0%					



(1) Only patients using cisplatin 50 mg/m2 were analyzed

(2) Only patients using cisplatin 80 mg/m2 were analyzed

Analysis 3.1. Comparison 3 Sensitivity analysis (only published trials), Outcome 1 Overall survival.

Review: Cisplatin versus carboplatin in combination with third-generation drugs for advanced non-small cell lung cancer

Comparison: 3 Sensitivity analysis (only published trials)

Outcome: 1 Overall survival

Study or subgroup	Carboplatin-based N	Cisplatin-based N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Weight	Hazard Ratio IV,Random,95% CI
Chen 2006	40	41	-0.16 (3.67)		1.1 %	0.85 [0.00, 1133.50]
Fossella 2003	406	408	0.01 (0.94)		16.3 %	1.01 [0.16, 6.37]
Mazzanti 2003	58	62	0.11 (1.25)		9.2 %	1.12 [0.10, 12.94]
Rosell 2002	309	309	-0.09 (0.91)		17.4 %	0.91 [0.15, 5.44]
Schiller 2002	299	303	0.05 (0.63)		36.3 %	1.05 [0.31, 3.61]
Sweeney 2001	15	18	-0.34 (7.85)		0.2 %	0.71 [0.00, 3421936.85]
Zatloukal 2003	89	87	-0.08 (0.86)		19.5 %	0.92 [0.17, 4.98]
Total (95% CI)					**100.0 %**	**1.00 [0.47, 2.10]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.04$, df = 6 (P = 1.00); $I^2 = 0.0\%$

Test for overall effect: Z = 0.01 (P = 0.99)

Test for subgroup differences: Not applicable

Analysis 3.2. Comparison 3 Sensitivity analysis (only published trials), Outcome 2 1-year survival rate.

Review: Cisplatin versus carboplatin in combination with third-generation drugs for advanced non-small cell lung cancer

Comparison: 3 Sensitivity analysis (only published trials)

Outcome: 2 1-year survival rate

Study or subgroup	Carboplatin-based n/N	Cisplatin-based n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Chen 2006	20/40	19/41		4.9 %	1.08 [0.69, 1.70]
Fossella 2003	154/406	188/408		38.1 %	0.82 [0.70, 0.97]
Mazzanti 2003	25/58	26/62		5.8 %	1.03 [0.68, 1.56]
Rosell 2002	98/309	116/309		21.3 %	0.84 [0.68, 1.05]
Schiller 2002	102/299	94/303		19.1 %	1.10 [0.87, 1.38]
Sweeney 2001	2/15	3/18		0.4 %	0.80 [0.15, 4.18]
Yan 2001	21/61	22/65		4.3 %	1.02 [0.63, 1.65]
Zatloukal 2003	32/89	29/87		6.1 %	1.08 [0.72, 1.62]
Total (95% CI)	**1277**	**1293**		**100.0 %**	**0.92 [0.83, 1.02]**

Total events: 454 (Carboplatin-based), 497 (Cisplatin-based)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 6.22$, df = 7 (P = 0.51); $I^2 = 0.0\%$

Test for overall effect: Z = 1.60 (P = 0.11)

Test for subgroup differences: Not applicable

Analysis 3.3. Comparison 3 Sensitivity analysis (only published trials), Outcome 3 Response rate.

Review: Cisplatin versus carboplatin in combination with third-generation drugs for advanced non-small cell lung cancer

Comparison: 3 Sensitivity analysis (only published trials)

Outcome: 3 Response rate

Study or subgroup	Carboplatin-based n/N	Cisplatin-based n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Cai 2002	13/20	12/20		6.8 %	1.08 [0.67, 1.75]
Chen 2006	16/40	16/41		5.4 %	1.03 [0.60, 1.76]
Fossella 2003	97/406	129/408		31.0 %	0.76 [0.60, 0.95]
Mazzanti 2003	18/58	26/62		6.7 %	0.74 [0.46, 1.20]
Rosell 2002	70/309	80/309		20.0 %	0.88 [0.66, 1.16]
Schiller 2002	48/290	62/288		13.6 %	0.77 [0.55, 1.08]
Sweeney 2001	2/15	3/18		0.6 %	0.80 [0.15, 4.18]
Yan 2001	22/61	21/65		6.6 %	1.12 [0.69, 1.81]
Zatloukal 2003	26/89	36/87		9.4 %	0.71 [0.47, 1.06]
Total (95% CI)	**1288**	**1298**		**100.0 %**	**0.83 [0.73, 0.94]**

Total events: 312 (Carboplatin-based), 385 (Cisplatin-based)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 5.06$, df = 8 (P = 0.75); $I^2 = 0.0\%$

Test for overall effect: Z = 2.96 (P = 0.0030)

Test for subgroup differences: Not applicable

Analysis 4.1. Comparison 4 Sensitivity analysis (fixed-effect model), Outcome 1 Overall survival.

Review: Cisplatin versus carboplatin in combination with third-generation drugs for advanced non-small cell lung cancer

Comparison: 4 Sensitivity analysis (fixed-effect model)

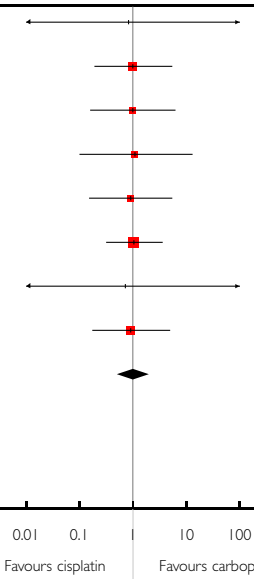
Outcome: 1 Overall survival

Study or subgroup	Carboplatin-based N	Cisplatin-based N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Fixed,95% CI	Weight	Hazard Ratio IV,Fixed,95% CI
Chen 2006	40	41	-0.16 (3.67)		0.9 %	0.85 [0.00, 1133.50]
Ferry 2011 (1)	453	910	0.008 (0.86)		16.3 %	1.01 [0.19, 5.44]
Fossella 2003	406	408	0.01 (0.94)		13.6 %	1.01 [0.16, 6.37]
Mazzanti 2003	58	62	0.11 (1.25)		7.7 %	1.12 [0.10, 12.94]
Rosell 2002	309	309	-0.09 (0.91)		14.6 %	0.91 [0.15, 5.44]
Schiller 2002	299	303	0.05 (0.63)		30.4 %	1.05 [0.31, 3.61]
Sweeney 2001	15	18	-0.34 (7.85)		0.2 %	0.71 [0.00, 3421936.85]
Zatloukal 2003	89	87	-0.08 (0.86)		16.3 %	0.92 [0.17, 4.98]
Total (95% CI)					**100.0 %**	**1.00 [0.51, 1.97]**

Heterogeneity: Chi^2 = 0.04, df = 7 (P = 1.00); I^2 =0.0%

Test for overall effect: Z = 0.01 (P = 1.0)

Test for subgroup differences: Not applicable



(1) All patients included

Analysis 4.2. Comparison 4 Sensitivity analysis (fixed-effect model), Outcome 2 1-year survival rate.

Review: Cisplatin versus carboplatin in combination with third-generation drugs for advanced non-small cell lung cancer

Comparison: 4 Sensitivity analysis (fixed-effect model)

Outcome: 2 1-year survival rate

Study or subgroup	Carboplatin-based n/N	Cisplatin-based n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Chen 2006	20/40	19/41		2.7 %	1.08 [0.69, 1.70]
Ferry 2011	174/453	314/910		29.7 %	1.11 [0.96, 1.29]
Fossella 2003	154/406	188/408		26.7 %	0.82 [0.70, 0.97]
Mazzanti 2003	25/58	26/62		3.6 %	1.03 [0.68, 1.56]
Rosell 2002	98/309	116/309		16.5 %	0.84 [0.68, 1.05]
Schiller 2002	102/299	94/303		13.3 %	1.10 [0.87, 1.38]
Sweeney 2001	2/15	3/18		0.4 %	0.80 [0.15, 4.18]
Yan 2001	21/61	22/65		3.0 %	1.02 [0.63, 1.65]
Zatloukal 2003	32/89	29/87		4.2 %	1.08 [0.72, 1.62]
Total (95% CI)	**1730**	**2203**		**100.0 %**	**0.98 [0.90, 1.06]**

Total events: 628 (Carboplatin-based), 811 (Cisplatin-based)

Heterogeneity: Chi^2 = 10.56, df = 8 (P = 0.23); I^2 =24%

Test for overall effect: Z = 0.47 (P = 0.64)

Test for subgroup differences: Not applicable

Analysis 4.3. Comparison 4 Sensitivity analysis (fixed-effect model), Outcome 3 Response rate.

Review: Cisplatin versus carboplatin in combination with third-generation drugs for advanced non-small cell lung cancer

Comparison: 4 Sensitivity analysis (fixed-effect model)

Outcome: 3 Response rate

Study or subgroup	Carboplatin-based n/N	Cisplatin-based n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cai 2002	13/20	12/20		2.4 %	1.08 [0.67, 1.75]
Chen 2006	16/40	16/41		3.2 %	1.03 [0.60, 1.76]
Ferry 2011	91/302	168/598		22.7 %	1.07 [0.87, 1.33]
Fossella 2003	97/406	129/408		25.9 %	0.76 [0.60, 0.95]
Mazzanti 2003	18/58	26/62		5.1 %	0.74 [0.46, 1.20]
Rosell 2002	70/309	80/309		16.1 %	0.88 [0.66, 1.16]
Schiller 2002	48/290	62/288		12.5 %	0.77 [0.55, 1.08]
Sweeney 2001	2/15	3/18		0.5 %	0.80 [0.15, 4.18]
Yan 2001	22/61	21/65		4.1 %	1.12 [0.69, 1.81]
Zatloukal 2003	26/89	36/87		7.3 %	0.71 [0.47, 1.06]
Total (95% CI)	**1590**	**1896**		**100.0 %**	**0.88 [0.79, 0.98]**

Total events: 403 (Carboplatin-based), 553 (Cisplatin-based)

Heterogeneity: $Chi^2 = 9.24$, df = 9 (P = 0.42); $I^2 = 3\%$

Test for overall effect: Z = 2.40 (P = 0.017)

Test for subgroup differences: Not applicable

Analysis 5.1. Comparison 5 Sensitivity analysis (phase III trials), Outcome 1 Overall survival.

Review: Cisplatin versus carboplatin in combination with third-generation drugs for advanced non-small cell lung cancer

Comparison: 5 Sensitivity analysis (phase III trials)

Outcome: 1 Overall survival

Study or subgroup	Carboplatin-based N	Cisplatin-based N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Weight	Hazard Ratio IV,Random,95% CI
Ferry 2011	453	910	0.008 (0.86)		17.9 %	1.01 [0.19, 5.44]
Fossella 2003	406	408	0.01 (0.94)		15.0 %	1.01 [0.16, 6.37]
Rosell 2002	309	309	-0.09 (0.91)		16.0 %	0.91 [0.15, 5.44]
Schiller 2002	299	303	0.05 (0.63)		33.3 %	1.05 [0.31, 3.61]
Zatloukal 2003	89	87	-0.08 (0.86)		17.9 %	0.92 [0.17, 4.98]
Total (95% CI)					**100.0 %**	**0.99 [0.49, 2.02]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.02$, df = 4 (P = 1.00); $I^2 = 0.0\%$

Test for overall effect: Z = 0.02 (P = 0.98)

Test for subgroup differences: Not applicable

Analysis 5.2. Comparison 5 Sensitivity analysis (phase III trials), Outcome 2 1-year survival rate.

Review: Cisplatin versus carboplatin in combination with third-generation drugs for advanced non-small cell lung cancer

Comparison: 5 Sensitivity analysis (phase III trials)

Outcome: 2 1-year survival rate

Study or subgroup	Carboplatin-based n/N	Cisplatin-based n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Ferry 2011	174/453	314/910		26.1 %	1.11 [0.96, 1.29]
Fossella 2003	154/406	188/408		24.7 %	0.82 [0.70, 0.97]
Rosell 2002	98/309	116/309		20.1 %	0.84 [0.68, 1.05]
Schiller 2002	102/299	94/303		19.2 %	1.10 [0.87, 1.38]
Zatloukal 2003	32/89	29/87		9.8 %	1.08 [0.72, 1.62]
Total (95% CI)	**1556**	**2017**		**100.0 %**	**0.97 [0.84, 1.13]**

Total events: 560 (Carboplatin-based), 741 (Cisplatin-based)

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 10.22$, df = 4 (P = 0.04); $I^2 = 61\%$

Test for overall effect: Z = 0.37 (P = 0.71)

Test for subgroup differences: Not applicable

Analysis 5.3. Comparison 5 Sensitivity analysis (phase III trials), Outcome 3 Response rate.

Review: Cisplatin versus carboplatin in combination with third-generation drugs for advanced non-small cell lung cancer

Comparison: 5 Sensitivity analysis (phase III trials)

Outcome: 3 Response rate

Study or subgroup	Carboplatin-based n/N	Cisplatin-based n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Ferry 2011	91/302	168/598		26.8 %	1.07 [0.87, 1.33]
Fossella 2003	97/406	129/408		25.6 %	0.76 [0.60, 0.95]
Rosell 2002	70/309	80/309		20.1 %	0.88 [0.66, 1.16]
Schiller 2002	48/290	62/288		15.6 %	0.77 [0.55, 1.08]
Zatloukal 2003	26/89	36/87		11.9 %	0.71 [0.47, 1.06]
Total (95% CI)	**1396**	**1690**		**100.0 %**	**0.85 [0.72, 1.00]**

Total events: 332 (Carboplatin-based), 475 (Cisplatin-based)

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 6.68$, df = 4 (P = 0.15); $I^2 = 40\%$

Test for overall effect: Z = 1.97 (P = 0.048)

Test for subgroup differences: Not applicable

APPENDICES

Appendix 1. Search strategies

MEDLINE (via PubMed)	#1 (Cisplatin [mh]) OR Cisplatin OR (cis-Diamminedichloroplatinum(II)) OR (Platinum Diamminodichloride) OR (Diamminodichloride, Platinum) OR cis-Platinum OR (cis Platinum) OR Cisplatinum OR (Dichlorodiammineplatinum) OR (cis-Diamminedichloroplatinum) OR (cis Diamminedichloroplatinum) OR (cis-Dichlorodiammineplatinum(II)) OR (Platinol) OR Platidiam OR Platino OR (NSC-119875) OR Biocisplatinum #2 (Carboplatin [mh]) OR Carboplatin OR (cis-Diammine(cyclobutanedicarboxylato)platinum II) OR CBDCA OR Ribocarbo OR (ribosepharm Brand of Carboplatin) OR Nealorin OR (Prasfarma Brand of Carboplatin) OR Neocarbo OR (Neocorp Brand of Carboplatin) OR Paraplatin OR Carboplat OR Paraplatine OR (Bristol-Myers Squibb Brand of Carboplatin) OR Carbosin OR (Pharmachemie Brand of Carboplatin) OR Carbotec OR (Columbia Brand of Carboplatin) OR Ercar OR (Almirall Brand of Carboplatin) OR JM-8 or (JM 8) OR JM8 OR NSC-241240 OR (NSC 241240) OR NSC241240 OR Platinwas OR (Chiesi Brand of Carboplatin) OR Blastocarb OR (Lemery Brand of Carboplatin) #3 (Lung Neoplasms [mh]) OR (Lung Neoplasms) OR (Neoplasms, Lung) OR (Lung Neoplasm) OR (Neoplasm, Lung) OR (Neoplasms, Pulmonary) OR (Neoplasm, Pulmonary) OR (Pulmonary Neoplasm) OR (Pulmonary Neoplasms) OR (Lung Cancer) OR (Cancer, Lung) OR (Cancers, Lung) OR (Lung Cancers) OR (Pulmonary Cancer) OR (Cancer, Pulmonary) OR (Cancers, Pulmonary) OR (Pulmonary Cancers) OR (Cancer of the Lung) OR (Cancer of Lung) OR (Carcinoma, Non-Small-Cell [mh]) OR (Carcinoma, Non-Small-Cell) OR (Carcinoma, Non Small Cell Lung) OR (Carcinomas, Non-Small-Cell Lung) OR (Lung Carcinoma, Non-Small-Cell) OR (Lung Carcinomas, Non-Small-Cell) OR (Non-Small-Cell Lung Carcinomas) OR (Non-Small-Cell Lung Carcinoma) OR (Non Small Cell Lung Carcinoma) OR (Carcinoma, Non-Small Cell Lung) OR (Non-Small Cell Lung Cancer) #4 #1 AND #2 AND #3 #5 randomized controlled trial [pt] #6 controlled clinical trial [pt] #7 randomized [tiab] #8 placebo [tiab] #9 drug therapy [sh] #10 randomly [tiab] #11 trial [tiab] #12 groups [tiab] #13 #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 #14 animals [mh] NOT humans [mh] #15 #13 NOT #14 #16 #4 AND #15
EMBASE via Ovid	1 Clinical trial/ 2 Randomized controlled trial/ 3 Randomization/ 4 Single blind procedure/ 5 Double blind procedure/ 6 Crossover procedure/ 7 Placebo/ 8 Randomi?ed controlled trial$.tw. 9 Rct.tw. 10 Random allocation.tw. 11 Randomly allocated.tw. 12 Allocated randomly.tw. 13 (allocated adj2 random).tw. 14 Single blind$.tw.

(*Continued*)

	15 Double blind$.tw. 16 ((treble or triple) adj (blind$).tw. 17 Placebo$.tw. 18 Prospective study/ 19 Or/1-18 20 Case study/ 21 Case report.tw. 22 Abstract report/ or letter/ 23 Or/20-22 24 19 not 23 25 exp Lung Cancer/ 26 exp Lung non Small Cell Cancer/ 27 non small cell.ti,ab. 28 NSCLC.ti,ab. 29 25 or 26 or 27 or 28 30 (Cisplatin [mh]) OR Cisplatin OR (cis-Diamminedichloroplatinum(II)) OR (Platinum Diamminodichloride) OR (Diamminodichloride, Platinum) OR cis-Platinum OR (cis Platinum) OR Cisplatinum OR (Dichlorodiammineplatinum) OR (cis-Diamminedichloroplatinum) OR (cis Diamminedichloroplatinum) OR (cis-Dichlorodiammineplatinum(II)) OR (Platinol) OR Platidiam OR Platino OR (NSC-119875) OR Biocisplatinum 31 (Carboplatin [mh]) OR Carboplatin OR (cis-Diammine(cyclobutanedicarboxylato)platinum II) OR CBDCA OR Ribocarbo OR (ribosepharm Brand of Carboplatin) OR Nealorin OR (Prasfarma Brand of Carboplatin) OR Neocarbo OR (Neocorp Brand of Carboplatin) OR Paraplatin OR Carboplat OR Paraplatine OR (Bristol-Myers Squibb Brand of Carboplatin) OR Carbosin OR (Pharmachemie Brand of Carboplatin) OR Carbotec OR (Columbia Brand of Carboplatin) OR Ercar OR (Almirall Brand of Carboplatin) OR JM-8 or (JM 8) OR JM8 OR NSC-241240 OR (NSC 241240) OR NSC241240 OR Platinwas OR (Chiesi Brand of Carboplatin) OR Blastocarb OR (Lemery Brand of Carboplatin) 32 30 and 31 33 29 and 32 34 24 and 33
CENTRAL	#1 LUNG-NEOPLASMS*:ME #2 CARCINOMA-NON-SMALL-CELL-LUNG*.ME #3 ((LUNG OR PULMON*) AND (NEOPLAS* OR CANCER OR CARCINOMA*)) #4 (#1 OR #2 OR #3) #5 CISPLATIN #6 CARBOPLATIN #7 (#5 AND #6) #8 (#4 AND #7)
LILACS	#1 ((Cisplatin [MeSH]) or Cisplatin OR Cisplatino OR (cis-Diamminedichloroplatinum(II)) OR (cis-Dichlorodiammineplatinum(II)) OR (Platinum Diamminodichloride)) AND ((Carboplatin [MeSH]) or Carboplatin OR Carboplatina OR Carboplatino OR (cis-Diammine(cyclobutanedicarboxylato) platinum II)) #2 (Lung Neoplasms) OR (Neoplasias Pulmonares) OR (Neoplasias Pulmonares) OR (Pulmonary Neoplasms) OR (Cancer of Lung) OR (Lung Cancer) OR (Pulmonary Cancer) or (Carcinoma, Non-Small-Cell Lung) or (Carcinoma de Pulmón de Células no Pequeñas) OR (Carcinoma Pulmonar de Células não Pequenas) OR (Carcinoma Pulmonar de não Pequenas Células) OR (Carcinoma de Pulmão

(*Continued*)

	de não Pequenas Células) OR (Carcinoma de Pulmão de Células não Pequenas) #3 (ENSAIO CLINICO) OR (ENSAIO CLINICO CONTROLADO) OR (ENSAIO CLINICO CONTROLADO ALEATORIO) OR (ENSAIO CLINICO FASE I) OR (ENSAIO CLINICO FASE II) OR (ENSAIO CLINICO FASE III) OR (ENSAIO CLINICO FASE IV) OR METANALISE" OR REVISAO [Tipo de publicação] #4 #1 AND #2 AND #3

CONTRIBUTIONS OF AUTHORS

Tiago Biachi Castria - background, objectives and outcomes definitions, selection of studies, data extraction, 'Risk of bias' assessment and review organisation in RevMan 5.

Rachel Riera - methodological topics and review organisation in RevMan 5.

Edina Mariko Koga Silva - critical appraisal of the last review.

Aécio Flavio Teixaira de Góis - selection of studies, data extraction, 'Risk of bias' assessment.

DECLARATIONS OF INTEREST

The review authors declare no conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- Brazilian Cochrane Center, Brazil.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We could not perform a quality of life analysis because only two trials evaluated this endpoint.

We took into account the wide range in doses of cisplatin and performed a separate analysis of 'higher' and 'lower' doses.

We had proposed to use odds ratios (OR) to evaluate dichotomous outcomes in the protocol; however, we reconsidered and used RRs to make the interpretation of the data easier to the reader. We also included one-year survival rate as a primary endpoint because it was used in several trials in this review and expresses a real benefit in clinical practice.

Given the difficulties in evaluating potential biases in unpublished trials, we performed a sensitivity analysis after excluding them.

INDEX TERMS

Medical Subject Headings (MeSH)

Antineoplastic Combined Chemotherapy Protocols [adverse effects; *therapeutic use]; Carboplatin [administration & dosage; adverse effects]; Carcinoma, Non-Small-Cell Lung [*drug therapy; pathology]; Cisplatin [administration & dosage; adverse effects]; Deoxycytidine [administration & dosage; adverse effects; analogs & derivatives]; Lung Neoplasms [*drug therapy; pathology]; Paclitaxel [administration & dosage; adverse effects]; Randomized Controlled Trials as Topic

MeSH check words

Humans