Second or third additional chemotherapy drug for non-small cell lung cancer in patients with advanced disease (Review)

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[Intervention Review]

Second or third additional chemotherapy drug for non-small cell lung cancer in patients with advanced disease

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ABSTRACT

Background

Randomized trials have demonstrated that adding a drug to a single-agent or to a two-agent regimen increased the tumor response rate in patients with advanced non-small cell lung cancer (NSCLC), although its impact on survival remains controversial.

Objectives

To evaluate the clinical benefit of adding a drug to a single-agent or two-agent chemotherapy regimen in terms of tumor response rate, survival, and toxicity in patients with advanced NSCLC.

Search methods

There were no language restrictions. Searches of MEDLINE and EMBASE were performed using the search terms non-small cell lung carcinoma/drug therapy, adenocarcinoma, large-cell carcinoma, squamous-cell carcinoma, lung, neoplasms, clinical trial phase III, and randomized trial. Manual searches were also performed to find conference proceedings published between January 1982 and June 2006.

Selection criteria

Data from all randomized controlled trials performed between 1980 and 2006 (published between January 1980 and June 2006) comparing a doublet regimen with a single-agent regimen or comparing a triplet regimen with a doublet regimen in patients with advanced NSCLC.

Data collection and analysis

Two independent investigators reviewed the publications and extracted the data. Pooled odds ratios (ORs) for the objective tumor response rate, one-year survival rate, and toxicity rate were calculated using the fixed-effect model. Pooled median ratios (MRs) for median survival also were calculated using the fixed-effect model. ORs and MRs lower than unity (< 1.0) indicate a benefit of a doublet regimen compared with a single-agent regimen (or a triplet regimen compared with a doublet regimen).

Main results

Sixty-five trials (13601 patients) were eligible. In the trials comparing a doublet regimen with a single-agent regimen, a significant increase was observed in tumor response (OR 0.42, 95% confidence interval [CI] 0.37 to 0.47, P < 0.001) and one-year survival (OR 0.80, 95% CI 0.70 to 0.91, P < 0.001) in favor of the doublet regimen. The median survival ratio was 0.83 (95% CI 0.79 to 0.89, P < 0.001). An increase also was observed in the tumor response rate (OR 0.66, 95% CI 0.58 to 0.75, P < 0.001) in favor of the triplet regimen, but not for one-year survival (OR 1.01, 95% CI 0.85 to 1.21, P = 0.88). The median survival ratio was 1.00 (95% CI 0.94 to 1.06, P = 0.97).

Authors' conclusions

Adding a second drug improved tumor response and survival rate. Adding a third drug had a weaker effect on tumor response and no effect on survival.

PLAIN LANGUAGE SUMMARY

Adding a second drug improved tumor response rate and survival rate in advanced non-small cell lung cancer (NSCLC). Adding a third drug had a weaker effect on tumor response and no effect on survival

Randomized trials have demonstrated that adding a drug to a single-agent or to a two-drug regimen increased the tumor response in patients with NSCLC, although its impact on survival remains controversial. Sixty-five trials (13601 patients) were eligible in this meta-analysis. Adding a second drug to a single-agent chemotherapy regimen significantly improved the objective tumor response rate and the survival. The addition of a third drug to a two-agent chemotherapy regimen increased the objective tumor response rate, but with a weaker effect and a higher toxicity and without improving survival.

BACKGROUND

Lung cancer is a major cause of mortality worldwide, with an estimated annual incidence of more than 1.2 million cases and mortality of more than 1.1 million cases (Jemal 2002). Non-small cell lung cancer (NSCLC) accounts for at least 80% of all lung tumors and approximately two thirds of patients initially present with inoperable NSCLC (Ihde 1991; Juretic 1999).

During the last two decades, numerous randomized clinical trials have investigated the effect of chemotherapy in patients with advanced NSCLC. A meta-analysis based on individual patient data demonstrated that cisplatin-based chemotherapy led to an absolute increase in one-year survival of 10% in patients with metastatic disease and increased median survival by two months (NSCLC 1995). Cisplatin-based chemotherapy was therefore considered the standard treatment in advanced NSCLC (NSCLC 1995; Natale 1997). Other meta-analyses on published data showed that systemic chemotherapy prolonged survival moderately compared with best supportive care (Souquet 1993; Marino 1994; Grilli 1993). Nevertheless, some trials demonstrated that systemic chemotherapy improved quality of life.

Although chemotherapy is recommended in patients with good performance status, the question as to whether adding a third agent (triplet) to a two-drug regimen (doublet), or even a second agent to a single-agent regimen is really beneficial continues to fuel debate (JCO 1997; Albain 1991; Ihde 1992; Bunn 2002). A meta-analysis demonstrated that combined chemotherapy increased the objective tumor response rate but led to greater toxicity than single-agent therapy (Lilenbaum 1998). The benefit of multi-drug regimens was found to be even more controversial in terms of survival (Juretic 1999; Breathnach 2001). The same meta-analysis showed that the benefit of combined chemotherapy in terms of survival was no longer significant when the single agents were platin compounds or vinorelbine (Lilenbaum 1998).

During the early 1990s, third generation cytotoxic agents yielded promising activity in the treatment of NSCLC in terms of tumor response and tolerance (Bunn 1998; Waters 2002). However, a recent review of 22 years of randomized clinical trials on advanced NSCLC in the United States showed that the improvement in median survival between investigational and control arms rarely exceeded two months (Breathnach 2001). There is no clear consensus concerning the number and the type of drugs likely to yield

better results in terms of tolerance and efficacy.

OBJECTIVES

The aim of the present literature-based meta-analysis was to evaluate the benefit of adding one drug to a single-agent or to a two-agent chemotherapy regimen (ie, doublet regimen vs single-agent regimen or triplet regimen vs doublet regimen) in terms of the tumor response rate, survival, and toxicity in patients with advanced NSCLC (Delbaldo 2004).

METHODS

Criteria for considering studies for this review

Types of studies

Only randomized controlled trials were included in the review. Trials were eligible if they compared the benefit of adding a drug to a single-agent regimen or to a doublet regimen.

Types of participants

Patients with a diagnosis of advanced, inoperable NSCLC. Patients should not have been candidates for curative surgery or radical radiotherapy. The histology of the tumours should have been described as squamous cell carcinoma, adenocarcinoma, large-cell carcinoma, undifferentiated, poorly differentiated or unclassified NSCLC, bronchioloalveolar or adenosquamous NSCLC.

Trials should have started recruitment after the 1st January 1980 and completed recruitment by June 2006. Exclusion of the oldest trials was based on the absence of benefit of the drugs used in these trials.

Trials were excluded if:

- patients received prior chemotherapy, combined treatment with chemotherapy and radiotherapy either sequentially or concomitantly.
- patients with limited stage NSCLC or operable disease.
- patients were randomized before January 1980.
- in the same arm a regimen was composed of both cisplatin and carboplatin together, as the mode of action of these two drugs was not sufficiently different for them to be considered as two different drugs, even though their respective efficacies might not be the same.
- cross-over was performed between the different arms of treatment.
- drugs not considered as established chemotherapy were used such as lonidamine (NSCLC 1995).
- they compared completely different drugs in the two arms.

Language and type (full paper, abstract only) of the publication were not an exclusion criteria.

Types of interventions

Any single agent regimen versus doublet chemotherapy or a doublet regimen versus triplet chemotherapy.

Types of outcome measures

The primary end-point was response rate. Survival and toxicity (grade III-IV) were the secondary end-points.

Search methods for identification of studies

We searched electronically data from all published randomized trials comparing a doublet regimen with a single-agent regimen or comparing a triplet regimen with a doublet regimen in patients with advanced NSCLC. The search period included trials published between January 1980 and October 2003. The search was performed without any language restrictions. The computerized bibliographic searches of MEDLINE and EMBASE were performed using the search terms:

MEDLINE (Pubmed) - ("Carcinoma, Non-Small-Cell Lung/drug therapy"[MAJR] AND ("clinical trial, phase iii"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized controlled trial"[Publication Type])) OR ("Carcinoma, Non-Small-Cell Lung/drug therapy"[MAJR] AND ("Clinical Trials, Phase III"[MeSH] OR "Randomized Controlled Trials"[MeSH]))

EMBASE (Dialog Star)- Lung-Non-Small-Cell-Cancer-DT.MJ. AND (Phase-3-Clinical-Trial.DE. OR Randomized-Controlled-Trial.DE. OR random$)

ASCO Abstracts Database 2001-2002: search for lung in Title, non-small cell in Title, randomized in Abstract.

The search results were supplemented with references in books, reviews, journals, and meeting proceedings that were found through handsearches. In addition, we also reviewed the conference proceedings published between January 1982 and June 2006 of the American Society of Clinical Oncology, the European Society of Medical Oncology, the European Cancer Conference, and the International Association for the Study of Lung Cancer. When an abstract was identified without the full paper corresponding to the same trial, a PubMed search by author was performed to look for the corresponding full paper in early 2006. The contents of Journal of Clinical Oncology and Lung cancer was also systematically search between 2004 and June 2006. When an abstract from a meeting and a full article referred to the same trial, only the full article was included in the analysis. When two articles or more used the same data, the most updated article was used. The intermediate analysis was not reported unless some additional information was found in the article.

Data collection and analysis

Two independent investigators reviewed the publications. When individuals failed to concur, a third investigator reviewed the publication independently. Each trial publication was searched for year of publication, inclusion period, number of patients (randomized and analyzed), disease stage, age, performance status, histological characteristics, objective tumor response rate, median survival, one-year survival, and specific (hematologic and nonhematologic) toxicity. When available, we recorded information on the randomization process and whether the trial used an intent-to-treat (ITT) analysis. The primary end point was the overall tumor response rate. The secondary end points were overall survival, whose evaluation was based on the one-year survival rate and median survival and toxicity.

Some trials compared both a doublet regimen with a single-agent regimen and a triplet regimen with a doublet regimen. When a trial compared more than two different chemotherapy regimens, the control or the investigational arm was counted twice or more in the analysis. Consequently, more comparisons than trials were studied. Third-generation cytotoxic agents termed newer drugs include vinorelbine, gemcitabine, docetaxel, paclitaxel, and tirapazamine. Newer drugs were analyzed separately from first or second-generation drugs termed older drugs. Cisplatin is considered more efficient than other older drugs, such as carboplatin. The activity of carboplatin is not recognized worldwide as equivalent to that of cisplatin (Rosell 2002; Soria 2002; Hotta 2004). However, because of the small number of trials with other older drugs, we decided to keep all older drugs together. According to the type of chemotherapy in the control arm, two categories of trials were identified: older drug-based and newer drug-based regimens. According to the type of chemotherapy added in the investigational arm, the trial categories were addition of an older drug and a newer drug. When the control arm was a doublet, regimens with at least one newer drug were considered newer drug-based regimens.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

See table of characteristics of included studies.

Risk of bias in included studies

All analyses were performed using ITT when possible. When the number of randomized patients in each arm was available, it was used as a denominator to compute the tumor response and toxicity rates. For survival, we used the number reported by the investigators. When the total number of randomized patients was different from the sum of the numbers of patients analyzed per arm, an ITT analysis was noted as non-applicable but the trial was still included in the calculations of the meta-analysis. When the number of patients per arm was not available and the results were expressed as percentages, the trials were excluded.

Treatment effects were displayed through odds ratios (ORs) for tumor response, one-year survival, and toxicity and through median ratios (MRs) for median survival. For one-year survival, the OR for death of doublet regimen over single-agent regimen (triplet regimen over doublet regimen) was used. The control arm was used as reference category for the computation of ratios, except for tumor response for which it was the experimental arm. Consequently, less than unity (< 1.0) for ORs and MRs indicates benefit of the doublet regimen over the single-agent regimen (triplet regimen over doublet regimen) and corresponds respectively to a higher tumor response rate, a higher survival rate, less toxicity, and a prolonged median survival.

The ORs for the treatment effect were calculated for individual trials. For each comparison (doublet regimen vs single-agent regimen; triplet regimen vs doublet regimen), a pooled OR was calculated using a fixed-effect model for the tumor response rate, one-year survival rate, and toxicity rates. The Mantel-Haenszel test stratified by trial was used for the treatment effect and the Cochran test was used for heterogeneity (Yusuf 1985). The ORs for tumor response and survival for the doublet regimen vs the single-agent regimen and for the triplet regimen vs the doublet regimen were compared using an interaction test. An additional analysis using median survival was also used for survival (Simes 1987). To facilitate interpretations, an absolute benefit between the control and the investigational arms was computed using the overall OR and the rate in the control arm (Stewart 1993).

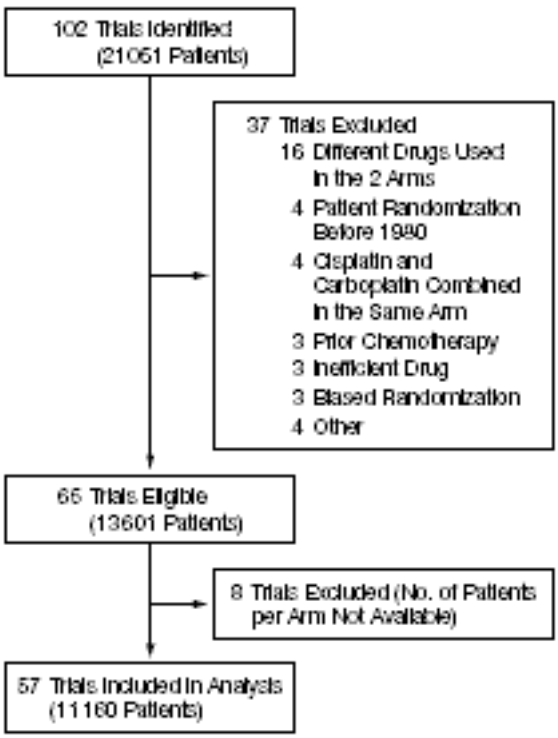
As trial designs were expected to be heterogeneous, several factors were studied to explore any significant heterogeneity in outcomes: type of regimen in the control arm; type of drugs added; planned lower dose in the investigational arm compared to the control arm for the drugs common to both arms (called dose reduction in the paper); and the use of ITT analysis. The test of heterogeneity between groups of trials defined by these factors was called test of interaction. Residual heterogeneity was tested using the difference between the Cochran test for global heterogeneity and the test for interaction. All P values are two-sided.

Effects of interventions

The searches in MEDLINE and EMBASE led respectively to the identification of 717 and 1101 publications. After screening this results, one hundred and two randomized trials including 21051 patients with advanced NSCLC, comparing single agent to doublet regimen or doublet regimen to triplet regimen, were initially

identified, from which 37 trials were secondarily considered ineligible for different reasons (Figure 1). In total, 65 trials (13601 patients) were considered eligible. Eight trials were excluded because the number of patients per arm was not available. Among them, six were reported as abstracts. Reason for exclusion of the ineligible and excluded trials are given in characteristics of excluded studies section. Their references are listed in the excluded studies section of the references. A full description of these trials or trial arms is available from the authors on request.

Figure 1. Selection of the Trials



After the selection procedure (Figure 1), 57 trials including 11160 patients were analyzed. Twenty of the analyzed trials were reported as abstracts. As several trials had more than two eligible arms, the number of comparisons was 68 (11989 patients). The analyzed comparisons of doublet regimens with single-agent regimens are described in the table of characteristics of included studies. The control regimen was cisplatin in 11 comparisons, carboplatin in 1, another older drug in 8, and a newer drug in 13. The drug added was cisplatin in 14 comparisons, carboplatin in 2, another older drug in 9, and a newer drug in 8. The analyzed comparisons of triplet regimens with doublet regimens are described in table of characteristics of included studies. The control regimen included cisplatin in 25 comparisons, another older drug in 1 comparison, and at least 1 newer drug in 9. The drug added was cisplatin in 2, carboplatin in 1 comparison, another older drug in 27, and a newer drug in 5.

Data on the tumor response rate was available for all patients, median survival for 88% of patients, and one-year survival rates were available for 53% of the patients in the analyzed comparisons. The availability of toxicity data was variable; neutropenia toxicity was the information most frequently reported in 61% of the patients.

Trials Comparing a Doublet Regimen With a Single-Agent Regimen

Objective Tumor Response Rate

Concerning the tumor response rate, 33 (7175 patients) comparisons were available from 29 analyzed trials. Adding a drug to a single-agent regimen was associated with a statistically significant increase in the objective tumor response rate (OR 0.42, 95% confidence interval [CI] 0.37 to 0.47, P < 0.001, Table 1). The absolute benefit was 13%, which corresponds to a two-fold increase in the tumor response rate from 13% with a single-agent regimen to 26% with a doublet regimen (Comparison 01-01). The benefit was higher when the control arm was an older drug (OR 0.35) than when it was a newer drug (OR 0.52) (P = 0.001, Comparison 01-01). The benefit was also higher when the added drug was older (OR 0.38) than when it was newer (OR 0.50), but not significantly (P = 0.06). Heterogeneity of the treatment effect was found between the comparisons (P < 0.001, Comparison 01-01). Two trials had a low tumor response rate in the control arm, probably due to the choice of the drug (vindesine for Luedke et al (Luedke 1990a) and teniposide for Splinter et al (Splinter 1996a)). One trial by Gil Deza et al (Gil Deza 1996) had an unusual high tumor response rate with vinorelbine alone. After exclusion of these trials, heterogeneity was no longer significant (P = 0.17) and the overall OR was similar (0.43, P < 0.001). The benefit was lower in the seven comparisons with dose reduction in the experimental arms (OR 0.62) than in those without dose reduction (OR 0.36, P < 0.001). No significant difference was noted between comparisons using an ITT analysis and those that had not (P = 0.27).

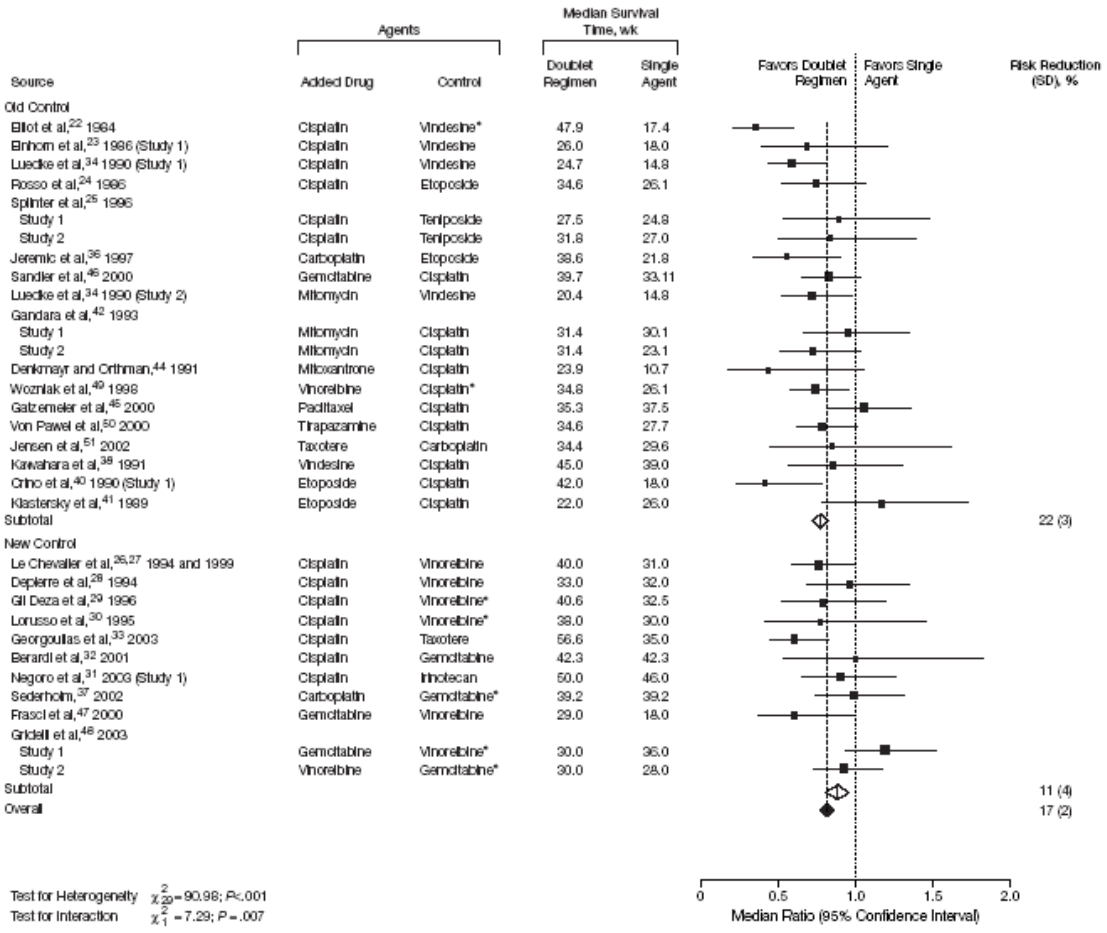
Survival

Thirteen comparisons were available for one-year survival and 30 for median survival. Adding a drug to a single-agent regimen was associated with a significant increase in one-year survival (OR 0.80, 95% CI 0.70 to 0.91, P < 0.001, Comparison 01-02). The absolute benefit was 5%, which corresponds to an increase in one-year survival from 30% with a single-agent regimen to 35% with a doublet regimen (Table 1). Adding a drug to a single-agent regimen significantly increased median survival (MR 0.83, 95% CI 0.79 to 0.89, P < 0.001, Figure 2). The benefit was higher when the control arm was an older drug than when it was a newer drug for both one-year survival rate (P = 0.03) and median survival (P = 0.007). Heterogeneity of the treatment effect was found between the comparisons for both one-year survival (P = 0.002) and median survival (P < 0.001). The benefit was lower in the comparison with dose reduction in the experimental arms (OR 1.12, MR 0.95) than in those without (OR 0.64, MR 0.78) for both one-year survival rate (P < 0.001) and median survival (P < 0.001). When the heterogeneity related to dose reduction was taken into account, there was no more residual heterogeneity (P = 0.64) for one-year survival. No significant difference was noted between comparisons using an ITT analysis and those trials that had not for one-year survival (P = 0.16).

Toxicity

As expected, the rates of grades 3 and 4 toxicity caused by doublet regimens were statistically increased compared with rates following single-agent therapy, with ORs ranging from 1.2 to 6.2 (Table 2). There was no increase in infection rates in doublet regimens.

Figure 2. Ratio of Median Survival With Doublet vs Single-Agent Regimens



Asterisk indicates decreased doses of drug in the investigational arm. $P<.001$ for treatment effect.

Trials Comparing a Doublet Regimen with a Triplet Regimen

Objective Tumor Response Rate

Concerning the tumor response rate, 35 comparisons (4814 patients) were analyzed from 28 trials. Adding a third drug to a doublet regimen was associated with a significantly increased objective tumor response rate (OR 0.66, 95% CI 0.58 to 0.75, P < 0.001, Comparison 02-01). The absolute benefit was 8%, which corresponds to an increase in tumor response from 23% with a doublet regimen to 31% with a triplet regimen (Table 1). There was no difference in tumor response rate whether the doublet regimens contained older or newer drugs (P = 0.33). There was no significant difference (P = 0.70) in terms of benefit according to the drug added (older drug OR of 0.64 vs newer drug OR of 0.74). The heterogeneity of the treatment effect between the comparisons was borderline (P = 0.06, Comparison 02-01). In 12 comparisons, investigators planned to decrease the drug doses in the triplet regimen to avoid additional toxicity. A significant difference was demonstrated between comparisons with (OR 0.76) and without (OR 0.57) a dose reduction (P = 0.03). No significant difference was noted between comparisons using an ITT analysis and those trials that had not (P = 0.40).

Survival

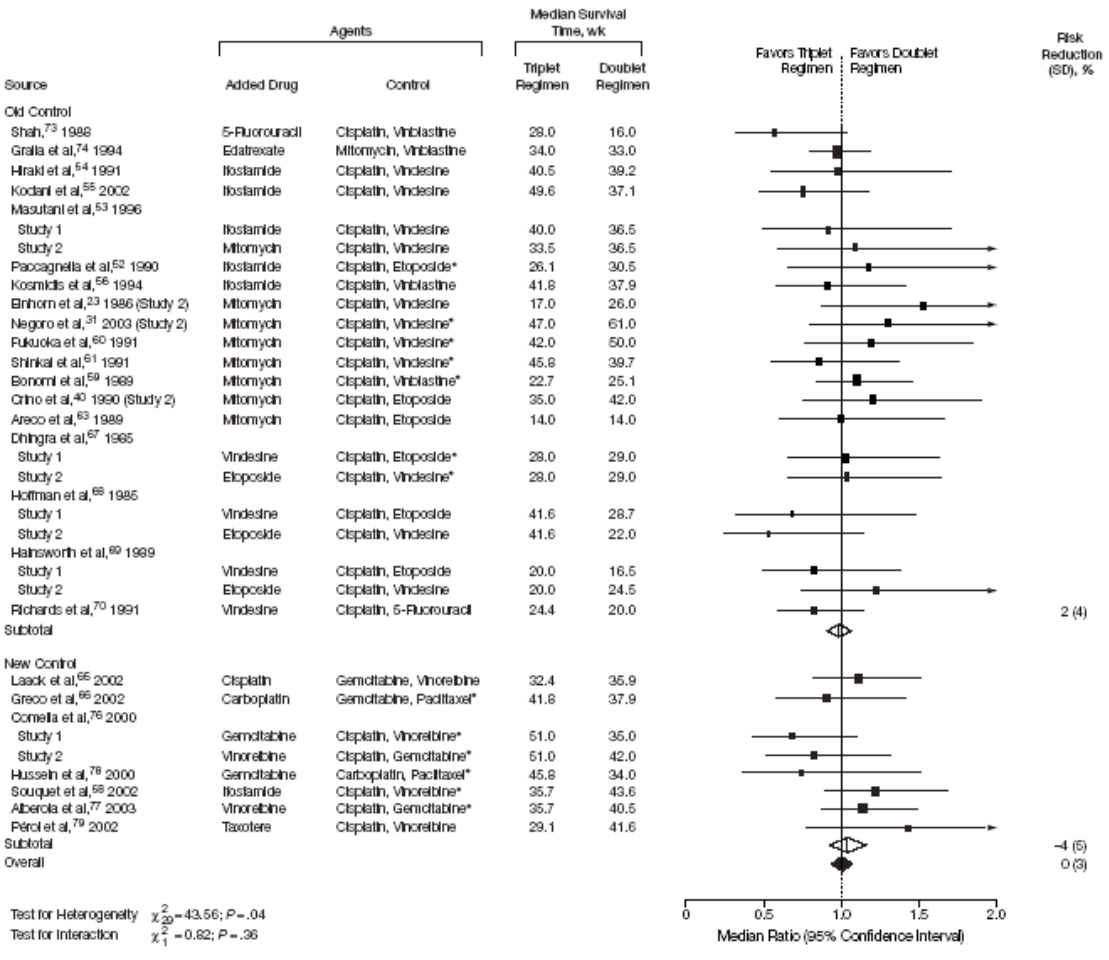
Ten comparisons, all using ITT analysis, were available for one-year survival. Data for 30 comparisons were available for median survival. Adding a third drug to a doublet regimen did not yield any additional benefit for one-year survival (OR 1.01, 95% CI 0.85 to 1.21, P = 0.88, Comparison 02-02) or for median survival (MR 1.00, 95% CI 0.94 to 1.06, P = 0.97, Figure 3). There were no significant differences according to the type of control regimens used (older drugs vs newer drugs) for both one-year survival rate (P = 0.28) and median survival (P = 0.36). The data

did not show heterogeneity for one-year survival (P = 0.59), but did show borderline heterogeneity for median survival (P =0.04). No differences were observed between comparisons with or without dose reduction for one-year survival (P = 0.30) and for median survival (P = 0.16).

Toxicity

Toxicity of grades 3 and 4 occurred more frequently in triplet regimens than in doublet regimens with ORs ranging from 1.4 to 2.9, except for neurological, renal, auditory, and gastrointestinal toxic effects (Table 2).

Figure 3. Ratio of Median Survival With Triplet vs Doublet Regimens



Asterisk indicates decreased doses of drug in the investigational arm. *P* = .97 for treatment effect.

DISCUSSION

A logical strategy for improving the treatment of inoperable NSCLC with cytotoxics is to combine agents whose mechanism of action and toxicity differ and do not overlap. However, whether more chemotherapy is better and how much of it is best for patients with advanced NSCLC is still debatable. The rationale for using multi-drug combinations is based on preclinical studies that demonstrated synergism between different cytotoxics in vitro. Synergistic and additive effects have indeed been observed with different combinations (Edelman 2001; Zoli 1999). This led to the development of cytotoxic regimens combining two or three agents with different mechanisms of action (Crino 2002). We designed the present meta-analysis to ascertain whether more chemotherapy is better for patients with advanced NSCLC.

Combining newer drugs appeared to be an attractive approach because they showed a clear benefit when used as single agents in terms of efficacy and lower toxicity (Bunn 2000). Currently, most cancer practitioners use platinum-based doublet chemotherapy as first-line treatment of patients with stage IIIB and IV NSCLC. The present meta-analysis provides data in favor of such an approach. Indeed, the data in the present study demonstrate that adding a second agent to a single-agent regimen yields a significant benefit in terms of tumor response and survival. The tumor response rate was doubled when a second drug was added to a single-agent regimen and led to a significant increase in survival rate. This compelling and valuable information supports current clinical practice. However, the present meta-analysis did not address major questions facing the medical community. For example, is a doublet regimen better than a single-agent regimen for patients with a poor performance status and/or in elderly patients? In that regard, there is no consensus in the literature; many clinicians opted for a single-agent regimen for a performance score of two or for elderly patients, while others believed that a standard approach should be preferred in such patients (Gridelli 2003a; Soria 2001; Sweeny 2001; Lilenbaum 2005; Langer 2003; Hotta 2004).

Although less commonly accepted, triplet combinations are used by several teams throughout the world. Some trials suggested a significant increase in the tumor response rate and median survival with triplet regimens and had acceptable levels of toxicity (Comella 2000a). Another trial did not confirm these results (Souquet 2002). The data from the present meta-analysis do not support the triplet regimen approach. A moderate but significantly increased tumor response rate was noted when a third drug was added to a doublet regimen, but this higher tumor response rate did not translate into a benefit in terms of survival. However, data on one-year survival were available in 47% of the patients and definite conclusions on survival are difficult to draw. The OR of tumor responses and one-year survival rates for doublet regimens compared with single-agent regimens were significantly different ($P < 0.001$ and $P < 0.04$, respectively) from those for triplet regimens compared with doublet regimens (Table 1). In this study, there was a correlation between the tumor response rate in the control arm and the OR for tumor response (data not shown). The benefit was lower in trials with a high tumor response rate in the control arm than in those with a low tumor response rate. This relationship may explain why the addition of a second drug led to better results than the addition of a third drug. Trials with a planned decreased dose of chemotherapy in the experimental arms had a significantly lower benefit in terms of tumor response rate for both comparisons (doublet regimen vs single-agent regimen and triplet regimen vs doublet regimen) and for survival for a doublet regimen compared with a single-agent regimen. No difference was noted with and without dose reduction for survival for triplet regimens compared with doublet regimens.

As expected, toxicity was significantly more severe in patients who received combination chemotherapy. Symptomatic improvement due to tumor shrinkage should be balanced with increased toxic effects. Unfortunately, data on quality of life, which might be used to balance the clinical benefit of chemotherapy, were rarely available in these trials and no conclusions could be drawn. However, the increased toxicity was relatively lower when a third drug was added to a doublet regimen compared with when a second drug was added to a single-agent regimen. A possible explanation was that when a third drug was added, decreased doses of the drugs common to both arms had been planned in the investigational arm in 12 (41% of the patients) of 35 comparisons compared with only 7 (27% of the patients) of 30 comparisons when a second drug was added to single-agent chemotherapy regimen. The increase in toxicity was less important in the trials with dose reduction than in those without dose reduction for both a doublet regimen compared with a single-agent regimen and a triplet regimen compared with a doublet regimen (data not shown). The imbalance in comparisons with dose reduction may explain the observed difference in survival between the addition of a second drug and of a third drug.

Whether the lack of improvement in survival when a third drug was added to a doublet regimen could be explained by different rates of patients treated with second-line chemotherapy remains unknown. Because triplet regimens yielded better tumor response rates, the clinical value of such results deserves debate. Does a better tumor response rate translate into better quality of life? If such is the case, then a triplet regimen approach could be considered beneficial in patients with stage IV cancer. If not, it might be more reasonable to capitalize on the higher tumor response rates yielded by triplet regimens by treating patients with earlier stage disease (eg, neoadjuvant therapy).

Some trials demonstrated that the survival benefit obtained with chemotherapy appeared to translate into an improvement in the quality of life (Klastersky 2001). If triplet regimens are to be developed, the mechanism of action of the third drug should be dif-

ferent as well as the targeted cells to achieve synergism. Unfortunately, to date, this has not been demonstrated with the newer targeted agents. Adding the epidermal growth factor inhibitor (gefitinib) to standard chemotherapy failed to demonstrate synergy in triplet regimens compared with a standard doublet regimen in two large phase three studies (Giaccone 2004; Herbst 2004). The matrix metalloproteinase inhibitor and trastuzumab also failed to improve results (Bissett 2005; Gatzemeier 2004).

The data reported herein can be contrasted with the rest of the literature. Based on 28 trials and using a different methodological approach, Baggstrom et al (Baggstrom 2003) also concluded that tumor response and survival were improved by adding a second drug to a single-agent regimen. They were unable to show any advantage in adding a third drug to a doublet regimen. Their study was limited to newer drugs and to trials published in English. Differences in risk were used instead of ORs. Although these meta-analyses used different statistical methods, their results are consistent. A previous literature-based meta-analysis by the same authors suggested that newer drugs resulted in better overall tumor response and one-year survival compared with older drugs (Baggstrom 2002). Our results showed that when the single-agent regimen consisted of a newer drug, the benefit gained in adding a second agent was significantly lower than when the single agent was an older drug. This suggests that newer agents were also more efficient in the single-agent setting. When triplet regimens were compared with doublet regimens and when the control arm contained a newer or an older agent, adding a third agent yielded a similar benefit in terms of tumor response. Most of the older doublet regimens were based on the use of cisplatin. This supports the hypothesis that cisplatin or third generation-based doublet regimens might be equally efficient. However, no definite conclusions can be drawn from our data on the superiority of third generation agents and further trials are needed to explore this question.

The present study had limitations. A meta-analysis based on published data might overestimate the treatment effect because such a method does not allow researchers to carefully double check data and conduct detailed survival analyses (Williamson 2000). The main limitation of our analysis was the amount of missing data. Data on median survival were reported in only 88% of the patients and one-year survival in 53% of the patients. In spite of exclusion rates quite high in some trials, the results were not significantly different in trials using or not an intent-to-treat analysis. However the power of such comparison is limited.

Significant heterogeneity was observed in the treatment effect between the trials. Drug efficacy improved during the period in which the trials were conducted (between 1980 and 2001), mainly due to the emergence of newer agents (Bunn 1998; Waters 2002). We showed that part of the heterogeneity might be due to dose reduction (lower dose in experimental arm compared to control arm for drugs common to both arms) in some trials. The heterogeneity was no longer significant in a doublet regimen compared with a single-agent regimen for one-year survival when the heterogeneity related to dose reduction was taken into account. Finally, we used median survival to analyze survival because this was reported more frequently in the analyzed trials. This method might lead to biased results compared with hazard ratios based on individual patient data, which estimate the overall treatment effect on survival (Michiels 2005).

AUTHORS' CONCLUSIONS

Implications for practice

In conclusion, our data do not provide any rationale for the use of triplet regimens in inoperable NSCLC and their use should be strictly limited to clinical trials.

Implications for research

This meta-analysis confirmed the superiority of a two-drug regimen in advanced non-small-cell lung cancer. The future analysis should explore the impact of adding a new drug regimen and/or a targeted drug on the response rate and survival.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Alberola 2003

Methods	Inclusion Period: 1998-2000
Participants	No. of Patients Analyzed/Randomized: 370/570. Stage III (80), IV (290). Performance status: 0-1 (310), > or equal 2 (60).
Interventions	Treatment regimens (Doublet vs Triplet): Cisplatin plus gemcitabine vs Cisplatin plus gemcitabine plus vinorelbine
Outcomes	Response Rate, Survival
Notes	Trial with 3 arms, 2 eligible; did not use intent-to-treat analysis; decreased dose of gemcitabine in investigational arm

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Areco 1989

Methods	Inclusion Period: NA
Participants	No. of Patients Analyzed/Randomized: 102/102. Stage III (NA), IV (63). Performance status: 0-1 (NA), > or equal 2 (NA).
Interventions	Treatment regimens (Doublet vs Triplet): Cisplatin plus etoposide vs Cisplatin plus etoposide plus mitomycin
Outcomes	Response Rate, Survival
Notes	Published as an abstract

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Bando 1986

Methods	Inclusion Period: NA
Participants	No. of Patients Analyzed/Randomized: 85/85. Stage III (NA), IV (NA). Performance status: 0-1 (NA), > or equal 2 (NA).
Interventions	Treatment regimens (Doublet vs Triplet): Cisplatin plus doxorubicin vs Cisplatin plus doxorubicin plus vincristine
Outcomes	Response Rate
Notes	In Japanese

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Berardi 2001

Methods	Inclusion Period: 1998-2000
Participants	No. of Patients Analyzed/Randomized: 72/72. Stage III (0), IV (72). Performance status: 0-1 (NA), > or equal 2 (NA).
Interventions	Treatment regimens (Single Agent vs Doublet): Gemcitabine vs Gemcitabine plus cisplatin
Outcomes	Response Rate, Survival
Notes	Performance scores < or equal 2

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Bonomi 1989

Methods	Inclusion Period: 1984-1985
Participants	No. of Patients Analyzed/Randomized: 351/743. Stage III (0), IV (351). Performance status: 0-1 (267), > or equal 2 (84).

Bonomi 1989 (*Continued*)

Interventions	Treatment regimens (Doublet vs Triplet): Cisplatin plus vinblastine vs Cisplatin plus vinblastine plus mitomycin
Outcomes	Response Rate, Survival, Toxicity
Notes	Trial with 5 arms, 2 eligible; did not use intent-to-treat analysis; palliative radiotherapy or surgery possible; decreased dose of cisplatin and vinblastine in investigational arm

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Breau 1988

Methods	Inclusion Period: NA
Participants	No. of Patients Analyzed/Randomized: 45/45. Stage III (NA), IV (NA). Performance status: 0-1 (NA), > or equal 2 (NA).
Interventions	Treatment regimens (Doublet vs Triplet): Cisplatin plus bleomycin vs Cisplatin plus bleomycin plus etoposide
Outcomes	Response Rate
Notes	Published as an abstract

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Comella 2000a

Methods	Inclusion Period: 1997-1999
Participants	No. of Patients Analyzed/Randomized: 180/218. Stage III (76), IV (104). Performance status: 0-1 (180), > or equal 2 (0).
Interventions	Treatment regimens (Doublet vs Triplet): Cisplatin plus vinorelbine vs Cisplatin plus vinorelbine plus gemcitabine
Outcomes	Response Rate, Survival, Toxicity

Comella 2000a (*Continued*)

Notes	Trial with 3 arms‡‡; did not use intent-to-treat analysis; decreased dose of cisplatin in investigational arm

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Comella 2000b

Methods	Inclusion Period: 1997-1999
Participants	No. of Patients Analyzed/Randomized: 180/218. Stage III (76), IV (104). Performance status: 0-1 (180), > or equal 2 (0).
Interventions	Treatment regimens (Doublet vs Triplet): Cisplatin plus gemcitabine vs Cisplatin plus gemcitabine plus vinorelbine
Outcomes	Response Rate, Survival, Toxicity
Notes	Trial with 3 arms‡‡; did not use intent-to-treat analysis; decreased dose of cisplatin in investigational arm

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Crino 1990a

Methods	Inclusion Period: 1984-1987
Participants	No. of Patients Analyzed/Randomized: 93/156. Stage III (51), IV (99). Performance status: 0-1 (55), > or equal 2 (42).
Interventions	Treatment regimens (Single Agent vs Doublet): Cisplatin vs Cisplatin plus etoposide
Outcomes	Response Rate, Survival, Toxicity
Notes	Trial with 2 comparisons, 3 arms‡; performance score not available in 59 patients

Risk of bias

Crino 1990a (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Crino 1990b

Methods	Inclusion Period: 1984-1987
Participants	No. of Patients Analyzed/Randomized: 126/156. Stage III (51), IV (99). Performance status: 0-1 (55), > or equal 2 (42).
Interventions	Treatment regimens (Doublet vs Triplet): Cisplatin plus etoposide vs Cisplatin plus etoposide plus mitomycin
Outcomes	Response Rate, Survival, Toxicity
Notes	Trial with 2 comparisons, 3 arms‡; performance score not available in 59 patients

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Denkmayr 1991

Methods	Inclusion Period: NA-1991
Participants	No. of Patients Analyzed/Randomized: 36/66. Stage III (16), IV (17). Performance status: 0-1 (5), > or equal 2 (31).
Interventions	Treatment regimens (Single Agent vs Doublet): Cisplatin vs Cisplatin plus mitoxantrone
Outcomes	Response Rate, Survival
Notes	Published as an abstract; trial did not use intent-to-treat analysis

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Depierre 1994

Methods	Inclusion Period: 1989-1991
Participants	No. of Patients Analyzed/Randomized: 240/240. Stage III (95), IV (131). Performance status: 0-1 (170), > or equal 2 (68).
Interventions	Treatment regimens (Single Agent vs Doublet): Vinorelbine vs Vinorelbine plus cisplatin
Outcomes	Response Rate, Survival, Toxicity
Notes	None

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Dhingra 1985a

Methods	Inclusion Period: 1981-1983
Participants	No. of Patients Analyzed/Randomized: 129/191. Stage III (191), IV (0). Performance status: 0-1 (NA), > or equal 2 (NA).
Interventions	Treatment regimens (Doublet vs Triplet): Cisplatin plus etoposide vs Cisplatin plus etoposide plus vindesine
Outcomes	Response Rate, Survival
Notes	Trial with 2 comparisons, 3 arms; palliative radiotherapy or surgery possible; patients with performance scores of 0-2 or 3-4; decreased dose of etoposide in investigational arm

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Dhingra 1985b

Methods	Inclusion Period: 1981-1983
Participants	No. of Patients Analyzed/Randomized: 124/191. Stage III (191), IV (0). Performance status: 0-1 (NA), > or equal 2 (NA).

Dhingra 1985b (*Continued*)

Interventions	Treatment regimens (Doublet vs Triplet): Cisplatin plus vindesine vs Cisplatin plus vindesine plus etoposide
Outcomes	Response Rate, Survival
Notes	Trial with 2 comparisons, 3 arms; palliative radiotherapy or surgery possible; patients with performance scores of 0-2 or 3-4; decreased dose of cisplatin in investigational arm

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Einhorn 1986a

Methods	Inclusion Period: 1982-1984
Participants	No. of Patients Analyzed/Randomized: 83/129. Stage III (17), IV (NA). Performance status: 0-1 (NA), > or equal 2 (56).†
Interventions	Treatment regimens (Single Agent vs Doublet): Vindesine vs Vindesine plus cisplatin
Outcomes	Response Rate, Survival, Toxicity
Notes	Trial with 2 comparisons, 3 arms‡; did not use intent-to-treat analysis; Karnofsky scores >50

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Einhorn 1986b

Methods	Inclusion Period: 1982-1984
Participants	No. of Patients Analyzed/Randomized: 82/129. Stage III (17), IV (NA). Performance status: 0-1 (NA), > or equal 2 (56).†
Interventions	Treatment regimens (Doublet vs Triplet): Cisplatin plus vindesine vs Cisplatin plus vindesine plus mitomycin
Outcomes	Response Rate, Survival, Toxicity

Einhorn 1986b (*Continued*)

Notes	Trial with 2 comparisons, 3 arms‡; did not use intent-to-treat analysis; Karnofsky scores >50	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Elliott 1984

Methods	Inclusion Period: 1980-1982	
Participants	No. of Patients Analyzed/Randomized: 105/105. Stage III (72), IV (33). Performance status: 0-1 (80), > or equal 2 (21).	
Interventions	Treatment regimens (Single Agent vs Doublet): Vindesine vs Vindesine plus cisplatin.	
Outcomes	Response Rate, Survival, Toxicity	
Notes	Decreased dose of vindesine in nvestigational arm	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Erkisi 1995

Methods	Inclusion Period: 1991-1992	
Participants	No. of Patients Analyzed/Randomized: 74/77. Stage III (35), IV (39). Performance status: 0-1 (NA), > or equal 2 (NA).	
Interventions	Treatment regimens (Doublet vs Triplet): Cisplatin plus etoposide vs Cisplatin plus etoposide plus ifosfamide	
Outcomes	Response Rate, Survival, Toxicity	
Notes	Trial did not use intent-to-treat analysis; patients had performance scores of 0-2	
Risk of bias		
Item	**Authors' judgement**	**Description**

Erkisi 1995 (*Continued*)

Allocation concealment?	Unclear	B - Unclear

Frasci 2000

Methods	Inclusion Period: 1997-1999
Participants	No. of Patients Analyzed/Randomized: 125/152. Stage III (59), IV (71). Performance status: 0-1 (91), > or equal 2 (29).
Interventions	Treatment regimens (Single Agent vs Doublet): Vinorelbine vs Vinorelbine plus gemcitabine
Outcomes	Response Rate, Survival, Toxicity
Notes	Trial did not use intent-to-treat analysis; patients >70 y

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Fukuoka 1991

Methods	Inclusion Period: 1986-1988
Participants	No. of Patients Analyzed/Randomized: 137/210. Stage III (115), IV (88). Performance status: 0-1 (141), > or equal 2 (62).
Interventions	Treatment regimens (Doublet vs Triplet): Cisplatin plus vindesine vs Cisplatin plus vindesine plus mitomycin
Outcomes	Response Rate, Survival, Toxicity
Notes	Trial with 3 arms, 2 eligible; did not use intent-to-treat analysis; decreased dose of cisplatin in investigational arm

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Gandara 1993a

Methods	Inclusion Period: 1988-1990
Participants	No. of Patients Analyzed/Randomized: 215/356. Stage III (0), IV (215). Performance status: 0-1 (168), > or equal 2 (46).
Interventions	Treatment regimens (Single Agent vs Doublet): Cisplatin vs Cisplatin plus mitomycin
Outcomes	Response Rate, Survival, Toxicity
Notes	Trial with 2 comparisons, 3 arms; did not use intent-to-treat analysis; palliative radiotherapy or surgery possible; 50 mg/m² (in single agent regimen) and 100 mg/m² (in doublet regimen) of cisplatin

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Gandara 1993b

Methods	Inclusion Period: 1988-1990
Participants	No. of Patients Analyzed/Randomized: 218/356. Stage III (0), IV (218). Performance status: 0-1 (173), > or equal 2 (45).
Interventions	Treatment regimens (Single Agent vs Doublet): Cisplatin vs Cisplatin plus mitomycin
Outcomes	Response Rate, Survival, Toxicity
Notes	Trial with 2 comparisons, 3 arms; did not use intent-to-treat analysis; palliative radiotherapy or surgery possible; 100 mg/m² of cisplatin

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Gatzemeier 2000

Methods	Inclusion Period: 1995-1996
Participants	No. of Patients Analyzed/Randomized: 414/414. Stage III (124), IV (290). Performance status: 0-1 (74), > or equal 2 (337) †.
Interventions	Treatment regimens (Single Agent vs Doublet): Cisplatin vs Cisplatin plus paclitaxel
Outcomes	Response Rate, Survival, Toxicity
Notes	Palliative radiotherapy or surgery possible; decreased dose of cisplatin in investigational arm

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Georgoulias 2003

Methods	Inclusion Period: 1999-2001
Participants	No. of Patients Analyzed/Randomized: 279/302. Stage III (109), IV (193). Performance status: 0-1 (275), > or equal 2 (27).
Interventions	Treatment regimens (Single Agent vs Doublet): Taxotere vs Taxotere plus cisplatin
Outcomes	Response Rate, Survival, Toxicity
Notes	Trial did not use intent-to-treat analysis

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Gil Deza 1996

Methods	Inclusion Period: 1991-1995
Participants	No. of Patients Analyzed/Randomized: 162/162. Stage III (42), IV (114). Performance status: 0-1 (128), > or equal 2 (34).
Interventions	Treatment regimens (Single Agent vs Doublet): Vinorelbine vs Vinorelbine plus cisplatin

Gil Deza 1996 (*Continued*)

Outcomes	Response Rate, Survival, Toxicity	
Notes	Decreased dose of vinorelbine in investigational arm; published as an abstract	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Gorospe 2000

Methods	Inclusion Period: NA	
Participants	No. of Patients Analyzed/Randomized: 34/34. Stage III (NA), IV (NA). Performance status: 0-1 (NA), > or equal 2 (NA).	
Interventions	Treatment regimens (Single Agent vs Doublet): Gemcitabine vs Gemcitabine plus cisplatin	
Outcomes	Response Rate	
Notes	Published as an abstract; patients with stage III and stage IV cancer; performance scores of 0-2	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

Gralla 1994

Methods	Inclusion Period: NA	
Participants	No. of Patients Analyzed/Randomized: 673/673. Stage III (NA), IV (NA). Performance status: 0-1 (NA), > or equal 2 (NA).	
Interventions	Treatment regimens (Doublet vs Triplet): Mitomycin plus vinblastine vs Mitomycin plus vinblastine plus edatrexate	
Outcomes	Response Rate, Survival, Toxicity	
Notes	Published as an abstract; patients with Karnofsy scores > or equal 60%	
Risk of bias		

Gralla 1994 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Greco 2002

Methods	Inclusion Period: 1998-2001
Participants	No. of Patients Analyzed/Randomized: 135/135. Stage III (31), IV (104). Performance status: 0-1 (116), > or equal 2 (19).
Interventions	Treatment regimens (Doublet vs Triplet): Paclitaxel plus gemcitabine vs Paclitaxel plus gemcitabine plus carboplatin
Outcomes	Response Rate, Survival, Toxicity
Notes	Decreased dose of gemcitabine in investigational arm

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Gridelli 2003a

Methods	Inclusion Period: 1998-2000
Participants	No. of Patients Analyzed/Randomized: 707/707. Stage III (209), IV (489). Performance status: 0-1 (568), > or equal 2 (130).
Interventions	Treatment regimens (Single Agent vs Doublet): Vinorelbine vs Vinorelbine plus gemcitabine
Outcomes	Response Rate, Survival, Toxicity
Notes	Patients >70 y; decreased dose of vinorelbine in investigational arm

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Gridelli 2003b

Methods	Inclusion Period: 1998-2000
Participants	No. of Patients Analyzed/Randomized: 707/707. Stage III (209), IV (489). Performance status: 0-1 (568), > or equal 2 (130).
Interventions	Treatment regimens (Single Agent vs Doublet): Gemcitabine vs Gemcitabine plus vinorelbine
Outcomes	Response Rate, Survival, Toxicity
Notes	Patients >70 y; decreased dose of gemcitabine in investigational arm

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Hainsworth 1989a

Methods	Inclusion Period: 1982-1985
Participants	No. of Patients Analyzed/Randomized: 100/152. Stage III (34), IV (118). Performance status: 0-1 (96), > or equal 2 (56).
Interventions	Treatment regimens (Doublet vs Triplet): Cisplatin plus etoposide vs Cisplatin plus etoposide plus vindesine
Outcomes	Response Rate, Survival, Toxicity
Notes	Trial with 2 comparisons, 3 arms; palliative radiotherapy or surgery possible

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Hainsworth 1989b

Methods	Inclusion Period: 1982-1985
Participants	No. of Patients Analyzed/Randomized: 103/152. Stage III (34), IV (118). Performance status: 0-1 (96), > or equal 2 (56).

Hainsworth 1989b (*Continued*)

Interventions	Treatment regimens (Doublet vs Triplet): Cisplatin plus vindesine vs Cisplatin plus vindesine plus etoposide
Outcomes	Response Rate, Survival, Toxicity
Notes	Trial with 2 comparisons, 3 arms; palliative radiotherapy or surgery possible

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Hiraki 1991

Methods	Inclusion Period: 1987-NA
Participants	No. of Patients Analyzed/Randomized: 83/89. Stage III (37), IV (46). Performance status: 0-1 (NA), > or equal 2 (NA).
Interventions	Treatment regimens (Doublet vs Triplet): Cisplatin plus vindesine vs Cisplatin plus vindesine plus ifosfamide
Outcomes	Response Rate, Survival
Notes	Published as an abstract; trial did not use intent-to-treat analysis

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Hoffman 1985a

Methods	Inclusion Period: 1981-1983
Participants	No. of Patients Analyzed/Randomized: 46/103. Stage III (NA), IV (NA). Performance status: 0-1 (NA), > or equal 2 (NA).
Interventions	Treatment regimens (Doublet vs Triplet): Cisplatin plus etoposide vs Cisplatin plus etoposide plus vindesine
Outcomes	Response Rate, Survival

Hoffman 1985a (*Continued*)

Notes	Published as an abstract; trial with 2 comparisons, 4 arms; patients with performance scores < or equal 2	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Hoffman 1985b

Methods	Inclusion Period: 1981-1983	
Participants	No. of Patients Analyzed/Randomized: 45/103. Stage III (NA), IV (NA). Performance status: 0-1 (NA), > or equal 2 (NA).	
Interventions	Treatment regimens (Doublet vs Triplet): Cisplatin plus vindesine vs Cisplatin plus vindesine plus etoposide	
Outcomes	Response Rate, Survival	
Notes	Published as an abstract; trial with 2 comparisons, 4 arms; patients with performance scores < or equal 2	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Hussein 2000

Methods	Inclusion Period: 1997-1999	
Participants	No. of Patients Analyzed/Randomized: 53/71. Stage III (NA), IV (NA). Performance status: 0-1 (NA), > or equal 2 (NA).	
Interventions	Treatment regimens (Doublet vs Triplet): Paclitaxel plus carboplatin vs Paclitaxel plus carboplatin plus gemcitabine	
Outcomes	Response Rate, Survival	
Notes	Published as an abstract; trial did not use intent-to-treat analysis; patients with stage IIIB cancer only and with performance scores of 0-1; decreased dose of carboplatin and paclitaxel in investigational arm	
Risk of bias		

Hussein 2000 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Jensen 2002

Methods	Inclusion Period: 1999-2000
Participants	No. of Patients Analyzed/Randomized: 66/66. Stage III (NA), IV (NA). Performance status: 0-1 (NA), > or equal 2 (NA).
Interventions	Treatment regimens (Single Agent vs Doublet): Carboplatin vs Carboplatin plus taxotere
Outcomes	Response Rate, Survival
Notes	Published as an abstract; patients with stage IIIB cancer only

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Jeremic 1997

Methods	Inclusion Period: NA
Participants	No. of Patients Analyzed/Randomized: 117/120. Stage III (0), IV (117). Performance status: 0-1 (40), > or equal 2 (77) †.
Interventions	Treatment regimens (Single Agent vs Doublet): Etoposide vs Etoposide plus carboplatin
Outcomes	Response Rate, Survival, Toxicity
Notes	Trial did not use intent-to-treat analysis

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Kawahara 1991

Methods	Inclusion Period: 1983-1985
Participants	No. of Patients Analyzed/Randomized: 160/160. Stage III (65), IV (85). Performance status: 0-1 (90), > or equal 2 (70).
Interventions	Treatment regimens (Single Agent vs Doublet): Cisplatin vs Cisplatin plus vindesine
Outcomes	Response Rate, Survival, Toxicity
Notes	Six patients with stage I cancer and 4 patients with stage II cancer

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Klastersky 1989

Methods	Inclusion Period: 1985-1986
Participants	No. of Patients Analyzed/Randomized: 176/176. Stage III (55), IV (107). Performance status: 0-1 (70), > or equal 2 (92) †.
Interventions	Treatment regimens (Single Agent vs Doublet): Cisplatin vs Cisplatin plus etoposide
Outcomes	Response Rate, Survival, Toxicity
Notes	None

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Kodani 2002

Methods	Inclusion Period: 1987-1992
Participants	No. of Patients Analyzed/Randomized: 132/132. Stage III (61), IV (71). Performance status: 0-1 (110), > or equal 2 (22).

Kodani 2002 (*Continued*)

Interventions	Treatment regimens (Doublet vs Triplet): Cisplatin plus vindesine vs Cisplatin plus vindesine plus ifosfamide
Outcomes	Response Rate, Survival, Toxicity
Notes	None

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Kosmidis 1994

Methods	Inclusion Period: 1989-1991
Participants	No. of Patients Analyzed/Randomized: 135/136. Stage III (82), IV (54). Performance status: 0-1 (97), > or equal 2 (37).
Interventions	Treatment regimens (Doublet vs Triplet): Cisplatin plus vinblastine vs Cisplatin plus vinblastine plus ifosfamide
Outcomes	Response Rate, Survival
Notes	Trial did not use intent-to-treat analysis

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Laack 2002

Methods	Inclusion Period: 1999-2001
Participants	No. of Patients Analyzed/Randomized: 287/300 Stage III (NA), IV (NA). Performance status: 0-1 (NA), > or equal 2 (NA).
Interventions	Treatment regimens (Doublet vs Triplet): Gemcitabine plus vinorelbine vs Gemcitabine plus vinorelbine plus cisplatin
Outcomes	Response Rate, Survival

Laack 2002 (*Continued*)

Notes	Trial did not use intent-to-treat analysis	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Le Chevalier 1994

Methods	Inclusion Period: 1989-1991	
Participants	No. of Patients Analyzed/Randomized: 412/412. Stage III (176), IV (236). Performance status: 0-1 (323), > or equal 2 (89).	
Interventions	Treatment regimens (Single Agent vs Doublet): Vinorelbine vs Vinorelbine plus cisplatin	
Outcomes	Response Rate, Survival, Toxicity	
Notes	Trial with 3 arms, 2 eligible	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Lorusso 1995

Methods	Inclusion Period: 1992-1993	
Participants	No. of Patients Analyzed/Randomized: 69/69. Stage III (40), IV (22). Performance status: 0-1 (33), > or equal 2 (29).	
Interventions	Treatment regimens (Single Agent vs Doublet): Vinorelbine vs Vinorelbine plus cisplatin	
Outcomes	Response Rate, Survival, Toxicity	
Notes	Decreased dose of vinorelbine in investigational arm; palliative radiotherapy or surgery possible	
Risk of bias		
Item	**Authors' judgement**	**Description**

Lorusso 1995 (*Continued*)

Allocation concealment?	Unclear	B - Unclear

Luedke 1990a

Methods	Inclusion Period: NA
Participants	No. of Patients Analyzed/Randomized: 291/435. Stage III (NA), IV (NA). Performance status: 0-1 (187), > or equal 2 (247) †.
Interventions	Treatment regimens (Single Agent vs Doublet): Vindesine vs Vindesine plus cisplatin
Outcomes	Response Rate, Survival, Toxicity
Notes	Trial with 2 comparisons, 3 arms; no intent-to-treat analysis; palliative radiotherapy or surgery possible; patients with stage III and stage IV cancer

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Luedke 1990b

Methods	Inclusion Period: NA
Participants	No. of Patients Analyzed/Randomized: 284/435. Stage III (NA), IV (NA). Performance status: 0-1 (187), > or equal 2 (247) †.
Interventions	Treatment regimens (Single Agent vs Doublet): Vindesine vs Vindesine plus mitomycin
Outcomes	Response Rate, Survival, Toxicity
Notes	Trial with 2 comparisons, 3 arms; no intent-to-treat analysis; palliative radiotherapy or surgery possible; patients with stage III and stage IV cancer

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Masutani 1996a

Methods	Inclusion Period: 1987-1992	
Participants	No. of Patients Analyzed/Randomized: 68/105. Stage III (31), IV (37). Performance status: 0-1 (55), > or equal 2 (13).	
Interventions	Treatment regimens (Doublet vs Triplet): Cisplatin plus vindesine vs Cisplatin plus vindesine plus ifosfamide	
Outcomes	Response Rate, Survival, Toxicity	
Notes	Trial with 2 comparisons, 3 arms; Trial did not use intent-to-treat analysis	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Masutani 1996b

Methods	Inclusion Period: 1987-1992	
Participants	No. of Patients Analyzed/Randomized: 70/105. Stage III (35), IV (35). Performance status: 0-1 (52), > or equal 2 (18).	
Interventions	Treatment regimens (Doublet vs Triplet): Cisplatin plus vindesine vs Cisplatin plus vindesine plus mitomycin	
Outcomes	Response Rate, Survival, Toxicity	
Notes	Trial with 2 comparisons, 3 arms; Trial did not use intent-to-treat analysis	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Mencoboni 1997

Methods	Inclusion Period: NA
Participants	No. of Patients Analyzed/Randomized: 20/20. Stage III (8), IV (12). Performance status: 0-1 (15), > or equal 2 (5).

Mencoboni 1997 (*Continued*)

Interventions	Treatment regimens (Doublet vs Triplet): Ifosfamide plus vinorelbine vs Ifosfamide plus vinorelbine plus cisplatin
Outcomes	Response Rate, Toxicity
Notes	None

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Nakabayashi 1986

Methods	Inclusion Period: 1982-NA
Participants	No. of Patients Analyzed/Randomized: 40/47. Stage III (NA), IV (NA). Performance status: 0-1 (NA), > or equal 2 (NA).
Interventions	Treatment regimens (Doublet vs Triplet): Cisplatin plus mitomycin vs Cisplatin plus mitomycin plus ftorafur
Outcomes	Response Rate
Notes	Published as an abstract; trial did not use intent-to-treat analysis; patients with performance scores of 0-3

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Negoro 1988

Methods	Inclusion Period: 1986-NA
Participants	No. of Patients Analyzed/Randomized: 110/167. Stage III (NA), IV (NA). Performance status: 0-1 (NA), > or equal 2 (NA).
Interventions	Treatment regimens (Doublet vs Triplet): Cisplatin plus vindesine vs Cisplatin plus vindesine plus mitomycin
Outcomes	Response Rate, Survival

Negoro 1988 (*Continued*)

Notes	Published as an abstract; trial with 3 arms, 2 eligible; did not use intent-to-treat analysis; decreased dose of cisplatin in investigational arm

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Negoro 2003

Methods	Inclusion Period: 1995-1998
Participants	No. of Patients Analyzed/Randomized: 265/398. Stage III (93), IV (165). Performance status: 0-1 (242), > or equal 2 (16).
Interventions	Treatment regimens (Single Agent vs Doublet): Irinotecan vs Irinotecan plus cisplatin
Outcomes	Response Rate, Survival
Notes	Trial with 3 arms, 2 eligible. Decreased dose of irinotecan in investigational arm; published as an abstract

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Paccagnella 1990

Methods	Inclusion Period: 1987-1988
Participants	No. of Patients Analyzed/Randomized: 78/78. Stage III (27), IV (51). Performance status: 0-1 (NA), > or equal 2 (NA).
Interventions	Treatment regimens (Doublet vs Triplet): Cisplatin plus etoposide vs Cisplatin plus etoposide plus ifosfamide
Outcomes	Response Rate, Survival
Notes	Palliative radiotherapy or surgery possible; 60 patients with Karnofsky scores > or equal 70 and 9 patients with scores of 50-60; decreased dose of cisplatin and etoposide in investigational arm

Risk of bias

Paccagnella 1990 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Pérol 2002

Methods	Inclusion Period: NA
Participants	No. of Patients Analyzed/Randomized: 70/70. Stage III (0), IV (70). Performance status: 0-1 (56), > or equal 2 (14).
Interventions	Treatment regimens (Doublet vs Triplet): Cisplatin plus vinorelbine vs Cisplatin plus vinorelbine plus taxotere
Outcomes	Response Rate, Survival, Toxicity
Notes	None

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Richards 1991

Methods	Inclusion Period: 1985-1986
Participants	No. of Patients Analyzed/Randomized: 240/247. Stage III (NA), IV (NA). Performance status: 0-1 (194), > or equal 2 (46).
Interventions	Treatment regimens (Doublet vs Triplet): Cisplatin plus 5-fluorouracil vs Cisplatin plus 5-fluorouracil plus vinblastine
Outcomes	Response Rate, Survival, Toxicity
Notes	Palliative radiotherapy or surgery possible; did not use intent-to-treat analysis

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Rivero 1999

Methods	Inclusion Period: 1996-1998
Participants	No. of Patients Analyzed/Randomized: 94/94. Stage III (46), IV (48). Performance status: 0-1 (NA), > or equal 2 (NA).
Interventions	Treatment regimens (Single Agent vs Doublet): Vinorelbine vs Vinorelbine plus ifosfamide
Outcomes	Response Rate, Toxicity
Notes	Published as an abstract; performance score of 0 in 14 patients and 1-2 in 80 patients

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Rosso 1990

Methods	Inclusion Period: 1985-1987
Participants	No. of Patients Analyzed/Randomized: 216/216. Stage III (101), IV (115). Performance status: 0-1 (178), > or equal 2 (38).
Interventions	Treatment regimens (Single Agent vs Doublet): Etoposide vs Etoposide plus cisplatin
Outcomes	Response Rate, Survival, Toxicity
Notes	Palliative radiotherapy or surgery possible

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Sandler 2000

Methods	Inclusion Period: 1995-1997
Participants	No. of Patients Analyzed/Randomized: 522/522. Stage III (164), IV (358). Performance status: 0-1 (73), > or equal 2 (439) †.

Sandler 2000 (*Continued*)

Interventions	Treatment regimens (Single Agent vs Doublet): Cisplatin vs Cisplatin plus gemcitabine
Outcomes	Response Rate, Survival, Toxicity
Notes	Palliative radiotherapy or surgery possible

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Sederholm 2002

Methods	Inclusion Period: 1998-2001
Participants	No. of Patients Analyzed/Randomized: 332/334. Stage III (139), IV (186). Performance status: 0-1 (277), > or equal 2 (45).
Interventions	Treatment regimens (Single Agent vs Doublet): Gemcitabine vs Gemcitabine plus carboplatin
Outcomes	Response Rate, Survival, Toxicity
Notes	Trial did not use intent-to-treat analysis

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Shah 1988

Methods	Inclusion Period: 1985-1987
Participants	No. of Patients Analyzed/Randomized: 75/75. Stage III (NA), IV (NA). Performance status: 0-1 (NA), > or equal 2 (NA).
Interventions	Treatment regimens (Doublet vs Triplet): Cisplatin plus vinblastine vs Cisplatin plus vinblastine plus 5-fluorouracil
Outcomes	Response Rate, Survival
Notes	Published as an abstract

Shah 1988 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Shinkai 1991

Methods	Inclusion Period: 1986-1989
Participants	No. of Patients Analyzed/Randomized: 126/126. Stage III (44), IV (80). Performance status: 0-1 (111), > or equal 2 (13).
Interventions	Treatment regimens (Doublet vs Triplet): Cisplatin plus vindesine vs Cisplatin plus vindesine plus mitomycin
Outcomes	Response Rate, Survival, Toxicity
Notes	Decreased dose of cisplatin in investigational arm

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Souquet 2002

Methods	Inclusion Period: 1998-1999
Participants	No. of Patients Analyzed/Randomized: 259/259. Stage III (0), IV (259). Performance status: 0-1 (259), > or equal 2 (0).
Interventions	Treatment regimens (Doublet vs Triplet): Cisplatin plus vinorelbine vs Cisplatin plus vinorelbine plus ifosfamide
Outcomes	Response Rate, Survival
Notes	Decreased dose of cisplatin and vinorelbine in investigational arm

Risk of bias		
Item	**Authors' judgement**	**Description**

Souquet 2002 (*Continued*)

Allocation concealment?	Unclear	B - Unclear

Splinter 1996a

Methods	Inclusion Period: 1988-1992
Participants	No. of Patients Analyzed/Randomized: 105/225. Stage III (25), IV (80). Performance status: 0-1 (83), > or equal 2 (22).
Interventions	Treatment regimens (Single Agent vs Doublet): Teniposide vs Teniposide plus cisplatin
Outcomes	Response Rate, Survival, Toxicity
Notes	Trial did not use intent-to-treat analysis; 120 mg/m² of teniposide

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Splinter 1996b

Methods	Inclusion Period: 1988-1992
Participants	No. of Patients Analyzed/Randomized: 106/225. Stage III (37), IV (69). Performance status: 0-1 (91), > or equal 2 (15).
Interventions	Treatment regimens (Single Agent vs Doublet): Teniposide vs Teniposide plus cisplatin
Outcomes	Response Rate, Survival, Toxicity
Notes	Trial did not use intent-to-treat analysis; 360 mg/m² of teniposide

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Tsuruta 1986

Methods	Inclusion Period: 1983-1984
Participants	No. of Patients Analyzed/Randomized: 80/84. Stage III (NA), IV (NA). Performance status: 0-1 (NA), > or equal 2 (NA).
Interventions	Treatment regimens (Single Agent vs Doublet): Cisplatin vs Cisplatin plus vindesine
Outcomes	Response Rate
Notes	Published as an abstract; trial did not use intent-to-treat analysis

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Von Pawel 2000

Methods	Inclusion Period: NA
Participants	No. of Patients Analyzed/Randomized: 446/446. Stage III (74), IV (362). Performance status: 0-1 (143), > or equal 2 (295) †.
Interventions	Treatment regimens (Single Agent vs Doublet): Cisplatin vs Cisplatin plus tirapazamine
Outcomes	Response Rate, Survival, Toxicity
Notes	One patient with stage II cancer and 66 patients with stage IIIB cancer and pleural effusion

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Wozniak 1998

Methods	Inclusion Period: 1993-1995
Participants	No. of Patients Analyzed/Randomized: 415/432. Stage III (33), IV (382). Performance status: 0-1 (NA), > or equal 2 (NA).
Interventions	Treatment regimens (Single Agent vs Doublet): Cisplatin vs Cisplatin plus vinorelbine
Outcomes	Response Rate, Survival, Toxicity
Notes	Trial did not use intent-to-treat analysis; palliative radiotherapy or surgery was possible; patients with performance score of 0-1

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Abbreviation: NA, data not available.
*According to the World Health Organization or Karnofsky criteria.
†Karnofsky performance score of < or equal 70% or < or equal 80%.
‡Multiple treatment arms comparing doublet with single agent chemotherapy and triplet compared with doublet regimens.
‡‡There is a risk of bias due to the knowledge by the investigators of the results of the interim analysis (J Clin Oncol. 2001;19:593). Therefore, we kept only the data corresponding to the interim analysis.

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

Study	Reason for exclusion
Baldini 1998	Completely different drugs in the two arms
Berghmans 1999	Not correctly randomized
Bokkel 1999	Completely different drugs in the two arms
Bonomi 1994	Inefficient drug (Acivicin)
Breau 1988b	Inefficient drug (Lonidamine)
Brocato 1995	Combination chemo-radiotherapy
Cartei 1991	Excluded due to number of patients/arm NA

(*Continued*)

Citron 1985	Excluded due to number of patients/arm NA
Colleoni 1997	Completely different drugs in the two arms
Comella 2001	Excluded due to interim analysis
Contu 1993	Inefficient drug (Lonidamine)
Crawford 1996	Leucovorin was the cytotoxic agent
Crino 1995	Completely different drugs in the two arms
Crino 1999	Completely different drugs in the two arms
Danson 2003	Completely different drugs in the two arms
Davis 1980	Randomized before January 1980
Fujii 1987	Excluded due to number of patients/arm NA
Gatzemeier 1991	Inefficient drug (Lonidamine)
Gebbia 2002	Completely different drugs in the two arms
Hansen 1976	Randomized before January 1980
Itri 1982	Prior chemotherapy
Klastersky 1982	Not correctly randomized
Kris 1984	Prior chemotherapy
Langer 2000	Excluded due to number of patients/arm NA
Lilenbaum 2002	Excluded due to number of patients/arm NA. Data published after the time of the analysis (Lilenbaum 2005)
Luedke 1983	Randomized before January 1980
Luporini 1985	Not correctly randomized
Melo 2002	Completely different drugs in the two arms
Murray 1990	Analysis of drug delivery
Mylonakis 1992	Prior chemotherapy

(*Continued)*

Paccagnella 2002	Excluded due to number of patients/arm NA. Data published after the time of the analysis (Paccagnella 2006)
Perng 1997	Completely different drugs in the two arms
Perry 1987	Excluded due to number of patients/arm NA
Polyzos 1997	Completely different drugs in the two arms
Popkin 1985	Excluded due to number of patients/arm NA
Rapp 1988	Completely different drugs in the two arms
Rosso 1994	Combination CaP and C in the same arm
Ruckdeschel 1984	Randomized before January 1980
Ruckdeschel 1986	Completely different drugs in the two arms
Rudd 2002	Completely different drugs in the two arms
Sculier 1994	Combination CaP and C in the same arm
Sculier 1998	Combination CaP and C in the same arm
Sculier 2002	Combination CaP and C in the same arm
Serke 2000	Completely different drugs in the two arms
Vansteenkiste 2001	Completely different drugs in the two arms
White 2000	Completely different drugs in the two arms

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

Bodkin 2003

Trial name or title	Randomized phase II trial of three irinotecan-based chemotherapy regimens in patients (pts) with previously untreated, stage IIIB/IV non-small cell lung cancer (NSCLC): Prelimary results
Methods	
Participants	69
Interventions	Treatment regimens (Doublet vs Triplet): Irinotecan plus Paclitaxel vs Irinotecan plus Paclitaxel plus Carboplatin / Irinotecan plus Carboplatin vs Irinotecan plus Carboplatin plus Paclitaxel

Bodkin 2003 (*Continued*)

Outcomes	Response Rate, Survival, Toxicity
Starting date	Inclusion period: NA
Contact information	NA
Notes	Trial with 3 arms

Chen 2005

Trial name or title	A randomized phase II study of vinorelbine plus gemcitabine with/without cisplatin against inoperable non-small-cell lung cancer previously untreated
Methods	
Participants	86
Interventions	Treatment regimens (Doublet vs Triplet): Vinorelbine plus Gemcitabine vs Vinorelbine plus Gemcitabine plus Cisplatin
Outcomes	Response Rate, Survival, Toxicity
Starting date	Inclusion period: 2002 - 2003
Contact information	NA
Notes	None

Comella 2004

Trial name or title	SICOG 9909
Methods	
Participants	264
Interventions	Treatment regimens (Single Agent vs Doublet): Gemcitabine vs Gemcitabine plus Vinorelbine / Paclitaxel vs Paclitaxel plus Gemcitabine
Outcomes	Survival, Toxicity
Starting date	Inclusion period: 1999 - 2003
Contact information	NA
Notes	Trial with 4 arms

Comella 2006

Trial name or title	SICOG 0101
Methods	
Participants	431
Interventions	Treatment regimens (Doublet vs Triplet): Gemcitabine plus Vinorelbine vs Gemcitabine plus Vinorelbine plus Cisplatin / Gemcitabine plus Paclitaxel vs Gemcitabine plus Paclitaxel plus Cisplatin
Outcomes	Response Rate, Survival, Toxicity
Starting date	Inclusion period: 2001 - 2005
Contact information	NA
Notes	Trial with 4 arms

Georgoulias 2005

Trial name or title	Docetaxel in combination with gemcitabine (DG) versus docetaxel (D) as front-line treatment in patients with advanced/metastatic NSCLC: A multicentre, randomized, phase III trial
Methods	
Participants	925
Interventions	Treatment regimens (Single Agent vs Doublet): Docetaxel vs Docetaxel plus Gemcitabine
Outcomes	Response Rate, Survival, Toxicity
Starting date	Inclusion period: NA
Contact information	NA
Notes	None

Groen 2003

Trial name or title	Docetaxel and carboplatin once every 3 weeks versus weekly docetaxel in advanced non-small cell lung cancer (NSCLC). An interim analysis of a multicenter phase III trial
Methods	
Participants	150
Interventions	Treatment regimens (Single Agent vs Doublet): Docetaxel vs Docetaxel plus Carboplatin
Outcomes	Response Rate, Survival,Toxicity

Groen 2003 (*Continued*)

Starting date	Inclusion period: 2000-2002
Contact information	NA
Notes	None

Kosmidis 2004

Trial name or title	Gemcitabine (G) vs gemcitabine-carboplatin (GCB) for patients with advanced non-small cell lung cancer (NSCLC) and PS:2. A prospective randomized phase II study of the Hellenic Co-Operative Oncology Group
Methods	
Participants	102
Interventions	Treatment regimens (Single Agent vs Doublet): Gemcitabine vs Gemcitabine plus Carboplatin
Outcomes	Response Rate, Survival,Toxicity
Starting date	Inclusion period: NA
Contact information	NA
Notes	None

Lilenbaum 2005

Trial name or title	CALGB 9730
Methods	
Participants	584
Interventions	Treatment regimens (Single Agent vs Doublet): Paclitaxel vs Paclitaxel plus Carboplatin
Outcomes	Response Rate, Survival, Toxicity
Starting date	Inclusion period: 1997 - 2000
Contact information	NA
Notes	This study was excluded at the time of the analysis because data were not yet available

Mainwaring 2005

Trial name or title	Weekly docetaxel versus weekly docetaxel/gemcitabine as first-line therapy for patients who are elderly or with poor performance status (PS) or with serious comorbidities with advanced non-small cell lung cancer (NSCLC): Interim safety analysis of a Minnie Pearl Cancer Research Network phase III trial
Methods	
Participants	214
Interventions	Treatment regimens (Single Agent vs Doublet): Docetaxel vs Docetaxel plus Gemcitabine
Outcomes	Response Rate, Survival, Toxicity
Starting date	Inclusion period: NA
Contact information	NA
Notes	None

Paccagnella 2006

Trial name or title	Adding gemcitabine to paclitaxel/carboplatin combination increases survival in advanced non-small-cell lung cancer: results of a phase II-III study
Methods	
Participants	324
Interventions	Treatment regimens (Doublet vs Triplet): Paclitaxel plus Carboplatin vs Paclitaxel plus Carboplatin plus Gemcitabine
Outcomes	Response Rate, Survival, Toxicity
Starting date	Inclusion period: 1998 - 2004
Contact information	NA
Notes	This study was excluded at the time of the analysis because data were not yet available

Williamson 2005

Trial name or title	SWOG S0003
Methods	
Participants	396
Interventions	Treatment regimens (Doublet vs Triplet): Paclitaxel plus Carboplatin vs Paclitaxel plus Carboplatin plus Tirapazamine

Williamson 2005 (*Continued*)

Outcomes	Response Rate, Survival, Toxicity
Starting date	Inclusion period: 2000 - 2002
Contact information	NA
Notes	None

Abbreviation: NA, data not available.
This table presents the characteristics of studies that were not available at the time of the analysis.