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Treatment of Inoperable Advanced Non-small-cell Lung Cancer: Regimens with or without Taxane

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Treatment of Inoperable Advanced Non-small-cell Lung Cancer: Regimens with or without Taxane

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September 2002

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Authorship

Srabani Banerjee was involved in conception and design of the project; review of the literature; data extraction, analyses and interpretation; preparation of the draft report and subsequent revisions. David Moher contributed to the design of the project and participated in revisions to the report. David J. Stewart contributed to the design of the project and participated in the review of literature, data extraction and interpretation and revisions to the report. All approved the final version of the report.

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Srabani Banerjee: none

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REPORT *IN BRIEF*

September 2002

Treatment of Inoperable and Advanced Non-small-cell Lung Cancer: Regimens with or without Taxane

Target Audience

The review will be helpful to oncologists and other health care providers, researchers and health authorities involved in the management of cancer care and/or the development of cancer care guidelines.

Technology Name

The anticancer drugs paclitaxel (Taxol®) and docetaxel (Taxotere®) belong to the taxane family.

Disease/Condition

Lung cancer is the leading cause of cancer death in Canada. In 2002, an estimated 18,400 Canadians will die of lung cancer and 20,800 new cases will be diagnosed. There are two main types of lung cancer: small-cell-lung cancer and non-small-cell lung cancer. Non-small-cell lung cancer (NSCLC) makes up about 80% of lung cancers. The symptoms of lung cancer are not usually evident until the disease is at an advanced stage. At the time of diagnosis 75% of NSCLC patients have advanced disease not amenable to surgery. Therapeutic options include supportive care, chemotherapy and palliative radiation therapy.

Technology Description

Taxanes are relatively new anticancer drugs that have been in use since the early 1990s. They inhibit cancer cell growth by stopping cell division. Administered intravenously, they are used either as single agent or in combination with other anticancer drugs as part of a chemotherapy regimen.

The Issue

Although a number of systematic reviews and meta-analyses have assessed chemotherapy in the treatment of advanced NSCLC, they have not evaluated taxane-containing regimens versus non-taxane regimens.

Assessment Objective

To compare, through a systematic review of the literature, the clinical efficacy of regimens containing taxanes with regimens not containing taxanes, in the treatment of advanced inoperable NSCLC. Outcomes examined include response, survival, toxicity and quality of life (QoL).

Methodology

A comprehensive literature search identified 124 potentially relevant articles. On further examination, 49 potentially relevant randomized controlled trials were selected; 30 of these were ultimately excluded due to data overlap. Nineteen trials with 7,433 patients were used for the meta-analyses.

Conclusions

- Taxane-regimens (TRs) do not significantly improve one-year survival when compared with non-taxane regimens (NTRs) for the treatment of inoperable and advanced NSCLC patients. It should be noted that TRs and NTRs both varied considerably in drug combinations used.
- TRs showed a greater response rate than NTRs. However, when TRs were compared with NTRs that contained newer chemotherapeutic drugs such as vinorelbine, there was no significant increase in response rate.
- Treatment regimens typically contain other drugs in addition to a taxane. The companion drug(s) varied from trial to trial, making overall comparison of toxicity difficult.
- Comparison of impact on QoL between TRs and NTRs was also difficult. Few studies reported QoL data; those that did used different QoL scales. Overall, it appears TRs and NTRs were similar in terms of QoL impact, but a formal analysis was not possible.

This summary is based on a comprehensive health technology assessment report available from CCOHTA's web site (www.ccohta.ca): Banerjee S, Moher D, Stewart DJ. **Treatment of inoperable advanced non-small-cell lung cancer: regimens with or without taxane**.

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EXECUTIVE SUMMARY

The Issue

Optimal chemotherapy regimens, which will provide a substantial benefit to patients with advanced non-small-cell lung cancer (NSCLC), need to be determined. The taxanes (paclitaxel and docetaxel) are relatively new anti-cancer drugs with a unique mechanism of action. The present study was undertaken to evaluate the efficacy of taxanes in the treatment of advanced and inoperable NSCLC.

Objective

The purpose of this systematic review is to compare the clinical efficacy of taxane-containing-regimens (TR) with regimens not containing taxanes (NTR) in the treatment of inoperable advanced NSCLC.

Methods

Relevant trials were identified by searching electronic databases (Biological Abstracts, CANCERLIT®, CINAHL®, Current Contents, Dissertation Abstracts, EMBASE®, EBM reviews, and MEDLINE®), hand searching and contacting content experts and the drug manufacturers. Only randomized controlled trials enrolling advanced NSCLC patients with unresectable tumours were considered. In addition, the trials were required to have at least one treatment arm containing a taxane and one arm not containing a taxane and to have reported survival, response, toxicity or quality of life (QoL) data. Information on study characteristics, patient characteristics and details of interventions and outcomes from each trial were extracted independently by two reviewers. Where possible odds ratios were calculated and summary estimates were derived from pooled odds ratios.

Results

Nineteen trials were included in the meta-analysis. The pooled odds ratios and 95% confidence intervals for response rate and one-year mortality were 1.34 (1.09, 1.66) and 0.94 (0.83, 1.05) respectively. The TRs produced a statistically significant increase in response rate when compared with the NTRs. However, the difference in one-year mortality between the TRs and NTRs did not achieve statistical significance. Toxicity profiles in the different studies varied considerably, making overall comparisons between TRs and NTRs difficult. QoL was reported in only six trials and TRs and NTRs appeared to be similar in terms of overall impact on QoL.

Conclusions

This meta-analysis showed that for inoperable advanced NSCLC taxane-containing regimens do not offer a statistically significant advantage in terms of one-year survival when compared to regimens not containing taxane. However the TRs did produce a statistically significant effect on response rate when compared to NTRs. It should be noted that the trials were heterogeneous with respect to the drug combinations used and hence the pooled results should be viewed with caution. Toxicity profiles in the different studies varied considerably. To allow valid comparisons to be made between regimens with and without a taxane, more RCTs using uniform drug combinations are needed. Sufficient data on QoL were not available to enable meaningful QoL comparisons between TRs and NTRs; efforts should be made to address this issue when conducting trials.

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ABBREVIATIONS

ab	abstract
ab+	abstract + copy of presentation
AUC	area under the curve
c	cisplatin
CALGB	Cancer and Leukemia Group B
cb	carboplatin
CI	confidence interval
e	etoposide, VP16
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
g	gemcitabine
h	high dose
i	ifosfamide
m	merbarone
nc	no prior chemotherapy
NIH	National Institute of Health, US
NSCLC	non-small-cell lung cancer
NTR	non-taxane containing regimen(s)
OR	odds ratio
p	paclitaxel or Taxol
pc	prior chemotherapy
pf	full article (published)
pi	piroxantrone
PS	performance status
q	every
QoL	quality of life
t	docetaxel or Taxotere
tn	teniposide, VM26
tp	topotecan
TR	taxane containing regimen(s)
TRD	treatment related death(s)
u	unknown
v	vinorelbine or Navelbine
vn	vindesin

1 INTRODUCTION

1.1 Background

Lung cancer is one of the most lethal human malignancies and its incidence is increasing worldwide. Lung cancer is comprised of two major categories – small-cell lung cancer and non-small-cell lung cancer (NSCLC). In Canada in 2002, the number of new cases and deaths due to lung cancer are estimated to be 20,800 and 18,400 respectively.[1] It is the leading cause of cancer death among Canadians. Almost one-third of the cancer deaths in men and almost one-quarter in women are due to lung cancer. NSCLC accounts for approximately 80% of lung cancers.

At the time of diagnosis 75% of NSCLC patients present with locally advanced or metastatic disease,[2] not amenable to surgery. Usually the symptoms of lung cancer are not evident until the disease is at an advanced stage. The anatomic extent of disease in patients with lung cancer is classified according to the International System for Staging Lung Cancer.[3] Advanced stage disease includes stages III (when tumour has spread locally and there is nodal involvement but no distant metastasis) and IV (when there is distant metastasis).

The therapeutic options for advanced NSCLC include supportive care (measures to control symptoms of the cancer), chemotherapy or palliative radiation therapy.[4-6] However, the optimum treatment strategy still needs to be determined.

1.2 Technology Overview

The previously available chemotherapeutic regimens, such as alkylating agents and anti-metabolites, which were highly effective against some cancers, produced response rates of <15% in advanced NSCLC. They did not improve survival rates.[7] Consequently, there has been considerable controversy regarding the value of chemotherapy in advanced NSCLC. With the advent of platinum-based chemotherapeutic drugs, a modest improvement in survival rates was achieved.[8] Results of meta-analyses have demonstrated that platinum-based chemotherapy regimens provide a survival advantage when compared to best supportive care.[9,10] However this survival benefit is small.

Guidelines developed by the Cancer Care Ontario Lung Disease Site Group and others have addressed the role of chemotherapy in advanced NSCLC. The guidelines recognize that cisplatin-based chemotherapy offers a modest survival advantage compared to best supportive care, and that it is reasonable to offer such treatment to patients.[5]

Various studies have also suggested that newer agents may be superior to older agents, and newer agents are generally chosen for inclusion in combination therapy. For example, it has been reported that cisplatin-vinorelbine is superior to cisplatin-vindesine[11] and cisplatin-paclitaxel is superior to cisplatin-etoposide.[12] A variety of studies have suggested that there is relatively little difference between the newer agents, and a variety of regimens are currently regarded as being acceptable. Among the more commonly used newer regimens are cisplatin-vinorelbine, cisplatin-gemcitabine, carboplatin-paclitaxel and cisplatin-docetaxel.[13]

Some randomized studies have also suggested that combination chemotherapy is superior to single agent chemotherapy.[11,14] Single agent chemotherapy has been shown to be superior to best supportive care, and it is regarded as being an acceptable alternative choice in the elderly and in patients with medical contraindications to combination chemotherapy.[15,16] There is no evidence at this time that three-drug combinations are superior to two-drug combinations. Optimal chemotherapy regimens that will have a substantial impact on survival for patients with advanced NSCLC still must be determined.

In recent years, a number of new chemotherapeutic drugs, with different mechanisms of action, have been developed and have shown promising anti-cancer activity. Included among these are the taxanes: paclitaxel (Taxol®; Bristol-Myers Squibb) and docetaxel (Taxotere®, RP56976, NSC628503; Aventis). The taxanes have a unique mechanism of action; they stabilize microtubules by inhibiting depolymerization and thereby inhibit cell proliferation.[17] A number of systematic reviews and meta-analyses have assessed chemotherapy in the treatment of advanced NSCLC.[10,18-20] However these reviews have not evaluated taxane-containing-regimens versus non-taxane regimens. An evaluation of the potential of taxanes in the treatment of advanced NSCLC is therefore warranted.

2 OBJECTIVES

The objective of this systematic review was to compare the clinical efficacy of taxane containing regimens (TR) with regimens not containing taxanes (NTR) in the treatment of advanced inoperable NSCLC. Clinical efficacy with respect to response, survival, toxicity and quality of life (QoL) were assessed.

3 METHODS

A protocol for this systematic review was written *a priori* and followed throughout the review process.

3.1 Literature Search Strategy

A comprehensive search was undertaken to identify relevant trials. Electronic databases searched, using the OVID platform, included: Biological Abstracts (1990 to 2001 Mar), CANCERLIT® (1983 to 2001 Oct), CINAHL® (1982 to 2001 Feb), Current Contents, (1993 Week 26 to 2001 Week 15), Dissertation Abstracts (1990 to 2001 Mar), EBM Reviews (Cochrane, DARE, Best Evidence), MEDLINE® (1966 to 2001 Oct), and PreMedline (2001 Oct).

MeSH headings and keywords for the disease and drugs were employed. Generic and trade names as well as registry numbers for taxanes were used in the search strategy. The original search was performed using a randomized controlled trial (RCT) filter designed by the Thomas C. Chalmers Centre for Systematic Reviews, Ottawa.[21]

The search strategy for Medline is shown in Appendix 1a. The same search strategy, with modifications where necessary, was used for searching the other databases. The search was not restricted by language or publication status. A second search using a modified search strategy and including the EMBASE® database was also performed, using the Ovid platform. Searches were updated by setting up Dialog® alerts. PubMed and the Cochrane Library were also searched to identify additional studies. Details on the search strategy and results are included in Appendix 1b.

Web sites of regulatory agencies, health technology assessment agencies and near-technology assessment agencies were searched. The Cochrane Library's Controlled Clinical Trials Registry and specialty trial registries available on the Current Controlled Trials web site were searched as well. These searches were supplemented by hand-searching the bibliographies of selected papers, the Proceedings of the American Society of Clinical Oncology and proceedings of meetings and conferences documented in the European Journal of Cancer and Annals of Oncology.

In addition, content experts, corresponding authors of published studies and drug manufacturers (Bristol-Myers Squibb and Aventis) were contacted for information regarding unpublished and/or ongoing trials.

3.2 Eligibility Criteria

Trials were selected for inclusion if they satisfied each of the following criteria:

(i) they were RCTs enrolling advanced NSCLC patients with inoperable tumours;
(ii) they had at least one intervention arm containing a taxane and one arm containing no taxane; and
(iii) they reported data on one-year survival rate, response rate, toxicity or QoL.

Trials including patients who had received prior chemotherapy were eligible. Trials with combined modality treatment (chemotherapy plus radiotherapy) or comparisons only with best supportive care were not considered. Trials utilizing radiotherapy with curative intent in inoperable patients were not considered.

Trials were independently selected for inclusion by two reviewers (SB & DJS) and kappa statistics were used to assess inter-rater agreement.[22] Differences in opinion were resolved by consensus reached after discussion.

3.3 Data Extraction Strategy

After the selection of relevant trials, data were extracted using a structured form. The form was designed to capture information on:

(i) details of the trial (first author, year of publication, journal, publication status, period and country of study, number of centres, sources of funding, study design, sample size);
(ii) patient characteristics (age, gender, stage of disease, performance status, weight loss, tumour histology and prior treatment status); and
(iii) details of the intervention and outcomes (dosage, frequency of administration, toxicity, response rate, survival rate and QoL).

3.4 Quality Assessment

Quality of the included trials was evaluated using the Jadad five point scale.[23] This scale assesses randomization (0-2 points), double blinding (0-2 points) and withdrawals and dropouts (0-1 point); with higher values indicating superior quality. In addition, concealment of allocation was categorized as adequate, inadequate or unclear. Quality was scored using a quality assessment form (Appendix 3), based on the Jadad scale.

3.5 Data Analysis

In most of the trials, survival was the primary endpoint. Response, toxicity, and less frequently, QoL were secondary endpoints. Response rate is defined as the percentage of patients having a complete or a partial response. A complete response was defined as complete disappearance of all known sites of disease. A partial response was defined as a 50% decrease in the sum of the products of the perpendicular diameters of all measurable lesions.[18] One-year survival rate referred to the percentage of patients surviving for at least one year and one-year mortality rate referred to the percentage of deaths in one year. Estimated one-year survival rates (from survival curves) reported in the literature were used for the analyses of survival/mortality.

All comparisons were performed between regimens including a taxane and regimens without a taxane. Some studies had more than one taxane-containing arm and/or more than one arm not containing a taxane. In these cases, a combined response rate and 1-year survival rate were calculated.[12,18]

Analyses were carried out on an intention-to-treat basis (patients analyzed according to their allocated treatment), irrespective of whether they actually received treatment.

To compare survival/mortality and response in the two arms, odds ratios (ORs) with corresponding 95% confidence intervals (CI) were computed and forest plots generated using RevMan 4.0 software. ORs were computed such that a value greater than one indicates better response with the TR and a value less than one indicates reduced mortality, i.e. better survival with TR.

The χ^2 test was used to assess effect size variance among trials. If this test indicated there was no heterogeneity present, the ORs were pooled using the fixed effects model. If, however, heterogeneity was present, the random effects model was used.[24] Publication bias was explored using funnel plots[25] for both outcomes.

Subgroup analyses were performed by categorizing the trials by pre-treatment status, taxane type used, drug type in the non-taxane arm and disease stage, in order to determine if a subset of patients had a more favourable outcome with TRs.

4 RESULTS

4.1 Quantity and Quality of Research Available

At the time of the original literature search, the EMBASE® database was not accessible; therefore a second search was done including this database at a later date. Although this second search included EMBASE® and a different RCT filter, no new trials were identified. Figure 1, Appendix 2 is a flow chart demonstrating the sequential screening process by which relevant trials were finally selected for inclusion in the analyses. Reasons for exclusion of trials are also documented in the flow chart.

Articles from the literature search were broadly screened on the basis of titles and abstracts. A total of 124 potentially relevant articles were retrieved for further scrutiny. On further examination of these articles, 49 potentially appropriate trial reports were retained. Thirty of these 49 trial reports were excluded because they were either preliminary results of trials subsequently reported in full, retrospective analyses for a particular subset, or they did not contain relevant data. This resulted in 19 trials[12,26-49] with 7,433 patients, available for the purpose of analysis. Excluded trials are listed in Appendix 4. Trials were independently selected by two reviewers (SB and DJS). For inter-rater agreement a κ value of 0.88 was obtained, indicating substantial agreement.

Trial reports which satisfied the eligibility criteria were assessed using the Jadad scale and the quality was generally determined to be low (score: 1.5 ± 0.5, mean ± standard deviation). Allocation concealment was unclear for all the trials reviewed.

4.2 Assessment of Clinical Effectiveness

4.2.1 Study characteristics

The details of the 19 included studies are shown in Table 1, Appendix 2. All were RCTs. The year of publication ranged between 1993 and 2002, with 15 trials being in the year range 2000-2002. All studies were in English, although no language restrictions had been imposed during the search process. These included nine abstracts (five of which had copies of a presentation available) and 10 full papers (published). The patient sample size ranged from 70 to 1,218.

Patient characteristics are listed in Table 2, Appendix 2. The median age ranged between 52 and 64 years. The percentage of male patients varied between 61% and 89%. The percentage of patients having stage IV disease ranged between 75% and 100%, except in three studies where the range was 57-70%. The majority of patients had Eastern Co-operative Oncology Group (ECOG) performance status (PS) in the range 0-1, with only a few having PS>1. Tumour histology of the patients was classified as squamous, adenocarcinoma, large cell, undifferentiated and other. However, histology was not reported in all the studies. There were 16 trials where patients had received no prior chemotherapy (nc), two trials where the patients had received prior chemotherapy (pc) and one trial where the pre-treatment status was unknown (u).

Details of the interventions and outcomes are described in Table 3, Appendix 2. There are a wide variety of drugs, doses and schedules in the taxane arm as well as in the arm not containing a taxane. Response rate data were available in all 19 trials but survival rate data were available in only 16 trials. A description of toxicity was reported, to varying degrees, in all the trials. QoL was reported only in six trials.

4.2.2 Data analyses and synthesis

a) Analyses of response

An analysis of response rate data was possible in all 19 trials. Figure 2, Appendix 2 shows the ORs for each individual trial and the pooled OR for all the trials together with their corresponding 95% confidence intervals (CI). The χ^2 test indicated considerable heterogeneity, therefore the random effects model was used to pool data. ORs greater than one represented greater efficacy of the TR. The overall OR for response rate was 1.34 with a 95% CI of 1.09-1.66, indicating a statistically significant increase in response rate for patients receiving the TRs as compared with those receiving the NTRs.

The results of subgroup analyses are given in Table 4, Appendix 2. The increase in response rate remains significant when paclitaxel-containing regimens are compared with NTRs. Response rate is significantly higher [OR 1.92; (95% CI 1.54-2.40)] in TRs when compared to NTRs with "old drugs" (cisplatin, carboplatin, etoposide, teniposide, and vindesine), but not when compared to NTRs with "new drugs" (gemcitabine, vinorelbine, topotecan and ifosfamide). Also response rate is not significantly higher with TRs not containing the new drugs, gemcitabine or vinorelbine when compared to NTRs with these new drugs. Response rate is significantly higher (OR 1.36; [95% CI 1.11-1.68]) in TRs as compared to NTRs for patients who received no prior chemotherapy. A significant increase (OR 1.4; [95% CI 1.15-1.71]) is observed in response rate for the TRs when the trials included 57-70% of the patients with stage IV disease. When 75-100% of the patient group was comprised of stage IV disease, no significant difference is observed in the two treatment arms.

The funnel plot of standard error of the log OR versus OR for each trial for response rate data, is shown in Figure 3, Appendix 2. It does not appear to be asymmetrical; therefore publication bias may not be a major problem. However the number of trials is not large and a definitive conclusion is not possible.

b) Analyses of overall survival

Figure 4, Appendix 2 shows the ORs for one-year mortality for each individual trial and the pooled OR for all trials, together with their corresponding 95% CIs. Since the random effects model was used in the case of response data analyses, the same model was used for reporting mortality data analyses, although significant heterogeneity was not present (as indicated by χ^2 test). However, in the case of mortality data, results of the analyses obtained with either of the models were similar.

The overall OR for mortality rate is 0.94 with a 95% CI of 0.83-1.05, indicating no significant difference between TR and NTR. Results of subgroup analyses are shown in Table 5, Appendix 2. No significant differences in mortality rate were detected between TR and NTR, even when considering different subgroups based on drug type, disease status or pre-treatment status. The median survival times in the different studies were in the range 5.5-11.8 months and 4.6-10.7 months for the TR and the NTR respectively (Table 3, Appendix 2).

Figure 5, Appendix 2 shows the funnel plot for the mortality data from each of the 16 trials. It appears symmetrical and publication bias may not be a major problem. However, a definitive conclusion is not possible, since the number of trials is not large.

c) Toxicity

Quantitative toxicity data is reported in 19 trials. However, not all trials report the same types or grades of toxicities. The toxicities reported included anemia, leukopenia, neutropenia, thrombocytopenia, febrile neutropenia, alopecia, nausea, vomiting, diarrhea, myalgia/arthralgia, fatigue and peripheral neuropathy. Peripheral neuropathy and alopecia seemed to be more common in the TR and nausea/vomiting and thrombocytopenia seemed to be more common in the NTR. There is a wide variety of drugs in the different regimens, therefore pooling of data was not feasible.

Treatment-related deaths (TRD) were reported in 10 trials and were in the range 2-5.2% and 1.5-11.4% in the TRs and the NTRs respectively (Table 3, Appendix 2). However, the range for TRDs in the NTR groups was reduced to 1.5-3.7% when two particularly toxic regimens (cisplatin plus topotecan and merbarone), accounting for 9.1% and 11.4% of TRDs, were excluded. Comparisons of toxicities of regimens containing taxanes with regimens containing other new drugs (gemcitabine or vinorelbine) are shown in Tables 6 and 7, Appendix 2. The toxicity result for each trial is represented in Appendix 5.

d) Quality of life

Formal QoL assessment was reported as an outcome in only six trials; details are included in Table 8, Appendix 2. The results from each trial are summarized below.

1. Bonomi et al.[12]

QoL was assessed using the Functional Assessment of Cancer – Lung (FACT-L), version 2 instrument. In the short term (six weeks) the TR (cisplatin with low or high dose paclitaxel) demonstrated improved QoL compared to the NTR (cisplatin plus etoposide). At 26 weeks, the QoL scores decreased for all three regimens and there was no difference between the TR and the NTR.

2. Gatzemeier et al. [32]

QoL was assessed using the European Organization for Research and Treatment of Cancer (EORTC) Core QoL questionnaire (QLQ-C30, version 1.0) and the lung-cancer specific module (LC-13, version 1.0). QoL scores for nausea/vomiting, loss of appetite and constipation favoured the TR (paclitaxel+cisplatin). The QoL score for hair-loss and peripheral neuropathy favoured the NTR (high dose cisplatin). However, overall QoL was similar in both regimens.

3. Giaccone et al.[34]
Only selected centres in this trial participated in the QoL assessment. The assessment was performed using the EORTC QLQ-C30 and LC-13 questionnaire. At six weeks, the TR (paclitaxel+cisplatin) showed significant benefit in functional status: emotional (p=0.004), cognitive (p=0.028), social functioning (p=0.023), and global health status (p=0.002), compared to the NTR (cisplatin+teniposide). Also with respect to symptoms, fatigue (p=0.004), and appetite loss (p<0.001) were significantly lower in the TR. However, at the 12 week assessment, these benefits were no longer significantly different in the two regimens and peripheral neuropathy was significantly greater (p=0.001) in the TR.

4. Fossella et al.[29]
Global QoL assessment and pain were improved for both the TR (docetaxel+cisplatin; docetaxel+carboplatin) compared to the NTR (vinorelbine+cisplatin).

5. Kelly et al.[35]
A QoL study was initiated halfway through the study and was measured using the FACT-L, version 3, instrument. There were no statistically significant differences between the TR (paclitaxel+carboplatin) and the NTR (cisplatin+vinorelbine), at either 13 weeks (p=0.097) or 25 weeks (p=0.74), using the three categories of QoL status (improved, stable and declined).

6. Kunitoh et al.[36]
QoL impact appeared to be generally favourable in the TR (taxotere+cisplatin) compared to the NTR (vindesin+cisplatin), although no statistically significant differences were observed. However, for both treatment regimens, the mean QoL parameters worsened after chemotherapy.

Three trials[31,42,47] reported that QoL analyses were still pending.

5 DISCUSSION

The results of this meta-analysis demonstrated a statistically significant increase in response rate in patients with inoperable advanced NSCLC when they are treated with regimens containing a taxane compared to regimens without a taxane [OR 1.34; (95% CI 1.09-1.66)]. However, there is no significant increase in response rate when the regimens with taxane are compared with non-taxane regimens containing the newer drugs - gemcitabine, vinorelbine, topotecan and ifosfamide [OR 1.06; (95% CI 0.87-1.30)].

There was no significant reduction in one-year mortality in patients with inoperable advanced NSCLC when they are treated with regimens containing a taxane compared to regimens without a taxane [OR 0.94; (95% CI: 0.83, 1.05)]. Comparison of the studies was difficult due to the wide variations in the treatments. Both the treatment arms with a taxane and those without a taxane also contain other drugs, which vary considerably.

Deciding when to combine data into a meta-analysis is a complex decision particularly in the presence of clinical and/or statistical heterogeneity. As such, the results reported here should be interpreted cautiously. It should be noted that some of the sub-group analyses contain only a few studies, which limits the power of the analyses.[50,51]

A recent systematic review examining new chemotherapeutic drugs reported that paclitaxel, gemcitabine and vinorelbine as first line, and docetaxel as second line treatment for NSCLC, increased survival by two to four months as compared to best supportive care.[52]

Another recent meta-analysis[53] comparing paclitaxel-containing regimens with regimens not containing paclitaxel showed a significant increase in response rate but no significant advantage in one-year survival rate. This analysis included only five trials. Our meta-analysis, which included 19 trials with taxanes corroborate these findings. For our analysis the survival rate data used were obtained from published results, which represent estimated values from the Kaplan-Meier curves. This method of analysis has also been used by others.[19,53-55] Individual patient data offers another option for data analysis, particularly if it is possible to obtain the data from the various authors.

Toxicity associated with the different regimens varied considerably as different combinations of drugs were used in both the TR and the NTR. It is therefore difficult to compare toxicity levels in the TR and the NTR and draw definitive conclusions.

Although QoL is an important issue in the treatment of patients with advanced NSCLC, not all trials addressed this issue. Also trials that assessed QoL did not always use the same QoL scale, making comparison between trials difficult. It should be noted however that performing QoL studies in advanced NSCLC patients is complicated by the fact that compliance rates with the QoL questionnaire are low and gradually decline in this group of patients. It appears that QoL in the TR and the NTR were not very different. Data on QoL are limited and definitive conclusions cannot be reached.

It is difficult to estimate the influence of publication bias on our results. However, the absence of asymmetry in the funnel plots suggests publication bias may not be an issue. Identification of unpublished trials remains a challenge. Prospective registration of all trials and ability to access such registries would assist in the identification of unpublished trials.

During the process of selection of relevant trials it was discovered that out of 49 potentially appropriate trials 30 were multiple publications of the same trials. This trend of duplicate reporting can lead to biased results. For example, it has been reported that inclusion of duplicated data in a meta-analysis of ondansetron led to a 23% overestimation of ondansetron's antiemetic efficacy.[56] Therefore, considerable caution should be exercised to ensure that duplicate publications of the same trials or published articles of single centre trials, which are part of multi-centre trials, are not included. A trial (and patients) should not be counted more than once in a systematic review. A number of trials had an identification number assigned and the authors documented these in their publications, making it easy for the reader to distinguish multiple publications of the same trial. When reporting trials, if this procedure is uniformly adopted by all authors, confusion arising from multiple publications can be avoided.[57]

Although no language restriction was imposed on the search process, only trials in English were identified; this may not be a serious drawback. In one methodological study in the literature, it was reported that a language-restricted meta-analysis, compared to a language inclusive meta-analysis, did not differ with respect to estimate of benefit of the effectiveness of an intervention.[58]

All relevant trials identified were published between 1993 and 2002, although our search strategy had no limits assigned regarding year of publication; taxanes are relatively new drugs and have only been in use since the early 1990s. Also, most of the initial trials with the taxanes were single-arm studies.

Assessment of the methodological quality of trials is important because several studies have noted that low quality reports, compared to high quality ones, tend to exaggerate the estimates of an intervention's effectiveness by an average of 30%.[59-61] A number of different methods are available for quality assessment;[62] we used the Jadad scale as it is a validated scale. All the trials included in this report scored low on this scale. Forty percent of the points awarded by this index are given for reporting of double blinding. The trials included in this review, like many oncology trials, are not blinded, for a variety of ethical and logistical reasons. For this reason, they did not score particularly well on the quality assessment scale. We could be faulted for using this instrument rather than one that focuses less on double blinding. However it is possible that, despite the reasons for not double blinding oncology trials, this may expose trials to the introduction of bias. This issue, and other methodological ones, can best be addressed through further methodological research.

Performing this review revealed to us that efforts should be made to improve the quality of trial reporting. None of the trials included here described their methods of randomization; some studies did not report data on certain patient characteristics; and although most of the trials included detailed information on toxicity profiles, not all reported the same aspects of toxicity. Uniformity in reporting would enable better comparison of trials and would mean evidence obtained through pooling of results would be more reliable.

6 CONCLUSIONS

This meta-analysis showed that for inoperable advanced NSCLC taxane-containing regimens do not offer a statistically significant advantage in terms of one-year survival when compared to regimens not containing taxane. However the TRs did produce a statistically significant effect on response rate when compared to NTRs. It should be noted that the trials were heterogeneous with respect to the drug combinations used and hence the pooled results should be viewed with caution. Toxicity profiles in the different studies varied considerably. To allow valid comparisons to be made between regimens with and without a taxane, more RCTs using uniform drug combinations are needed. Sufficient data on QoL were not available to enable meaningful QoL comparisons between TRs and NTRs; efforts should be made to address this issue when conducting trials.

NOTE

After completion of this report, abstracts of four new trials[63-66] were identified from the Proceedings of the American Society of Clinical Oncology, 2002; these trials were discovered too late to be included in our analyses. Details of the trials are included in Appendix 6. Addition of these trials to our original report would not alter our overall conclusions. Our calculated values would be altered slightly (see table below).

	Response rate (95% CI)	**One-year mortality (95% CI)**
Original report	1.34 (1.09-1.66)	0.94 (0.83-1.05)
Original report with the addition of four new trials	1.35 (1.10-1.64)	0.90 (0.78-1.03)

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Appendix 1a: Medline Literature Search Strategy

```
1     randomized controlled trial.pt.
2     clinical trial.pt.
3     controlled clinical trial.pt.
4     crossover$.tw.
5     cross-over$.tw.
6     ((singl$ or doubl$ or tripl$ or trebl$) adj3 (blind$ or
       mask$)).tw.
7     randomi?ed.tw.
8     (random$ adj3 (select$ or assign$ or allocat$ or sampl$)).tw.
9     "PLACEBO$".mp.
10    exp clinical trials/
11    exp case-control studies/
12    exp cohort studies/
13    or/1-10
14    (11 or 12) not 1
15    13 not 14
16    PACLITAXEL/
17    paclitaxel.mp.
18    paclitaxel.ab,tw,ti.
19    taxol.ab,tw,ti.
20    taxol.mp.
21    taxotere.mp.
22    taxotere.ab,tw,ti.
23     docetaxel.mp.
24    docetaxel.ab,tw,ti.
25    RP56976.mp.
26    taxane?.mp.
27    taxane?.ab,tw,ti.
28    RP56976.ab,tw,ti.
29    taxoid?.mp.
30    taxoid?.ab,tw,ti.
31    Carcinoma, Non-Small-Cell Lung/
32    non small cell lung cancer?.ab,tw,ti.
33    non small cell lung carcinoma?.ab,tw,ti.
34    nsclc.ab,tw,ti.
35    Lung Neoplasms/
36    or/16-30
37    or/31-35
38     15 and 36 and 37
```

Appendix 1b: Second Literature Search Strategy

Databases	Limits	Headings/Descriptors/Keywords
OVID Multiple Database Search CancerLIT Current Contents® /All Editions EMBASE® EBM Reviews HealthSTAR® MEDLINE® Duplicates Removed	**Human** **1989 - 2001**	Taxoid/ OR taxoid.mp. OR RP56976.mp. OR docetaxel.ab,tw,ti,mp. OR taxotere.ab,tw,ti. OR taxol.mp. OR paclitaxel. ti,tw,ab. or Taxol/ OR paclitaxel.mp. OR Paclitaxel/ **AND** Lung Non Small Cell Cancer/ OR carcinoma non small cell lung.mp. OR Carcinoma, Non-Small-Cell Lung/ OR non small cell lung cancer$.ab,ti,tw. OR non small cell lung carcinoma$.ab,ti,tw. OR NSCLC.ab,tw,ti. OR Lung Tumor/ or lung tumo$r$.mp. OR Lung Cancer/ OR lung cancer.mp. **AND** exp Meta Analysis/ OR meta analysis.mp,pt. OR metaanal$.tw. OR meta analy$.tw. OR exp Clinical Trial/ OR clinical trial$.mp,tw. OR clinical trial.pt. OR exp Clinical Trials/ OR Controlled Study/ OR controlled clinical trial.pt. OR controlled clinical trial$.tw. OR controlled clinical trial$.mp. OR exp Crossover Procedure/ OR crossover stud$.mp,tw,ab,ti. OR crossover$.tw. OR cross-over.tw. OR exp Randomized Controlled Trial/ OR random$ OR (Random$ adj3 (select$ OR assign$ OR allocat$ OR sampl$)).tw. OR Randomi$ed.tw. OR Placebo/ OR placebo.mp. OR case control stud$.tw. OR exp Case Control Study/ OR Cohort Analysis/ OR cohort studies.mp. or exp Cohort Studies/ OR cohort stud$.tw.

Databases	Limits	Headings/Descriptors/Keywords
		Unique references = 1632 hits *EMBASE® = 674 hits* *MEDLINE® = 643 hits* *Current Contents/All Editions = 102 hits* CancerLIT = 212 hits
The Cochrane Collaboration & Update Software Ltd. The Cochrane Library, Issues 3 & 4, 2001 and Issue 1, 2002		***Taxol OR paclitaxel OR taxotere OR docetaxel OR taxane* OR taxoid*** AND Carcinoma-non-Small-Cell-Lung:ME OR non-small cell lung cancer OR lung cancer OR lung tumor* OR lung tumour* (appropriate syntax was used for phrase searching) *Total hits = 106 hits* *The Cochrane Database of Systematic Reviews = 3 Reviews* *Database of Abstracts of Reviews of Effectiveness =13 hits* *The Cochrane Controlled Trials Register = 96 hits* *NHS Economic Evaluations = 5 hits*
DIALOG Alerts MEDLINE® BIOSIS Previews® EMBASE® PUBMED Update	**Weekly**	Same headings and keywords as full search.

Appendix 2: Tables and Figures

Table 1: Details of included RCTs

No.	Study (First Author)	Year	Participating Countries	Centres	Sponsor	Publ. Status[5]	Study Design[6]	Sample Size	Quality Score (Jadad)
1	Belani[26]	1998	USA	Multi	NM[1]	ab	ph III	369	1
2	Bonomi[12]	2000	USA	Multi	NM[1]	pf	ph III	574	2
3	Chang[27]	1993	USA	Multi	NM[1]	pf	ph II	103	2
4	Comella[28]	2001	Italy	Multi	NM[1]	pf	ph III	343	1
5	Fossella[31]	2000	USA	Multi	Rhone-Poulenc Rorer	pf	ph III	373	2
6	Fossella[29, 30]	2001	Several	Multi	NM[1]	ab+	ph III	1218	1
7	Gatzemeier[32]	2001	Several	Multi	Bristol-Myers Squibb	pf	ph III	414	1
8	Gervais[33]	2000	Europe		NM[1]	ab		95	1
9	Giaccone[34]	1998	Europe	Multi	Bristol-Myers Squibb	pf	ph II/III	332	2
10	Kelly[35]	2001	USA		NIH, Bristol-Myers Squibb, Glaxo-Wellcome	pf	ph III	408	2
11	Kunitoh[36, 37]	2001	Japan	Multi	Aventis, Chugai Pharma K.K.	ab+	ph III	302	2
12	Manegold[38, 39]	2000	Europe		Lilly, Rhone Poulenc Rorer; Germany	ab	ph II	147	1
13	Pérol[40]	2000	France	Multi	Aventis	pf	ph II	70	2
14	Perry[41]	2000	USA		CALGB[2]	pf	ph II	93	1
15	Scagliotti[42, 43]	2001	Italy	Multi	NM[1]	ab+	ph III	607	2
16	Schiller[44]	2000	USA		ECOG[3]	pf	ph III	1155	2
17	Thompson[45, 46]	2001	USA	Multi	NM[1]	ab+		267	1
18	van Meerbeeck[47,48]	2001	Europe	Multi	EORTC[4]	ab+	ph III	480	1
19	Wiesenfeld[49]	1997	USA		NM[1]	ab	ph II	83	1

[1]NM = not mentioned
[2]CALGB = Cancer and Leukemia Group B
[3]ECOG = Eastern Cooperative Oncology Group
[4]EORTC = European Organization for Research and Treatment of Cancer
[5] Publ. status: ab=abstract, pf=full article (published), ab+=abstract plus copy of presentation
[6]Study design: ph=phase

Table 2: Patient characteristics

Study (First Author)	Median Age (yr)	Age Range (yr)	% of Patients in the Following Categories											Pretreat-ment Status[3]
			Male	Stage IV	Performance Status (PS)[1]	Weight Loss		Histology[2]						
						<5%	≥5%	Squa-mous	Adeno	Large	Undiff	Large+ Undiff	Other	
Belani[26]			61.2	78.0	56.6(KPS 90-100%), 43.4(KPS 70-80%)		64.5							nc
Bonomi[12]	60.8-62.7		63.7	80.7	31.7(PS 0), 68.3 (PS 1)	70.0	30.0							nc
Chang[27]	61-62	31-85	68.0	100	35.0 (PS 0), 63.1(PS 1)	28.2	37.9	20.4	54.4	17.5			7.8	nc
Comella[28,*]	62	30-70	89.2	57	21.6 (PS 0), 78.4 (PS 1)	26.2		55.7					44.3	nc
Fossella[31]	59-60		65.4	89	16.7 (PS 2)			27.3	49.7				23.4	pc
Fossella[29, 30]	59-60		73.0	67	58 (KPS 90-100%), 42 (KPS 70-80%)			33.3	42.3			11.3	13	nc
Gatzemeier[32]	60	32-75	81.5	70	10.5(KPS 100%), 71(KPS 80-90%), 18(KPS 60-70%)									nc
Gervais[33]	56-58	39-75	82.1	100	35.8(PS 0), 43.2(PS 1), 21.1 (PS 2)									nc
Giaccone[34]	58.5	28-75	70.3	61.5	34.4(PS 0), 54.9(PS 1), 10.7(PS 2)	70.7	27.4	26.5	51.4	21.1	0.9			nc
Kelly[35]	61-62	26-83	68.6	89	100(PS 0-1)									nc
Kunitoh[36, 37]	63-64	30-74	66.2	100	28.8(PS 0), 67.5(PS 1), 3(PS 2), 0.7(PS 3)			16.6	73.8	6.6			3	nc
Manegold[38, 39]	64		70.0	85	71 (PS 0-1), 29(PS>1)			22	51		27			nc
Pérol[40]	52-56.5		87.1	100	35.7(PS 0), 44.3(PS1), 20(PS 2)	50	44.3	31.4	38.6	27.1	2.9			nc
Perry[41]	63	32-81	63.0	84	32(PS 0), 68(PS 1)	67								nc
Scagliotti[42, 43]	62-63	28-81	78.4	81.3	93(PS 0-1)			30.7	51	7			11	nc
Schiller[44]	63	27-87	63.0	87	30(PS 0), 64(PS 1), 6(PS 2)	67	33							nc
Thompson[45, 46]	62-64	33-82	68.5	76.4	87.3(PS 0-1), 12.7(PS 2)			21.7	45.3	10.9			22.1	nc
van Meerbeeck[47,48]	56-57	27-75	67.4	80.7	88.3(PS 0-1), 11.7(PS 2)									pc
Wiesenfeld[49]														u

[1]Performance status: Various scales are available to evaluate performance status (ability to perform routine tasks) of patients. The two most commonly used scales are the Eastern Cooperative Oncology Group (ECOG) and the Karnofsky scales. PS=ECOG performance status (lower values indicate better performance status) and KPS=Karnofsky performance status (higher values indicate better performance status).

[2]Histology: Squamous=squamous cell carcinoma, adeno=adenocarcinoma, large=large cell carcinoma, undiff = undifferentiated

[3]Pretreatment status: nc=no prior chemotherapy, pc=prior chemotherapy, u=unknown

[*](unpublished data, 2002)

Table 3: Details of interventions and outcomes

Study (First Author)	Treat-ment Arm	Intervention†	Patient No.	Median Survival‡ (mth)	1 yr Survival‡ (%)	Objective Res-ponse (%)	Treat-ment Related Deaths (%)
Belani[26]	1	p(225;d1)+cb(AUC6;d1); q3wk	190			21.6	
	2	c(75;d1)+e(1,000; d1-3); q3wk	179			14	
Bonomi[12]	1	p(250;d1)+c(75;d2); q3wk	191	10.1	40.3	27.7	5
	2	p(135;d1)+c(75;d2); q3wk	190	9.5	37.4	25.3	4
	3	c(75;d1)+e(1,000; d1-3); q3wk	193	7.6	31.8	12.4	1.5
Chang[27]	1	p(250; d1); q3wk	24	5.6	41.7	20.8	4
	2	m(1,000;d1-5); q3wk	35	4.6	21.6	5.7	11.4
	3	pi(150;d1); q3wk	44	6.8	22.6	2.3	5
Comella[28,*]	1	p(125;d1,8)+c(50;d1,8)+g(1,000;d1,8); q3wk	114	11.8	48	48	
	2	c(50;d1,8)+g(1,000;d1,8)+v(25;d1,8); q3wk	117	11.8	47	44	
	3	c(100;d1)+g(1,000;d1,8,15); q4wk	112	8.8	34	28	
Fossella[31]	1	t(100); q3wk	125	5.5	21	10.8	2
	2	t(75); q3wk	125	5.7	32	6.7	0
	3	v(30;d1,8,15) or i(2,000;d1-3); q3wk	123	5.6	19	0.8	2
Fossella[29, 30]	1	t(75;d1)+c(75;d1); q3wk	408	11.3	46	32	2
	2	t(75;d1)+cb(AUC6;d1); q3wk	406	9.4	38	24	2
	3	v(25;d1,8,5,22)+c(100;d1); q4wk	404	10.1	41	25	2
Gatzemeier[32]	1	p(175)+c(80); q3wk	207	8.1	30	24	
	2	c(100); q3wk	207	8.6	36	16	
Gervais[33]	1	t(75;d1)+c(100;d1); q3wk	51			23	
	2	v(30;d1,8)+c(100;d1); q3wk	44			19	
Giaccone[34]	1	p(175;d1)+c(80;d1); q3wk	166	9.7	43	41	1.9
	2	c(80;d1)+tn(100;d1,3,5); q3wk	166	9.9	41	28	3.7
Kelly[35]	1	p(225;d1)+cb(AUC6;d1); q3wk	206	8.6	38	25	2.4
	2	c(100;d1)+v(25;d1,8,15,22 wkly); q4wk	202	8.1	36	28	4
Kunitoh[36, 37]	1	t(60;d1)+c(80;d1); q3wk-q4wk	151	11.4	47.7	37.1	
	2	c(80;d1)+vn(3;d1,8,15); q4wk	151	9.7	42.9	21.2	
Manegold[38, 39]	1	t(35;d1;8;15); q4wk	49			20	
	2	g(1,000;d1,8,15); q4wk	98			17	
Pérol[40]	1	t(100;d1)+c(100;d22)+v(30;d22,29,36); q6wk	38	6.7	39	4	5.2
	2	c(80;d1)+v(30;d1,8,15); q3wk	32	9.6	42	8	3.2
Perry[41]	1	p(250;d1)+i(1,600;d1-3); q3wk	48	8.5	35	38	2.1
	2	v(30;d1-3)+i(1,600;d1-3); q3wk	45	7.4	38	31	2.2

†Intervention: drug name (dose in mg/m^2; day administered); cycle

‡Survival: overall survival

Drugs: c=cisplatin, cb=carboplatin, e=etoposide, g=gemcitabine, i=ifosfamide, m=merbarone, p=paclitaxel, pi=piroxantrone, t=docetaxel, tn=teniposide, tp=topotecan, v=vinorelbine, vn=vindesine

d=day, q=every, wk=week

* (unpublished data, 2002)

Table 3: contd.

Study (First Author)	Treat-ment Arm	Intervention†	Patient No.	Median Survival‡ (mth)	1 yr Survival‡ (%)	Objective Res-ponse (%)	Treat-ment Related Deaths (%)
Scagliotti[42, 43]	1	p(225;d1)+cb(AUC6;d1); q3wk	201	9.9	43	32	
	2	c(75;d2)+g(1,250;d1,8); q3wk	205	9.8	37	30	
	3	c(100;d1)+v(25;wklyx12, then every other wk); q4wk	201	9.5	37	30	
Schiller[44]	1	p(135;d1)+c(75;d2); q3wk	288	7.8	31	21	
	2	p(135;d1)+cb(AUC6;d1);q3wk	290	8.1	34	17	
	3	t(75;d1)+c(75;d1); q3wk	289	7.4	31	17	
	4	c(100;d1)+g(1,000;d1,8,15); q4wk	288	8.1	36	22	
Thompson[45, 46]	1	p(200;d1)+cb(AUC5;d1)+ g(1,000;d1,8); q3wk	71	9.6	38	37	1.4
	2	p(200;d1)+cb(AUC6;d1)+ v(20;d1,8,15); q3wk	65	9.9	44	45	1.5
	3	p(200;d1)+g(1,000;d1,8,15); q3wk	64	8.7	38	32	3.1
	4	g(1,000;d1,8,15)+v(25;d1,8,15); q4wk	67	10.7	42	33	1.5
van Meerbeeck[47,48]	1	p(175;d1)+c(80;d1); q3wk	159	8.1	35.5	31	3
	2	p(175;d1)+g(1,250;d1,8); q3wk	161	6.9	26.5	27	4
	3	c(80;d1)+g(1,250;d1;8); q3wk	160	8.8	32.6	36	1
Wiesenfeld[49]	1	p(190;d1)+tp(1;d1-5); q4wk	61	6.2	18	24	
	2	c(75;d1)+tp(1.25;d1-5); q4wk	22	7.4	26	14	9.1

†Intervention: drug name (dose in mg/m^2; day administered); cycle
‡Survival: overall survival
Drugs: c=cisplatin, cb=carboplatin, e=etoposide, g=gemcitabine, i=ifosfamide, m=merbarone, p=paclitaxel, pi=piroxantrone, t=docetaxel, tn=teniposide, tp=topotecan, v=vinorelbine, vn=vindesine
d=day, q=every, wk=week
* (unpublished data, 2002)

Table 4: Subgroup analyses for response rates

Trial	No. of Trials	No. of Patients	Odds Ratio [95% CI]
All trials	19	7,433	1.34 [1.09, 1.66]
Subgroup analyses:			
Trials with paclitaxel in taxane arm	13	4,939	1.34 [1.05, 1.71]
Trials with docetaxel in taxane arm	7	2,782	1.21 [0.78, 1.88]
Trials with old drugs in non-taxane arm	5	1,991	1.92 [1.54, 2.40]
Trials with new drugs in non-taxane arm	13	5,339	1.06 [0.87, 1.30]
Trials with new drugs (g or v) in non-taxane arm but not in taxane arm	9	4,415	1.01 [0.83, 1.23]
Trials with patients having no prior chemotherapy	16	6,497	1.36 [1.11, 1.68]
Trials with 57-70% stage IV patients	4	2,307	1.4 [1.15, 1.71]
Trials with 75-100% stage IV patients	15	5,126	1.31 [0.98, 1.76]

Drugs: g=gemcitabine, v=vinorelbine

Table 5: Subgroup analyses for mortality rates

Trial	No. of Trials	No. of Patients	Odds Ratio [95% CI]
All trials	16	6,822	0.94 [0.83, 1.05]
Subgroup analyses:			
Trials with paclitaxel in taxane arm	12	4,570	0.95 [0.82, 1.10]
Trials with docetaxel in taxane arm	5	2,540	0.96 [0.78, 1.17]
Trials with old drugs in non-taxane arm	4	1,622	0.92 [0.71, 1.20]
Trials with new drugs in non-taxane arm	11	5,097	0.96 [0.85, 1.09]
Trials with new drugs (g or v) in non-taxane arm but not in taxane arm	7	4,173	0.95 [0.82, 1.09]
Trials with patients having no prior chemotherapy	13	5,886	0.94 [0.83, 1.06]
Trials with 57-70% stage IV patients	4	2,307	0.97 [0.79, 1.19]
Trials with 75-100% stage IV patients	12	4,515	0.91 [0.79, 1.06]

Drugs: g=gemcitabine, v=vinorelbine

Table 6: Comparison of toxicity of regimens containing paclitaxel with regimens containing other new drugs (gemcitabine or vinorelbine)

Toxicity	Perry et al.[41]		Scagliotti et al.[42, 43]			Schiller et al.[44]			van Meerbeeck et al.[47, 48]	
	p+i	v+i	p+c	v+c	g+c	p+c	p+cb	g+c	p+c	g+c
	N=48	N=31	N= 201	N= 201	N= 205	N= 300	N= 293	N= 293	N= 153	N= 158
Anemia	13	20				13	10	28	3	4
Febrile neutropenia			1	2	0.5	16	4	4	1	2
Infection	17	24				10	6	7		
Neutropenia	59	96				75	63	63	33	30
Leukopenia	48	98								
Thrombocytopenia			2	8	8	6	10	50	1	6
Lymphocytes	67	73								
Dyspnea	14	4							8	12
Pain	2	15								
Fatigue/weakness	12	22							9	11
Diarrhea						7	2	3		
Nausea						25	9	37	8	6
Vomiting						24	8	35	8	5
Nausea/Vomiting			1	13	7					
Peripheral neuropathy			30	4	7	5	10	9		
Neurosensory			52	11	10				3	1
Motor neuro	8	13							3	3
Alopecia			52	11	10					
Cardiac						3	3	5		
Renal			0	0	2	3	1	9		

Drugs: c=cisplatin, cb=carboplatin, g=gemcitabine, i=ifosfamide, p=paclitaxel, v=vinorelbine; drug doses are available in Table 3
N = number of patients in the treatment arm

Table 7: Comparison of toxicity of regimens containing docetaxel with regimens containing other new drugs (gemcitabine or vinorelbine)

Toxicity	Fossella et al.[31]			Fossella et al.[29, 30]			Gervais et al.[33]		Manegold et al.[38, 39]		Schiller et al.[44]	
	t(h)	t	v/i	t+c	t+cb	v+c	t+c	v+c	t	g	t+c	g+c
	N= 121	N= 121	N= 119	N= 406	N= 401	N= 396	N= 51	N= 44	N= 48	N= 98	N= 297	N= 293
Anemia	1	0	2	7	10	24				1	15	28
Febrile neutropenia	12	8	1	5	4	5	23	20			11	4
Infection	3	0	1	6	8	6			4	1	9	7
Neutropenia	77	54	31	75	74	79	53	73			69	63
Leukopenia	1	2	0						2			
Thrombo-cytopenia				3	7	4				1	3	50
Pain				8	9	8						
Fatigue/ Weakness											16	18
Diarrhea	3	2	2	7	5	3					10	3
Nausea	7	3	6	10	6	16			4	8	24	37
Vomiting	7	1	4	8	4	16			2	3	21	35
Peripheral neuropathy											5	9
Neurosensory	6	1	3	4	1	4						
Alopecia									8			
Cardiac											5	5

Drugs: c=cisplatin, cb=carboplatin, g=gemcitabine, i=ifosfamide, p=paclitaxel, v=vinorelbine; drug doses are available in Table 3
N = number of patients in the treatment arm

Table 8: Quality of Life (QoL)

Study	Treatment Regimens[1]	Compliance Rates[2] Data Reported at	QoL Scale[3] Used	QoL Data Reported at, (data reported as)
Bonomi et al.[12]	p+c vs p(h)+c vs c+e	Baseline, 6, 12 & 26 wk	FACT-L version 2	6 wk, (% of patients)
Gatzemeier et al.[32]	p+c vs c	Baseline, 5,8,11,14,17, 20,23,26 & 34 wk	QLQ-C30, version 1.0 and LC-13 version 1.0	All evaluation periods taken together, (p-values)
Giaccone et al.[34]	p+c vs c+tn	Baseline, 6,12,18 & 24 wk	QLQ-C30 and LC-13	6 wk, (p-values)
Fossella et al.[29]	t+c vs t+cb vs c+v	Not mentioned	LCSS and EQ5D	Cycles 1-6 (change from baseline, p-value)
Kelly et al.[35]	p+cb vs c+v	Baseline, 13 & 25 wk	FACT-L version 3	13 & 25 wk, (% of patients)
Kunitoh et al.[36]	t+c vs c+vn	Not mentioned	Not mentioned	Not mentioned

[1]Treatment regimens: c = cisplatin, cb = carboplatin, e = etoposide, p = paclitaxel, t = docetaxel, tn = teniposide, v = vinorelbine, vn = vindesine, (h) = high dose
[2]Compliance rates: percentage of patients filling a QoL questionnaire
[3]QoL scale: Various QoL scales are available. QoL questionnaires address different areas (eg. physical well-being, fuctional well-being, lung cancer symptoms and concern, social well-being, emotional well-being, cognitive functioning). FACT-L = Functional Assessment of Cancer-Lung; QLQ-C30 = European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life questionnaire and LC-13 = Lung Cancer specific module; LCSS = Lung Cancer Symptom Scale and EQ5D = EuroQoL scale

Figure 1: Flow chart of the selection of relevant trials

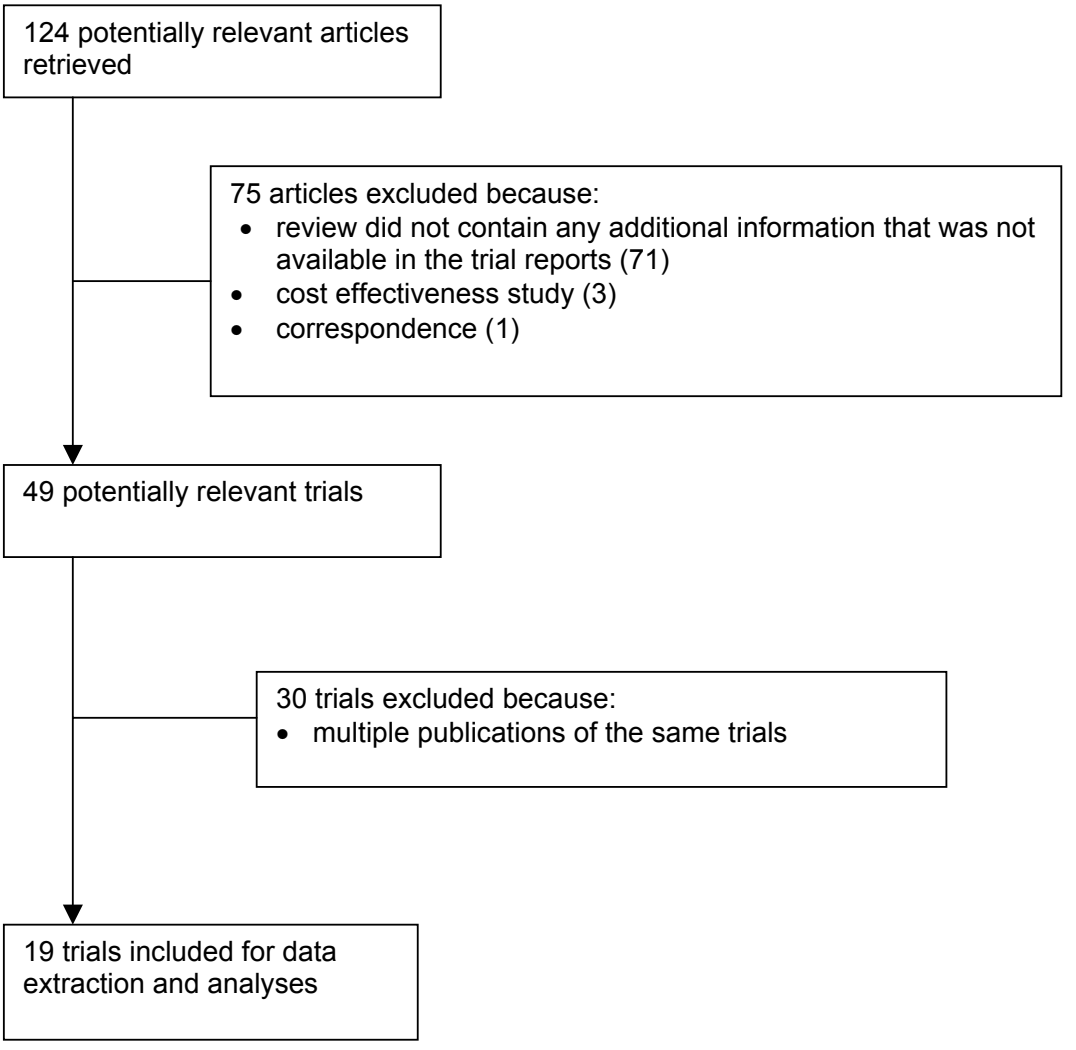


Figure 2: Odds ratios for response data

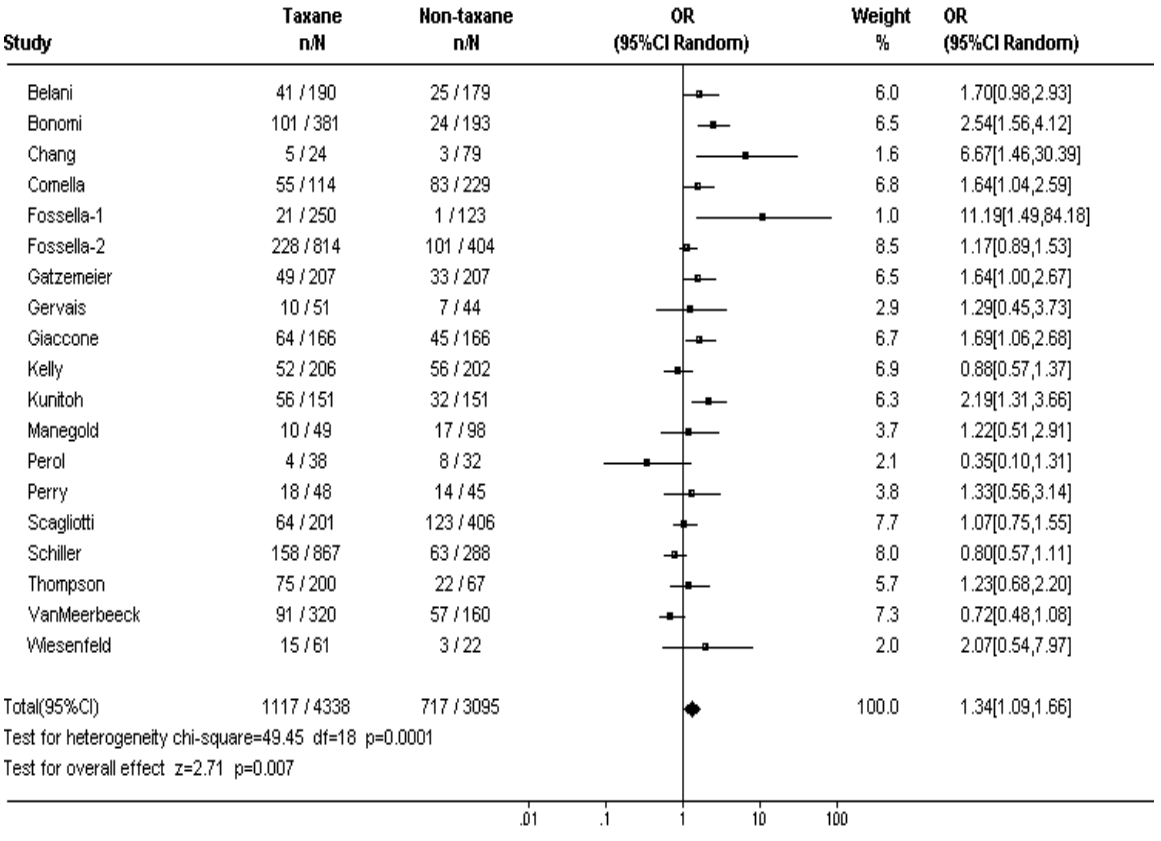


Figure 3: Funnel plot for response data

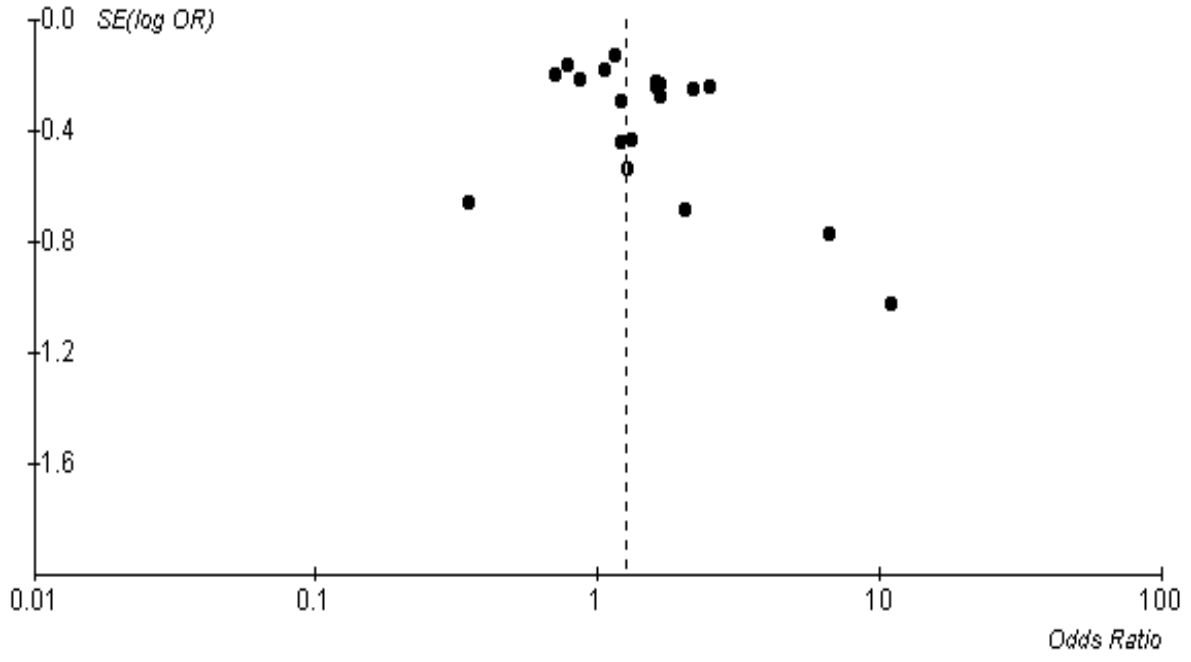


Figure 4: Odds ratios for mortality data

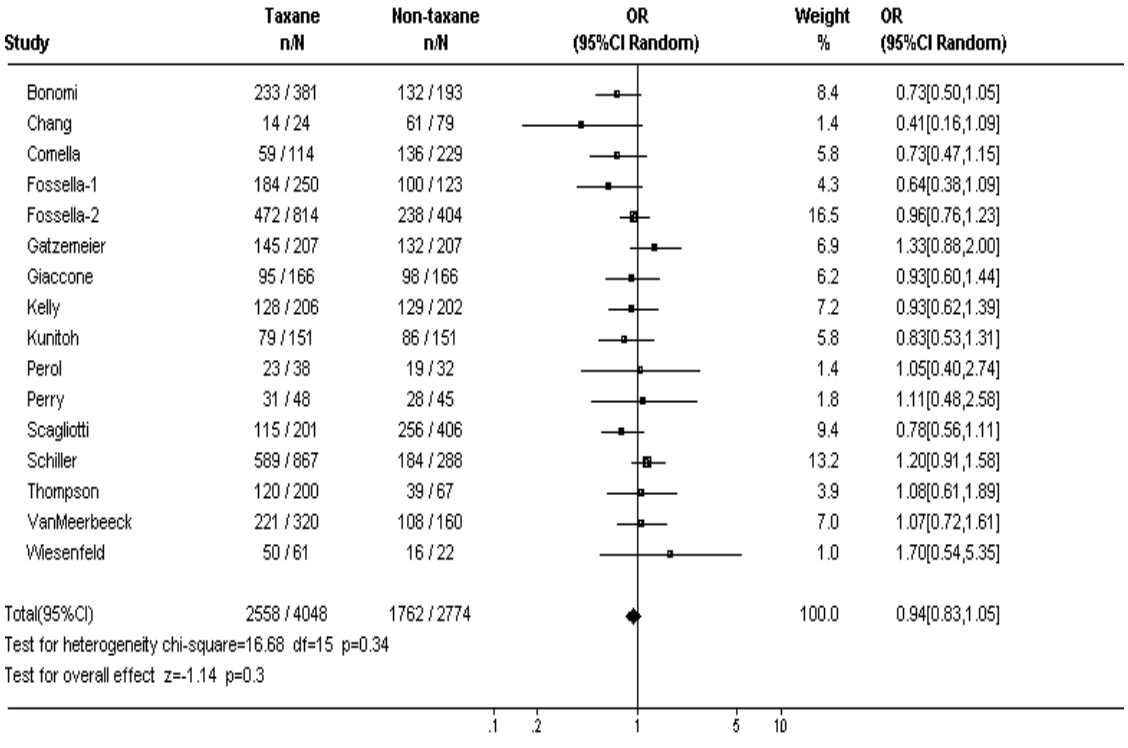
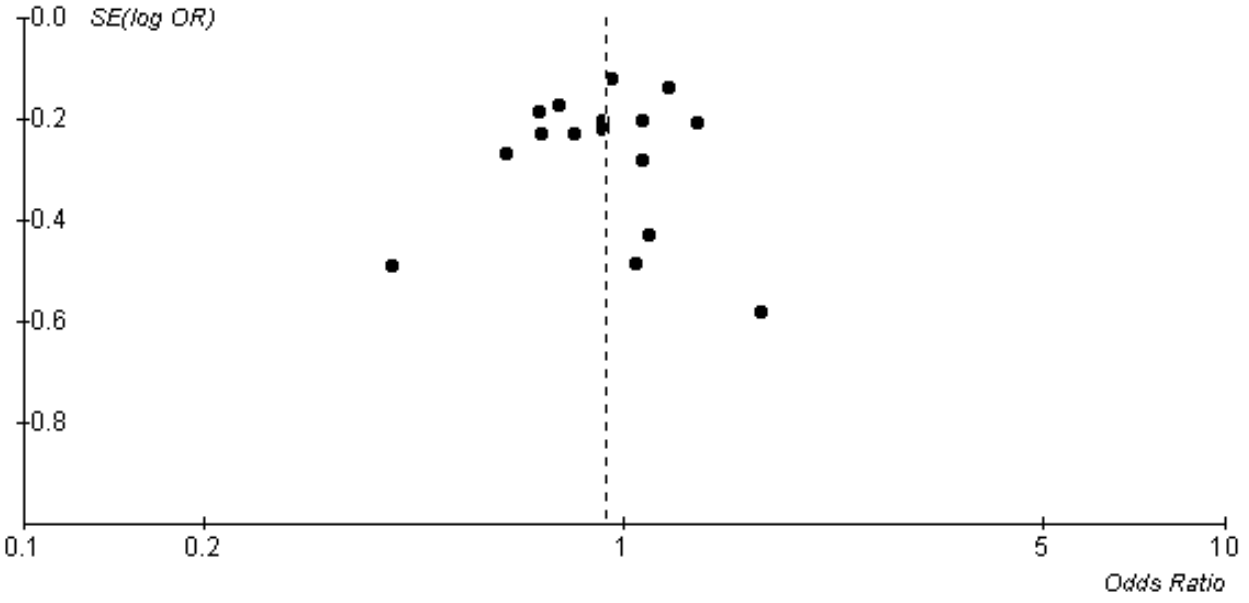


Figure 5: Funnel plot for mortality data



Appendix 3: Trial Quality Assessment Form

Reference:		
Reviewer:		
No	**Category**	**Score**
1	**Randomization:** Was the study described as randomized (i.e. Including words such as randomly, random, randomization)? A trial reporting that it is "randomized" is to receive one point. Yes=1 or No=0	
	Trials describing an appropriate method of randomization (table of random numbers, computer generated) receive an additional point. Appropriate =1, not appropriate =0	
	If the report describes the trial as randomized and uses an inappropriate method of randomization (e.g. Date of birth, hospital numbers), a point is deducted. Inappropriate = -1	
2	**Double-blinding:** Was the study described as double-blind? A trial reporting that it is "double-blind" is to receive one point. Yes =1, no =0.	
	Trials describing an appropriate method of double-blinding (identical placebo: colour, shape, taste) are to receive an additional point. Yes =1, No =0	
	If the report describes a trial as double-blind and uses an inappropriate method (e.g. comparison of tablets vs. injection with no dummy), a point is deducted. Inappropriate = -1	
3	**Withdrawals and dropouts:** Was there a description of withdrawals and dropouts? A trial reporting the number and reasons for withdrawals or dropouts is to receive one point. If there is no description, no point is given. Yes =1, No= 0	
	Total score (for above 3 categories) (0-2 = Low; 3-4 = Moderate, 5 = High)	
		Adequacy level
4	**Adequacy of allocation concealment:** Central randomization; numbered or coded bottles or containers; drugs prepared by a pharmacy, serially numbered, opaque, sealed envelopes etc. =Adequate	
	Alternation; reference to case record # or date of birth, etc. = Inadequate	
	Allocation concealment is not reported, or, fits neither category. = Unclear	

Appendix 4: Excluded Studies

The studies listed below were excluded, as they were duplicates of studies included in the report.

1. Belani C, TAX 326 Study Group. Phase III randomized trial of docetaxel in combination with cisplatin or carboplatin or vinorelbine plus cisplatin in advanced non-small cell lung cancer: interim analysis. **Semin Oncol** 2001;28(3 Suppl 9):10-4.

2. Bonomi P, Kim K, Chang A, Johnson D. Phase III trial comparing etoposide (E) cisplatin (C) versus taxol (T) with cisplatin-G-CSF(G) versus taxol-cisplatin in advanced non-small cell lung cancer. An Eastern Cooperative Oncology Group (ECOG) Trial [abstract]. **Proc Am Soc Clin Oncol** 1996;15:382.

3. Bonomi P, Kim K, Kugler J, Johnson D. Comparison of survival of stage IIIb versus stage IV non-small-cell lung cancer (NSCLC) patients treated with etoposide-cisplatin versus Taxol-cisplatin: an Eastern Cooperative Group (ECOG) trial [abstract]. **Proc Am Soc Clin Oncol** 1997;16:454a.

4. Chang A, Kim K, Glick J, Anderson T, Karp D, Johnson D. Phase II study of taxol in patients with stage IV non-small cell lung cancer (NSCLC); the Eastern Cooperative Oncology Group (ECOG) results. **Proc Am Soc Clin Oncol** 1992;11:293.

5. Comella G, Comella P, Frasci G, Panza N, Nicolella GP, Manzione L. Cisplatin-gemcitabine vs cisplatin-gemcitabine-vinorelbine, vs cisplatin-gemcitabine-paclitaxel in advanced non-small-cell lung cancer. First-stage analysis of a Southern Italy Cooperative Oncology Group (SICOG) Phase III Trial [abstract]. **ASCO Online** [database online] 2000. Available: http://www.asco.org/cgi-bin/prof/abst00.pl?absno=1933&div=luc&year= 00abstracts (accessed 2001 Feb 21).

6. Fossella F, DeVore R, Kerr R, Crawford J, Natale R, Anderson MD. Randomized phase III study of taxotere (T) (100MG/M^2 and 75 MG/$M^{2)}$ versus vinorelbine (V) or ifosfamide (1) in non-small cell lung cancer (NSCLC) patients, previously treated with platinum-based chemotherapy [abstract]. **Proc Am Soc Clin Oncol** 1998;17:483a.

7. Fossella FV, DeVore R, Kerr R, Crawford J, Natale R, Dunphy F. Phase III trial of docetaxel 100 Mg/M^2 or 75 Mg/M^2Vs vinorelbine/ifosfamide for non-small cell lung cancer (NSCLC) previously treated with platinum-based chemotherapy (PBC) [abstract]. **Proc Am Soc Clin Oncol** 1999;18:460a.

8. Gandara DR, Kelly K, Gumerlock P, Crowley J. Current status of therapy for advanced non-small cell lung cancer: a perspective from the Southwest Oncology Group (SWOG) [abstract]. **Lung Cancer** 2000;29:27.

9. Giaccone G, Splinter TAW, Postmus P, Van Meerbeeck J, Debruyne C, Sahmoud T. Teniposide-cisplatin vs paclitaxel-cisplatin in advanced non-small cell lung cancer (NSCLC). Results of a randomized phase II study of the EORTC-LCCG [abstract]. **Proc Am Soc Clin Oncol** 1995;14:356.

10. Giaccone G, Splinter T, Postmus P, Diaz-Puente M, van Zandwijk N, de Bruyne B, et al. Paclitaxel-cisplatin versus teniposide-cisplatin in advanced non-small cell lung cancer (NSCLC) [abstract]. **Proc Am Soc Clin Oncol** 1996;15:373.

11. Giaccone G, Postmus P, Debruyne C, Splinter T, Diaz-Puente M, van Zandwijk N. Final results of an EORTC phase III study of paclitaxel versus teniposide, in combination with cisplatin, in advanced NSCLE [abstract]. **Proc Am Soc Clin Oncol** 1997;16:460a.

12. Giaccone G, Postmus PE, Splinter TA, Diaz-Puente M, van Zandwijk N, Scagliotti G, et al. Cisplatin/paclitaxel vs cisplatin/teniposide for advanced non-small-cell lung cancer. **Oncology (Huntingt)** 1997;11(4 Suppl 3):11-4.

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Appendix 5: Toxicity Data (values represent % of patients)

1. Study - Belani et al.[26] **Toxicity**	**Treatment Arm = p+cb; (N=190)**	**Treatment Arm = c+e; (N=179)**
Febrile neutropenia	3.7	8.4
Neutropenia gr3/4	22.9/41	29.2/46.1
Diarrhea	0.5	2.8
Myalgia/Arthralgia	4.3	0
Peripheral neuro	12.8	0
Vomiting	3.7	10.1

2. Study - Bonomi et al. [12] **Toxicity**	**Treatment Arm = p+c; (N=190)**	**Treatment Arm = p (h)+c; (N=191)**	**Treatment Arm = c+e; (N+193)**
Anemia gr>or=3	28	19	19
Infection gr>or=3	7.4	9	8.5
Infection gr5	1.5	3	1
Leukopenia gr4	14	27	16
Neutropenia gr4	74	65	55
Thrombocytopenia gr4	0.5	5	5
Cardiac gr5	2	0.5	0.5
Myalgia gr>or=3	1	7	0
Nausea/vomiting gr4	10	9	6
Peripheral neruro gr3	23	40	21

3. Study - Chang et al. [27] **Toxicity**	**Treatment Arm = p; (N=24)**	**Treatment Arm = m; (N=35)**	**Treatment Arm = pi; (N=44)**
Anemia gr3/4/5	21/0/0	14/0/0	5/0/0
Infection gr3/4/5	4/8/4	3/0/3	0/5/0
Leukopenia gr3/4/5	17/67/0	2/0/0	23/0/0
Thrombocytopenia gr3/4/5	0/4/0	0/0/0	0/0/0
Cardiac gr3/4/5	13/4/0	3/3/3	0/0/2
Diarrhea gr3/4/5	8/0/0	0/0/0	0/0/0
Genito-urinary gr 3/4/5	0/0/0	3/3/0	0/0/0
Hepatic gr3/4/5	0/0/0	6/0/0	5/5/0
Nausea/vomiting gr 3/4/5	4/0/0	17/0/0	0/0/0
Neuroclinical gr3/4/5	4/0/0	11/0/0	2/2/0
Neuromotor gr3/4/5	13/0/0	14/0/0	0/0/0
Neuropsychologic gr3/4/5	4/0/0	9/0/0	0/0/0
Neurosensory gr3/4/5	8/0/0	0/0/0	0/0/0
Phebitis gr3/4/5	0/0/0	3/0/3	0/0/0
Pulmonary gr3/4/5	0/0/0	3/3/3	0/0/2
Stomatitis gr3/4/5	4/0/0	0/0/0	0/0/0

N=total number of patients, c=cisplatin, cb=carboplatin, e=etoposide, m=merbarone, p=paclitaxel, pi=piroxantrone, (h)=high dose

Appendix 5: Toxicity Data (values represent % of patients) (cont'd)

4. Study - Comella et al. [28]

Toxicity	Treatment Arm = p+c+g; (N=114)	Treatment Arm = c+g; (N=112)	Treatment Arm = c+g+v; (N=117)
Anemia gr3-4	21	12	14
Febrile neutropenia gr3-4	7	3	5
Neutropenia gr3-4	48	40	43
Thrombocytopenia gr3-4	20	35	25
Diarrhea gr3	6	3	1
Peripheral neuro gr1-2	38	5	17
Vomiting gr3-4	15	28	14
Mucositis gr3	6	5	3
Fatigue gr3	32	14	13
Renal gr1-2	6	8	5

5. Study - Fossella et al. [31]

Toxicity	Treatment Arm = t (h); (N=121)	Treatment Arm =t; (N=121)	Treatment Arm = v/i; (N=119)
Anemia gr4	1	0	2
Febrile neutropenia gr4	12	8	1
Infection gr4	3	0	1
Neutropenia gr4	77	54	31
Thrombocytopenia gr4	1	2	0
Asthenia gr3-4	17	12	11
Diarrhea gr3-4	3	2	2
Fluid retention gr3-4	4	1	2
Nausea gr3-4	7	3	6
Neurosensory gr3-4	6	1	3
Vomiting gr3-4	7	1	4

6. Study - Fossella et al. [29,30]

Toxicity	Treatment Arm = t+c; (N=406)	Treatment Arm = t+cb; (N=401)	Treatment Arm = v+c; (N=396)
Anemia gr3-4	7	10	24
Febrile neutropenia gr3-4	5	4	5
Infection gr3-4	6	8	6
Neutropenia gr3-4	75	74	79
Thrombocytopenia gr3-4	3	7	4
Anorexia gr3-4	5	3	5
Asthenia gr3-4	12	11	14
Diarrhea gr3-4	7	5	3
Nausea gr3-4	10	6	16
Neurosensory gr3-4	4	1	4
Pain gr3-4	8	9	8
Vomiting gr3-4	8	4	16

N=total number of patients, c=cisplatin, cb=carboplatin, g=gemcitabine, i=ifosfamide, p=paclitaxel, t=docetaxel, v=vinorelbine, (h)=high dose

Appendix 5: Toxicity Data (values represent % of patients) (cont'd)

7. Study - Gatzemeier et al. [32]

Toxicity	Treatment Arm = p+c; (N=202)	Treatment Arm = c; (N=206)
Anemia any/severe,gr3-4	67/10	68/6
Febrile Neutropenia	4	<1
Infection any/severe,gr3-4	26/4	24/6
Neutropenia any/severe,gr3-4	71/45	51/17
Thrombocytopenia any/severe,gr3-4	11/1	16/2
Asthenia any/severe	68/15	63/15
Hypersensitivity reac any/severe	7	2
Myalgia/artharalgia any/severe,gr3-4	46/5	20/2
Ototoxicity any/severe,gr3	4/0	16/1
Nausea/vomiting any/severe,gr3-4	67/12	80/16
Peripheral neuro any/severe,gr3	54/4	25/1
Renal any/severe,gr3	25/1	18/<1

8. Study - Gervais et al. [33]

Toxicity	Treatment Arm = t+c; (N=51)	Treatment Arm = c+v; (N=44)
Febrile Neutropenia	23	20
Neutropenia gr3-4	53	73

9. Study - Giaccone et al. [34]

Toxicity	Treatment Arm = p+c; (N=152)	Treatment Arm = c+tn; (N=160)
Anemia gr3-4	9/1	21/3
Febrile Neutropenia	3	27
Infection gr3-4	2/0	6/3
Leukopenia gr3-4	16/3	34/32
Neutropenia gr3-4	27/28	16/67
Thrombocytopenia gr3-4	1/1	18/18
Hypersensitivity reac.	7	1
Myalgia/artharalgia gr2/3	14/3	3/1
Peripheral neurotoxicity gr 2/3	20/9	6/1
Stomatitis gr2/3	3/1	12/1

N=total number of patients, c=cisplatin, p=paclitaxel, t=docetaxel, tn=teniposide, v=vinorelbine

Appendix 5: Toxicity Data (values represent % of patients) (cont'd)

10. Study - Kelly et al. [35]

Toxicity	Treatment Arm = p+cb; (N=203)	Treatment Arm = c+v; (N=197)
Anemia gr3/4	11/2	17/0
Leukopenia gr3/4	26/5	35/15
Neutropenia gr3/4	21/36	27/49
Thrombocytopenia gr3/4	10/0	4/0
Dehydration gr3/4	4/0	6/0
Fatigue gr3/4	8/0	11/0
Hyponatremia gr3/4	3/0	7/0
Nausea gr3-4	7/0	18/2
Neuromotor gr3/4	8/0	7/0
Neurosensory gr3/4	13/0	3/0
Respiratory infection with neutropenia gr3/4	1/0	5/0
Vomiting gr3/4	4/0	12/0

11. Study - Kunitoh et al. [36,37]

Toxicity	Treatment Arm = t+c; (N=151)	Treatment Arm = c+vn; (N=151)
Anemia gr1/2/3/4	21/55/10/0	19/47/23/0
Leukopenia gr1/2/3/4	11/35/44/2	9/19/61/7
Neutropenia gr1/2/3/4	6/11/42/33	2/14/27/40
Thrombocytopenia gr1/2/3/4	7/3/1/0	16/6/0/0
Alopecia gr1/2/3/4	42/21/0/0	36/9/0/0
Anorexia gr1/2/3/4	32/23/19/1	35/15/9/0
Arrhythmia gr1/2/3/4	1/0/2/0/	1/1/1/0
Constipation gr1/2/3/4	26/5/0/0	46/3/0/0
Diarrhea gr1/2/3/4	23/15/4/5	20/5/1/0
Fever gr1/2/3/4	21/31/1/0	22/28/1/0
Hearing loss gr1/2/3/4	3/0/0/0	2/0/0/0
Infection gr1/2/3/4	5/5/1/1	6/5/1/0
Malaise gr1/2/3/4	32/11/3/0	32/6/2/0
Nausea/vomiting gr1/2/3/4	25/56/10/0	26/44/4/0
Numbness gr1/2/3/4	8/0/1/1	25/4/1/0
Oedema gr1/2/3/4	26/9/0/0	11/2/0/0
Rash gr1/2/3/4	9/2/0/0	13/6/1/0
Stomatitis gr1/2/3/4	10/1/0/0	13/9/0/0
Renal gr1/2/3/4	27/8/1/0	23/13/1/1

N=total number of patients, c=cisplatin, cb=carboplatin, p=paclitaxel, t=docetaxel, v=vinorelbine, vn=vindesine

Appendix 5: Toxicity Data (values represent % of patients) (cont'd)

12. Study - Manegold et al. [38,39]

Toxicity	Treatment Arm = t; (N=48)	Treatment Arm = g; (N=98)
Anemia gr3	-	1
Leukopenia gr3	2	-
Thrombocytopenia gr3	-	1
Nausea gr3	4	8
Vomiting gr3	2	3
Allergy gr3	4	-
Alopecia gr3	8	-
Infection gr3	4	1

13. Study - Pérol et al. [40]

Toxicity	Treatment Arm = t+(c+v); (N=38)	Treatment Arm = c+v; (N=31)
Anemia gr3-4	21	32.2
Febrile neutropenia	10.5	12.9
Infection gr>2	10.5	3.2
Neutropenia gr4	60.5	61.2
Thrombocytopenia gr3-4	2.6	6.4
Alopecia gr2-4	36.8	9.7
Asthenia gr3-4	13.2	12.9
Constipation gr3-4	10.4	3.2
Diarrhea gr2-3	13.2	6.4
Mucositis gr>2	0	6.4
Nausea/vomiting gr>2	15.8	19.3
Perpheral neuropathy gr>1	0	3.2

14. Study - Perry et al. [41]

Toxicity	Treatment Arm = (p+i); (N=48)	Treatment Arm = (v+i); (N=31)
Anemia gr3-4	13	20
Leukopenia gr3-4	48	98
Neutropenia gr3-4	59	96
Lymphocytes gr3-4	67	73
Infection gr3-4	17	24
Dyspnea gr3-4	14	4
Motor gr3-4	8	13
Constipation gr3-4	2	11
Pain gr3-4	2	15
Malaise/fatigue gr3-4	12	22
Hyperglycemia gr3-4	10	0

N=total number of patients, c=cisplatin, g=gemcitabine, i=ifosfamide, p=paclitaxel, t=docetaxel, v=vinorelbine

Appendix 5: Toxicity Data (values represent % of patients) (cont'd)

15. Study - Scagliotti et al. [42,43]

Toxicity	Treatment Arm = p+c; (N=201)	Treatment Arm = c+g; (N=205)	Treatment Arm = c+v; (N=201)
Febrile neutropenia	1	0.5	3
Thrombocytopenia (Plt)	2	8	8
Alopecia gr3-4	52	10	11
Constipation gr3-4	0	1	2
Nausea/vomiting gr3-4	1	7	13
Peripheral neuro gr>or=2	30	7	4
Renal gr3-4	0	0	2
Skin gr3-4	0	1	1

16. Study - Schiller et al. [44]

Toxicity	Treatment Arm = p+c; (N=300)	Treatment Arm = p+cb; (N=293)	Treatment Arm = t+c; (N=297)	Treatment Arm = c+g; (N=293)
Anemia gr3/4	12/1	9/1	13/2	27/1
Febrile neutropenia gr3/4	2/14	0/4	1/10	1/3
Infection gr3/4/5	4/4/2	3/2/1	5/2/2	4/2/1
Neutropenia gr3/4	18/57	20/43	21/48	24/39
Thrombocytopenia gr3/4	4/2	8/2	2/1	22/28
Cardiac gr3/4/5	2/0/1	1/1/1	1/2/2	1/3/1
Diarrhea gr3/4	1/6	1/1	2/8	2/1
Hypersensitivity reac gr3/4	2/1	1/1	5/2	0/0
Nausea gr3	25	9	24	37
Peripheral neuro gr3	5	10	5	9
Renal gr3/4/5	3/0/0	1/0/0	3/0/0	6/2/1
Vomiting gr3/4	3/21	2/6	3/18	7/28
Weakness gr3/4	13/1	14/1	15/1	17/1

17. Study - Thompson et al. [45,46]

Toxicity	Treatment Arm = p+cb+g; (N=71)	Treatment Arm = p+cb+v; (N=65)	Treatment Arm = p+g; (N=64)	Treatment Arm = v+g; (N=67)
Febrile neutropenia gr3-4	4	25	9	6
Leukopenia gr3-4	44	63	17	30
Thrombocytopenia gr3-4	42	5	13	3
Platelet transfusion	11	3	2	0
RBC transfusion	28	18	13	13
Diarrhea gr2-3	13	8	11	3
Myalgia/artharalgia gr3-4	39	60	42	18
Nausea/vomiting gr2-3	23	18	25	9
Peripheral neuro gr2-4	31	49	20	13

N=total number of patients, c=cisplatin, cb=carboplatin, g=gemcitabine, p=paclitaxel, t=docetaxel, v=vinorelbine

Appendix 5: Toxicity Data (values represent % of patients) (cont'd)

18. Study – van Meerbeeck et al.[47,48]

Toxicity	Treatment Arm = p+c; (N=153)	Treatment Arm = p+g; (N=157)	Treatment Arm = c+g; (N=158)
Anemia gr3-4	3	11	4
Febrile neutropenia gr	1	3	2
Neutropenia gr3-4	33	43	30
Thrombocytopenia gr3-4	1	36	6
Bleeding gr3-4	1	0	1
Nausea gr3-4	8	13	6
Vomiting gr3-4	8	13	5
Allergy gr3-4	2	0	1
Motor neuropath gr3-4	3	1	3
Sensory gr3-4	3	2	1
Lethargy gr3-4	9	11	11
Dyspnea gr3-4	8	10	12

19. Study - Wiesenfeld et al. [49]

Toxicity	Treatment Arm = p+tp; (N=61)	Treatment Arm = c+tp; (N=227)
Leukopenia severe	22	62
Thrombocytopenia severe	1.6	76
Nausea/ vomiting/lethargy/diarrhea gr>or=3	24	43

N=total number of patients, c=cisplatin, g=gemcitabine, p=paclitaxel, tp=topotecan

Appendix 6: Details of Recent Studies (identified after the report was written and not included in the analyses)

Study (First Author)	Treatment Arm	Intervention†	Patient No.	Median Survival‡ (mth)	1 yr Survival‡ (%)	Objective Response (%)
Coudert [63]	1	t(75)+c(100)→t; q3wk	119		36	33.9
	2	v(30; d1,8)+c(100)→v; q3wk	120		35	26.3
Jensen [64]	1	t(80)+cb(AUC6); q3wk	33	7.9	29	36
	2	cb(AUC6); q3wk	33	6.8	18	12
Kakolyris [65]	1	t(100; d8)+g(1000; d1,8)	134	9		29
	2	v(30;d1,8)+c(80; d8)	117	11.5		36
Rocha Lima [66]	1	t(40;d1,8)+g(1000;d1,8); q3wk	39	12.8	55	23.1
	2	g(1000;d1,8)+ir(100;d1,8); q3wk	39	7.9	16	12.8

†Intervention: drug name (dose in mg/m^2; day administered); cycle
‡Survival = overall survival
Drugs: c=cisplatin, cb=carboplatin, g=gemcitabine, ir=irinotecan, t=docetaxel, v=vinorelbine;
d=day, q=every, wk=week