Chemotherapy and supportive care versus supportive care alone for advanced non-small cell lung cancer (Review)

Non-Small Cell Lung Cancer Collaborative Group

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[Intervention Review]

Chemotherapy and supportive care versus supportive care alone for advanced non-small cell lung cancer

Non-Small Cell Lung Cancer Collaborative Group[1]

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ABSTRACT

Background

Since our individual patient data (IPD) meta-analysis of supportive care and chemotherapy for non-small cell lung cancer (NSCLC), published in 1995, many trials have been completed. We have carried out an updated IPD meta-analysis to assess newer regimens and determine conclusively the effect of chemotherapy. The review was updated in 2012.

Objectives

To assess the effect on survival of supportive care and chemotherapy versus supportive care alone in advanced NSCLC.

Search methods

All randomised controlled trials (RCTs), published or unpublished. We searched bibliographic databases, trials registers, conference proceedings and reference lists of relevant trials. Searches were completed to August 2012.

Selection criteria

Trials had to have commenced accrual on or after 1 January 1965 and should have included patients with NSCLC who had received either chemotherapy and supportive care or supportive care alone. Patients should have not received any previous chemotherapy or had any prior malignancy.

Data collection and analysis

For trials included in 1995 we sought updated follow-up. For new trials we sought survival and baseline characteristics for all patients. We combined results from RCTs to calculate individual and pooled hazard ratios (HRs).

Main results

We obtained data on 2714 patients from 16 RCTs. No new RCTs were identified in 2012. There were 1293 deaths among 1399 patients assigned supportive care and chemotherapy and 1240 among 1315 assigned supportive care alone. Results showed a significant benefit of chemotherapy (HR = 0.77; 95% CI 0.71 to 0.83, P < 0.0001), equivalent to a relative increase in survival of 23%, an absolute improvement in survival of 9% at 12 months, increasing survival from 20% to 29% or an absolute increase in median survival of 1.5 months (from 4.5 months to six months). There was no clear evidence that this effect was influenced by the drugs used (P =

0.63) or whether they were used as single agents or in combination (P = 0.40). Despite changes in patient demographics, the effect of chemotherapy in recent trials did not differ from those included previously (P = 0.77). There was no clear evidence of a difference in the relative effect of chemotherapy across patient subgroups. Quality of life could not be formally assessed.

Authors' conclusions

All trials were of good methodological quality with no risk of bias. This meta-analysis of chemotherapy in the supportive care setting demonstrates that chemotherapy improves overall survival in all patients with advanced NSCLC. Patients who are fit enough and wish to receive it should be offered chemotherapy.

PLAIN LANGUAGE SUMMARY

Chemotherapy and supportive care versus supportive care alone for advanced non-small cell lung cancer

Non-small cell lung cancer (NSCLC) is the most common type of lung cancer. If the tumour has spread from the lung to other parts of the body (advanced) it cannot usually be cured. Doctors use different treatments to prevent or relieve symptoms and keep patients well for longer. This sort of treatment is sometimes called best supportive care.

In 1995, we did a systematic review and meta-analysis of individual patient data looking at adding chemotherapy (drug treatment) to best supportive care. It gathered together information from all patients who took part in similar trials. These trials compared what happened to people with NSCLC who were given chemotherapy and best supportive care with those who only had best supportive care. We found that giving chemotherapy helped patients with advanced NSCLC to live longer.

Since this study was published, many new trials have been done. Therefore, we did a new systematic review and meta-analysis of individual patient data that included all trials, old and new. This study aimed to find out how much better chemotherapy as well as best supportive care was at helping patients to live longer. It also looked to see if new drugs were better or worse than older drugs, and if chemotherapy helps all types of patients.

We found that people with advanced NSCLC that had chemotherapy and best supportive care lived longer than those who had best supportive care. After 12 months, 29 out of every 100 who were given chemotherapy and best supportive care were alive compared to 20 out of every 100 who just had best supportive care.

Some patients and doctors may be concerned that the side effects of chemotherapy outweigh the benefits of receiving it. In this project we were unable to look at this in detail. However, three of the trials included in this project reported that for those patients who received chemotherapy, quality of life was either the same or better than those that did not receive chemotherapy.

This study showed that chemotherapy in addition to supportive care helped some patients to live longer, even the elderly and less fit.

The review was updated in 2012.

BACKGROUND

Our previous meta-analysis (NSCLC Collaborative Group 1995), based on individual patient data (IPD) of more than 9000 patients from over 50 randomised trials, concluded that despite previous scepticism and controversy, platinum-based chemotherapy has a role in treating patients with non-small cell lung cancer (NSCLC). In particular, there was strong evidence that for advanced disease, chemotherapy given in addition to supportive care could prolong survival.

Description of the condition

Worldwide, around one and a half million new cases of lung cancer are diagnosed each year (Parkin 2002). About 85% of these tumours are of non-small cell histological type (Visbal 2005), including adenocarcinomas, squamous cell and large cell carcinomas. NSCLC is the main cause of death from cancer (World Health Organization 2003) and five-year survival across all stages of the disease is about 14% (Greenlee 2000).

Description of the intervention

Surgery is generally regarded as the best treatment option, but only about 30% of tumours are suitable for potentially curative resection (Rudd 1991). A further 20% of patients, usually those presenting with locally advanced disease, undergo radical thoracic radiotherapy or combined chemo-radiotherapy. The remaining 50% of patients, essentially those with metastatic disease, or who are medically unfit, are treated palliatively.

Supportive care may include palliative radiotherapy, antibiotics, corticosteroids, analgesics, antiemetics, transfusions and psychosocial support. Chemotherapy given in addition to supportive care may offer further benefits.

Why it is important to do this review

Since 1995, a considerable number of new trials exploring newer drugs and new modes of administration have been completed in the supportive care setting. To take account of the expanded evidence base and provide the most up-to-date and reliable assessment of the role of chemotherapy in NSCLC, the NSCLC Collaborative Group has carried out an updated IPD meta-analysis that examines the role of chemotherapy in seven treatment comparisons (Burdett 2005; NSCLC Collaborative Group 2010; Burdett 2011; Le Pechoux 2008; Auperin 2010; JCO 2008). In the supportive care setting reported here, we assessed the role of newer chemotherapy agents and assessed more reliably the effect of chemotherapy in different subgroups of patients. Quality of life is an important issue in patients with advanced non-small cell lung cancer and the side effects of having chemotherapy along with any potential benefit of treatment were assessed where appropriate data were available. This review was originally published in 2008 (JCO 2008) and 2010 (Cochrane 2010)and it was updated in 2012.

OBJECTIVES

The aim was to assess the effect on survival of supportive care and chemotherapy versus supportive care alone in advanced NSCLC. The meta-analysis followed a detailed and pre-specified protocol which set out the objectives, inclusion criteria for trials, data to be collected and analyses to be carried out. A copy of the protocol is available on request (from SB).

METHODS

Criteria for considering studies for this review

Types of studies

To be included in the meta-analysis, trials had to be randomised, have commenced accrual on or after 1 January 1965 and have completed accrual.

Types of participants

Trials should have included patients with NSCLC who had received either chemotherapy and supportive care or supportive care alone, that were unsuitable for surgery or radical radiotherapy. Patients should have not received any previous chemotherapy or had any prior malignancy.

Types of interventions

Trials should have compared supportive care and chemotherapy versus supportive care alone. Supportive care included palliative radiotherapy, antibiotics, corticosteroids, analgesics, antiemetics, transfusions and psychosocial support.

Types of outcome measures

Survival.

Search methods for identification of studies

To limit publication bias, we included all randomised trials, whether published or unpublished.

Electronic searches

Initially searches were completed for the period up to and including 2003. We revised these regularly to identify further trials published by our final analyses in September 2007. These have been updated to August 2012 for completeness and no new RCTs have been found. Access was via Ovid. We carried out bibliographic searches of MEDLINE and CancerLit using the Cochrane Collaboration optimal search strategy for identifying RCTs (Dickersin 1994). We completed later searches using an updated search strategy (Wong 2006). These were supplemented by searching the Cochrane Central Register of Controlled Trials (CENTRAL), The National Cancer Institute PDQ (Physicians Data Query), Clinical protocols (open and closed), ClinicalTrials.gov, United Kingdom Co-ordinating Committee for Cancer Research trials register and the Current Controlled Trials *meta*Register of trials to identify unpublished and ongoing trials. The more recent searches also included searching EMBASE. Search strategies of the most recent searches are in Appendix 1.

It is unlikely that any new RCTs will be carried out in this area again, therefore this review will not be updated again

Searching other resources

We carried out the following handsearches with the aim of identifying trials that may have only been reported as abstracts or that might have been missed in the searches described above:

- Proceedings of the American Society of Clinical Oncology (ASCO) 1990 to 1994 (electronically searched thereafter).
- Proceedings of the International Association for the Study of Lung Cancer (IASLC) World Lung Cancer Conference 1990 to 2011.
- Proceedings of the European Society of Medical Oncology (ESMO) 1990 to 2010.
- Proceedings of the European Cancer Conference Organization (ECCO) 1990 to 2009.
- Proceedings of the The European Multidisciplinary Cancer Congress (ESMO/ECCO) 2011.
- Bibliographies of all identified trials and review articles.

We asked all participating trialists to review and supplement a provisional list of trials.

Where there was uncertainty about the eligibility of a trial or particular treatment arms within a trial, this was discussed and resolved by consensus within the project secretariat and international Advisory Group. We did not search for trials that used long-term alkylating agents. These were included in the 1995 analyses, but due to their antiquity were not included in this update.

Data collection and analysis

We approached investigators for all eligible trials and asked them to supply the original individual patient data.

For trials already included in the 1995 analyses we sought updated follow-up. Most of the trials previously provided mature data and we did not anticipate much additional information. However, some additional data were received and included in the new analyses.

For new trials we sought survival and baseline characteristics for all patients randomised into each trial. This included date of randomisation, survival status and date of last follow-up or death, as well as information on date of birth, sex, performance status, tumour stage (TNM) and histological type.

We applied a number of standard checks to all new trials, including checks for missing values and data validity and consistency across variables. To assess the randomisation integrity, we looked for unusual patterns in the sequencing of allocation or imbalances in baseline characteristics between treatment arms. We also assessed follow-up of surviving patients to ensure that it was balanced by treatment arm and as up-to-date as possible. Any queries were resolved and the final database entries verified by the responsible trial investigator or statistician.

Selection of studies

One author (SB) screened the results of all searches were screened and collated a set of potentially eligible trials. Two authors (SB, LS) then assessed this set of trials for eligibility. Where queries regarding eligibility arose, we contacted the trial investigators directly.

Data extraction and management

We centrally collected, checked and re-analysed individual patient data.

Assessment of risk of bias in included studies

We assessed the risk of bias of included studies according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008Higgins 2011). We examined the adequacy of the methods used to generate the allocation sequence and the concealment of allocation. We also evaluated the risk associated with drop-outs, as estimated by the percentage of participants lost, as well as the selective outcome reporting and other sources of bias. We did not assess blinding due to the nature of the interventions evaluated. We used the following definitions:

Assessment of risk of bias in included studies

The risk of bias of included studies was assessed by one author (SB) according to the areas and criteria proposed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and results of those judgments are presented in the 'Risk of bias' tables.

1. *Sequence generation (checking for possible selection bias)*

For each included study we described the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assessed the risk of bias as:

· low risk (any truly random process, e.g. random number table; computer random number generator),

· high risk (any non-random process, e.g. odd or even date of birth; hospital or clinic record number), or

· unclear risk.

2. *Allocation concealment (checking for possible selection bias)*

For each included study we described the method used to conceal the allocation sequence and determined whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the risk of bias as:

· low risk (e.g. telephone or central randomization; consecutively numbered sealed opaque envelopes),

· high risk (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth),

· unclear risk.

3. *Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)*

For each included study and for each outcome or class of outcomes, we described the completeness of data including attrition

and exclusions from the analysis. We stated whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomized participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. We categorized the risk of bias as:

· low risk,
· high risk,
· unclear risk.

4. *Selective reporting bias*

For each included study we described how we investigated the possibility of selective outcome reporting bias and what we found. We assessed the risk of bias as:

· low risk (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
· high risk (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest were reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
· unclear risk.

5. *Other sources of bias*

Where relevant for each included study any important concern about other possible sources of bias is reported.

We assessed the risk of bias as:

· low risk,
· high risk,
· unclear risk.

Blinding was not appropriate in this set of trials due to the nature of the intervention.

Measures of treatment effect

Overall survival was defined as the time from randomisation until death by any cause. Patients still alive were censored at the date of last follow-up or date last known to be alive.

Analyses of outcomes, trial groups and patient groups were (unless otherwise stated) pre-specified in the protocol and carried out on an intention-to-treat basis; that is, patients were analysed according to their allocated treatment, irrespective of whether they received that treatment. We stratified analyses of all endpoints by trial, and used the log rank expected number of deaths and variance to calculate individual trial hazard ratios (HRs) and overall pooled HRs based on the fixed-effect model (Yusuf 1985). Thus, we used the times to death for individual patients within trials to calculate the HR, representing the overall risk of an event for those patients allocated to supportive care and chemotherapy compared with those allocated to supportive care alone. We also combined results using the random-effects model to assess the robustness of the results to the choice of meta-analysis model.

We also present results as absolute differences at one year, calculated using the overall HRs and the control arm event rate (Parmar 1995). We calculated confidence intervals for absolute differences from the baseline event rate and the HR at the 95% confidence interval (CI) boundary values. Survival curves are presented as simple (non-stratified) Kaplan-Meier curves (Kaplan 1958). All P values quoted are two-sided.

We calculated median follow-up by the reverse Kaplan-Meier method, based on surviving patients and using censoring as the event.

Dealing with missing data

We queried missing individual patient data with trial investigators and re-instated data where possible.

Assessment of heterogeneity

We used Chi^2 heterogeneity tests and the I^2 statistic for inconsistency (Higgins 2003Higgins 2011) to assess statistical heterogeneity across trials.

Assessment of reporting biases

Trials were included in the meta-analysis whether they were published or unpublished and there was no language restriction

Subgroup analysis and investigation of heterogeneity

To examine the potential impact of the treatments used, we predefined analyses that grouped trials by the type of chemotherapy regimen used. For these analyses, we calculated a pooled HR for each group of trials and for all trials together. As we specified that we would group those trials using platinum-based chemotherapy with a vinca-alkaloid or etoposide separately from those trials that did not use a vinca-alkaloid or etoposide, the BLT Trial (BLT1) was divided into two trials. BLT1 combined cisplatin with a vinca-alkaloid and BLT2 did not use a vinca-alkaloid.

We investigated the relative effects of chemotherapy in different subgroups of patients using similar stratified analyses. We performed analyses for each pre-specified subgroup, for example, comparing the effect of treatment and control for males and for females within each individual trial. These results were then combined to give overall HRs for males and for females. We used Chi^2 tests for interaction or trend to investigate whether there were any substantial differences in the effect of chemotherapy between groups of trials or subgroups of patients.

Sensitivity analysis

We calculated hazard ratios for overall survival excluding any trials that are clear outliers.

RESULTS

Description of studies

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

Results of the search

We identified a total of 19 eligible trials that had used supportive care and chemotherapy versus supportive care alone. Of these, data for two trials (Gasparini 1991; Thongprasert 1999) were no longer available and for one trial (Roszkowski 2000) adequate contact with the investigators could not be established. Therefore data from 16 trials were included. This is an additional seven trials to those included in 1995. No new trials were identified with the search run in 2012.

Included studies

We included 16 trials (Ancona 1; AOI-Udine; BLT1; BLT2; CEP-85; ELVIS; Gwent 2; JLCSG; Manchester 1; Manchester 2; MIC2; NCIC CTG BR5; NRH; Southampton; RLW 8351; UCLA) that randomised 2714 patients. These represent 84% of patients from all known randomised trials that compared supportive care and chemotherapy with supportive care alone and 65% more data (seven extra trials) than were available in 1995. The seven new trials included since 1995 are JLCSG, BLT1, BLT2, MIC2, ELVIS, Manchester 1 and Manchester 2.
Data for age and sex were provided for all trials. Histology data were provided for 15 trials and performance status and stage were supplied for 13 trials. Based on these available data, patients were mostly male, aged between 60 and 70 years, with good performance status. Performance status was defined as Good (WHO/ECOG 0 or 1, Karnofsky 100-70) or Poor (WHO/ECOG 2+, Karnofsky 60 or less).
Of the stage data we received, 90% of patients had tumours that were advanced (predominantly stage IIIb and IV). However, a small proportion (3%) of patients had stage I and II disease. This appears to be because some trials (BLT1; Manchester 1) did not restrict entry to advanced patients and these individuals were (presumably) randomised because their condition precluded or the patient declined surgery or radical radiotherapy.
Most patients had squamous cell tumours (43%) or adenocarcinomas (23%); the proportion of these tumour types has not substantially changed between 1995 and the current analysis.
The median follow-up for all surviving patients is 1 year 4 months (range < 1 month to 9.5 years).
The 16 trials accrued between 32 and 447 patients. Characteristics of these trials are summarised in the 'Characteristics of included studies'. Platinum-based chemotherapy was used in 12 trials (cisplatin in 11 and carboplatin in one (JLCSG)) and non-platinum single agents (etoposide, vinorelbine, gemcitabine and paclitaxel) were used in four trials.

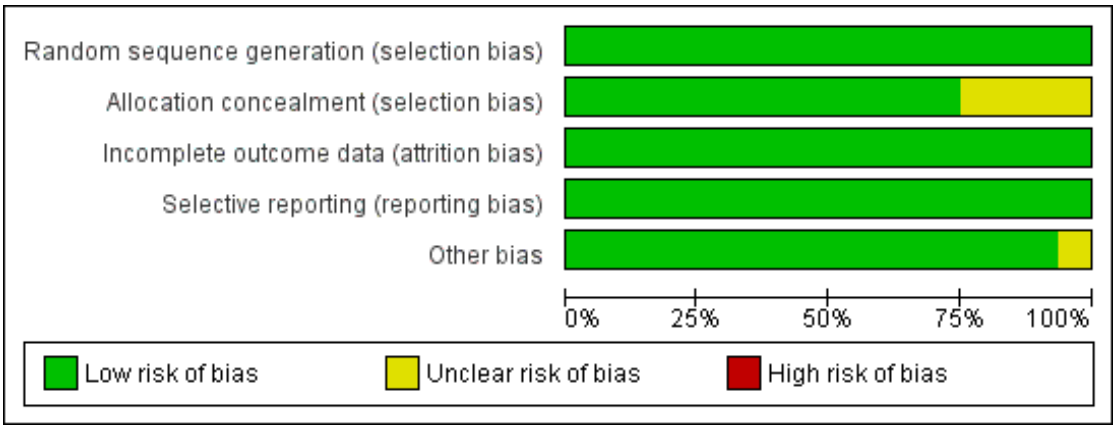
Excluded studies

Three eligible trials were not included in this review for the following reasons: data for two trials (Gasparini 1991; Thongprasert 1999) were no longer available and for one trial (Roszkowski 2000) adequate contact with the investigators could not be established.

Risk of bias in included studies

We obtained updated follow-up for most trials and outcome data for all so there is unlikely to be selective outcome reporting or follow-up bias. Unpublished studies were sought, but none identified, therefore it is unlikely that there is any publication bias. Figure 1 shows the assessment of the publications of studies included in the review.

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



Allocation

Of the 16 included trials, 12 trials had low risk for allocation concealment. Three trials were described as randomised but did not mention a concealment method and one trial was reported in a non-English language and was therefore unclear. Checks run on individual patient data suggest adequate sequence generation.

Incomplete outcome data

Individual patient data were obtained for all trials and checked for all outcomes.

Selective reporting

Individual patient data were obtained for all trials and checked for all outcomes.

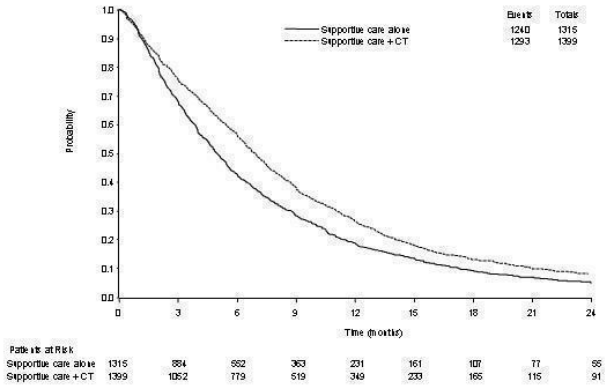
Other potential sources of bias

All studies appear to be free of other sources of bias, however one trial was reported in a non-English language so was unclear.

Effects of interventions

Survival analyses, based on 2533 deaths and 2714 patients from 16 trials show a highly statistically significant benefit of chemotherapy on survival (HR = 0.77; 95% CI 0.71 to 0.83, P < 0.0001) translating to an absolute improvement of 9% at 12 months, increasing survival from 20% to 29% or an absolute increase in median survival of 1.5 months (from 4.5 months to 6 months). There was some evidence of heterogeneity between the trials (P = 0.02, I^2 = 47%). However, repeating the sensitivity analysis carried out in 1995 (NSCLC Collaborative Group 1995), which excluded the extreme results of CEP-85 (CEP-85) (49 patients), resulted in considerably lower heterogeneity (P = 0.275, I^2 = 16%) with a similar effect of chemotherapy on overall survival (HR = 0.78; 95% CI 0.72 to 0.85). Also, based on all trials, results using the random-effects model were similar (HR = 0.75; 95% CI 0.67 to 0.84, P < 0.0001). The survival curve is shown in Figure 2.

Figure 2. Simple (non-stratified) Kaplan-Meier curve for survival by treatment



There was no clear evidence of a difference in the effect of chemotherapy between chemotherapy types (P = 0.63) or between trials that used combination chemotherapy and those that used single-agent chemotherapy (P = 0.40).

Of the three trials that we could not include in these analyses, we could estimate a hazard ratio for survival (Parmar 1998) for one trial of 207 patients (Roszkowski 2000). This trial used single-agent docetaxel, had a reported P value of 0.03 and gave a very similar result (HR = 0.70; 95% CI 0.51 to 0.95) to the included trial (Manchester 2) that used a single-agent taxane (HR = 0.69; 95% CI 0.49 to 0.97).

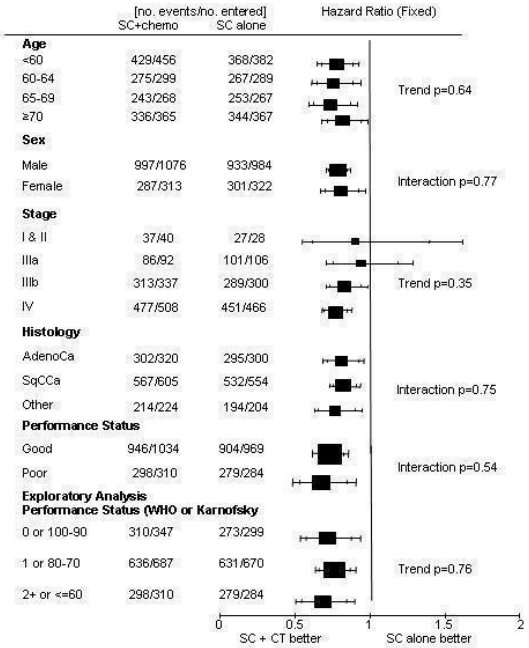
Since the 1995 meta-analysis the patient demographic may have changed and so the effect of chemotherapy may also have changed. Certainly, there was a higher proportion of patients aged over 70 in the more recent trials, probably due to ageing populations and widening eligibility criteria, although all trials included patients aged over 70 years old. The median age of patients in the trials included since the 1995 analysis was higher (66 years old, previously 61 years old), there were more women (28%, previously 19%) and far more stage IIIa patients (16%, previously 3%). There was no real change in the proportion of patients with adenocarcinoma or squamous cell histology. Despite these differences, there was no evidence of a difference in effect of chemotherapy between trials in the 1995 analysis and the recent trials (interaction P = 0.77) or between previous platinum-based trials and recent platinum-based trials (interaction P = 0.64).

The review was updated in 2012. No new trials were found and the results of the review did not change.

Patient subgroups

There was no clear evidence of a difference or trend in the relative effect of chemotherapy in patient subgroups defined by age (P = 0.64), sex (P = 0.77), stage (P = 0.35), histology (P = 0.75) or performance status (P = 0.54) (Figure 3). Furthermore, despite the difference in underlying survival by performance status, the absolute effect at 12 months was fairly similar: 8% for performance status 0/Karnofsky 100-90 (from 26% to 34%), 8% for 1/Karnofsky 80-70 (from 18% to 26%) and 6% for 2+/Karnofsky 60 or less (from 8% to 14%).

Figure 3. Hazard ratio plot showing effect of chemotherapy on survival by age, sex, stage, histology and performance status



DISCUSSION

Based on 16 RCTs and 2714 patients, this systematic review and meta-analysis includes 65% more data than available in 1995 and represents the most comprehensive and reliable review of chemotherapy in the supportive care setting. All trials were judged to be of good methodological quality and there was no risk of bias.

Results demonstrate a substantial benefit of chemotherapy for advanced NSCLC, improving survival by 9% at 12 months and median survival by 1.5 months. The benefit seen in new trials is consistent with that seen previously, despite changes in the lung cancer population and drug regimens used over time.

We now have substantially more power to look at the effect of chemotherapy in different groups of patients and can be more confident in these results than in 1995. Both the relative and absolute benefits of chemotherapy are remarkably consistent across patient subgroups, notably with benefits irrespective of age and performance status.

In our meta-analysis the effectiveness of newer drugs such as vinorelbine, paclitaxel and gemcitabine, used as single agents, appears to be similar to that of platinum-based chemotherapy combined with older agents such as vindesine and mitomycin C, potentially offering a greater range of treatment options and candidates for future trials. However, individually only one trial using single-agent paclitaxel (Manchester 2) is statistically significant in favour of chemotherapy (P = 0.03) and another using vinorelbine (ELVIS) is of borderline significance (P = 0.06). The trial of single-agent docetaxel (Roszkowski 2000) that we could not include was also significantly in favour of chemotherapy (P = 0.03).

In 1998 a meta-analysis that compared single-agent and combination chemotherapy in advanced NSCLC (Lilenbaum 1998) found that while the response rate for patients receiving combination chemotherapy was improved, overall survival was not significantly

better. There was also increased toxicity associated with combination chemotherapy. Similarly, this meta-analysis suggests no difference in effect between trials using single-agent and combination chemotherapy, however our observation is an indirect comparison. Two more recent literature-based meta-analyses (Delbaldo 2004; Hotta 2004) both reported that two agents were more beneficial than one, but that three agents were no more beneficial than two (Delbaldo 2004). It is important to remember, however, that these observations are based on indirect comparisons and the power to detect any differences is limited. Thus this conclusion should be interpreted with caution. A number of trials have been completed, or are still ongoing, which compare newer agents, such as docetaxel and gemcitabine, in combination or as single agents. One completed trial (Lilenbaum 2005) of carboplatin and paclitaxel versus paclitaxel alone suggested that although there was no evidence of a difference in effect between the treatments, combination chemotherapy could be an option for those able to tolerate a more aggressive treatment.

In the 1995 analysis, the platinum-based trials showed a 27% reduction in the risk of death equivalent to an increase in median survival of 1.5 months. This led to discussion about the impact on quality of life and whether the side effects of chemotherapy were worthwhile for this relatively small increase in survival. At that time only two (CEP-85; UCLA) of the included trials had tried to measure quality of life and both had failed to do so successfully. Although we did not collect quality of life data, three trials using platinum-based chemotherapy (BLT1; JLCSG; MIC2), one using vinorelbine, one using gemcitabine (Manchester 1) and one using paclitaxel (Manchester 2), which have been included since 1995, assessed quality of life. Of the trials we could not include, one trial of docetaxel (Roszkowski 2000) and one of platinum-based chemotherapy (Thongprasert 1999) also assessed quality of life. All reported that quality of life was either no worse or improved for those patients receiving chemotherapy. This suggests that platinum-based regimens and newer agents could offer both improved survival and possibly better quality of life.

AUTHORS' CONCLUSIONS

Implications for practice

This meta-analysis, based on 16 RCTs of sound methodological quality, demonstrates that chemotherapy increases overall survival for all types of patients with advanced NSCLC and that there should be no change in the treatment paradigm. Evidence from trials that collected quality of life data also suggests that this approach is unlikely to be detrimental to the patient's quality of life. Therefore, all patients who are fit enough and wish to receive it should be offered chemotherapy.

Implications for research

The current meta-analysis suggests that we do not need another trial of supportive care alone versus supportive care and chemotherapy. What we do need are more trials comparing third-generation chemotherapy combinations, doses and duration, and also further research on toxicity and side effects. Recent trials have shown the efficacy of EGFR tyrosine kinase inhibitors in advanced patients (Gridelli 2007) who have relapsed after first-line chemotherapy and so future trials may also exploit these encouraging developments.

ACKNOWLEDGEMENTS

The NSCLC Collaborative Group (composition below) thanks all patients who took part in the trials and contributed to this research. The meta-analysis would not have been possible without their participation or without the collaborating institutions that provided their trial data.

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BLT1 *{published and unpublished data}*
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BLT2 *{published and unpublished data}*
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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Ancona 1

Methods	1985 to 1988 Randomised controlled trial
Participants	128 patients Stage IIIB, IV
Interventions	Supportive care versus supportive care and chemotherapy Cisplatin, cyclophosphamide and epirubicin alternating with methotrexate and etoposide
Outcomes	Survival
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stated as randomised in paper, checks run on IPD suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Central randomisation, treatment assigned by telephone call
Incomplete outcome data (attrition bias) All outcomes	Low risk	Individual patient data obtained and checked for all outcomes
Selective reporting (reporting bias)	Low risk	Individual patient data obtained and checked for all outcomes
Other bias	Low risk	Study appears to be free of other sources of bias

AOI-Udine

Methods	1984 to 1986 Randomised controlled trial
Participants	102 patients Stage IV
Interventions	Supportive care versus supportive care and chemotherapy Cisplatin, mitomycin C, cyclophosphamide

AOI-Udine (*Continued*)

Outcomes	Survival	
Notes	-	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Stated as randomised in paper, checks run on IPD suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Random number table
Incomplete outcome data (attrition bias) All outcomes	Low risk	Individual patient data obtained and checked for all outcomes
Selective reporting (reporting bias)	Low risk	Individual patient data obtained and checked for all outcomes
Other bias	Low risk	Study appears to be free of other sources of bias

BLT1

Methods	1995 to 2001 Randomised controlled trial	
Participants	477 patients Stage I, II, IIIA, IIIB, IV	
Interventions	Supportive care versus supportive care and chemotherapy Cisplatin and vindesine or Cisplatin and vinorelbine or Cisplatin, mitomycin C and vinblastine	
Outcomes	Primary - survival Secondary - quality of life and costs	
Notes	-	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

BLT1 (*Continued*)

Random sequence generation (selection bias)	Low risk	Stated as randomised in paper, checks run on IPD suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Central randomisation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Individual patient data obtained and checked for all outcomes
Selective reporting (reporting bias)	Low risk	Individual patient data obtained and checked for all outcomes
Other bias	Low risk	Study appears to be free of other sources of bias

BLT2

Methods	1995 to 2001 Randomised controlled trial
Participants	248 patients Stage I, II, IIIA, IIIB, IV
Interventions	Supportive care versus supportive care and chemotherapy Cisplatin, mitomycin C, ifosfamide
Outcomes	Primary - survival Secondary - quality of life and costs
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Stated as randomised in paper, checks run on IPD suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Central randomisation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Individual patient data obtained and checked for all outcomes
Selective reporting (reporting bias)	Low risk	Individual patient data obtained and checked for all outcomes

BLT2 (*Continued*)

Other bias	Low risk	Study appears to be free of other sources of bias

CEP-85

Methods	1985 to 1988 Randomised controlled trial
Participants	49 patients Stage IIIA, IV
Interventions	Supportive care versus supportive care and chemotherapy Cisplatin and vindesine
Outcomes	Survival
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Stated as randomised in paper, checks run on IPD suggest adequate sequence generation
Allocation concealment (selection bias)	Unclear risk	Reported in non-English language
Incomplete outcome data (attrition bias) All outcomes	Low risk	Individual patient data obtained and checked for all outcomes
Selective reporting (reporting bias)	Low risk	Individual patient data obtained and checked for all outcomes
Other bias	Unclear risk	Reported in non-English language

ELVIS

Methods	1996 to 1997 Randomised controlled trial
Participants	161 patients Stage II, IIIA, IIIB, IV
Interventions	Supportive care versus supportive care and chemotherapy Vinorelbine
Outcomes	Survival

ELVIS (*Continued*)

Notes	-	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Stated as randomised in paper, checks run on IPD suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Central randomisation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Individual patient data obtained and checked for all outcomes
Selective reporting (reporting bias)	Low risk	Individual patient data obtained and checked for all outcomes
Other bias	Low risk	Study appears to be free of other sources of bias

Gwent 2

Methods	1982 to 1984 Randomised controlled trial	
Participants	186 patients Stage I, II, IIIA, IIIB, IV	
Interventions	Supportive care versus supportive care and chemotherapy Etoposide	
Outcomes	Response to chemotherapy Survival	
Notes	-	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Stated as randomised in paper, checks run on IPD suggest adequate sequence generation
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not reported in manuscript

Gwent 2 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Individual patient data obtained and checked for all outcomes
Selective reporting (reporting bias)	Low risk	Individual patient data obtained and checked for all outcomes
Other bias	Low risk	Study appears to be free of other sources of bias

JLCSG

Methods	1990 to 1995 Randomised controlled trial
Participants	48 patients Stage IIIB, IV
Interventions	Supportive care versus supportive care and chemotherapy Etoposide
Outcomes	Survival Time to progression
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Stated as randomised in paper, checks run on IPD suggest adequate sequence generation
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not reported in manuscript
Incomplete outcome data (attrition bias) All outcomes	Low risk	Individual patient data obtained and checked for all outcomes
Selective reporting (reporting bias)	Low risk	Individual patient data obtained and checked for all outcomes
Other bias	Low risk	Study appears to be free of other sources of bias

Manchester 1

Methods	1994 to 1996 Randomised controlled trial
Participants	300 patients 40/300 Stage IV, unknown stage for remainder of patients
Interventions	Supportive care versus supportive care and chemotherapy Gemcitabine
Outcomes	Change in symptoms Overall survival Tumour response
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Stated as randomised in paper, checks run on IPD suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Central randomisation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Individual patient data obtained and checked for all outcomes
Selective reporting (reporting bias)	Low risk	Individual patient data obtained and checked for all outcomes
Other bias	Low risk	Study appears to be free of other sources of bias

Manchester 2

Methods	1995 to 1997 Randomised controlled trial
Participants	157 patients Stage IIIB, IV
Interventions	Supportive care versus supportive care and chemotherapy Paclitaxel
Outcomes	Survival Quality of life assessment Disease progression Toxicity

Manchester 2 (*Continued*)

	Response	
Notes	-	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Stated as randomised in paper, checks run on IPD suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Central randomisation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Individual patient data obtained and checked for all outcomes
Selective reporting (reporting bias)	Low risk	Individual patient data obtained and checked for all outcomes
Other bias	Low risk	Study appears to be free of other sources of bias

MIC2

Methods	1988 to 1996 Randomised controlled trial	
Participants	359 patients Stage information not known	
Interventions	Supportive care versus supportive care and chemotherapy Cisplatin, mitomycin C, ifosphamide	
Outcomes	Survival	
Notes	-	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Stated as randomised in paper, checks run on IPD suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Central randomisation

MIC2 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Individual patient data obtained and checked for all outcomes
Selective reporting (reporting bias)	Low risk	Individual patient data obtained and checked for all outcomes
Other bias	Low risk	Study appears to be free of other sources of bias

NCIC CTG BR5

Methods	1983 to 1986 Randomised controlled trial
Participants	150 patients Stage IIIB, IV
Interventions	Supportive care versus supportive care and chemotherapy Cisplatin + vindesine or Cisplatin, doxorubicin and cyclophosphamide
Outcomes	Survival
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Stated as randomised in paper, checks run on IPD suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Central randomisation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Individual patient data obtained and checked for all outcomes
Selective reporting (reporting bias)	Low risk	Individual patient data obtained and checked for all outcomes
Other bias	Low risk	Study appears to be free of other sources of bias

NRH

Methods	1983 to 1987 Randomised controlled trial
Participants	87 patients Stage IIIA, IV
Interventions	Supportive care versus supportive care and chemotherapy Cisplatin, etoposide
Outcomes	Survival
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stated as randomised in paper, checks run on IPD suggest adequate sequence generation
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not reported in manuscript
Incomplete outcome data (attrition bias) All outcomes	Low risk	Individual patient data obtained and checked for all outcomes
Selective reporting (reporting bias)	Low risk	Individual patient data obtained and checked for all outcomes
Other bias	Low risk	Study appears to be free of other sources of bias

RLW 8351

Methods	1982 to 1986 Randomised controlled trial
Participants	167 patients Stage IIIB
Interventions	Supportive care versus supportive care and chemotherapy Cisplatin, vindesine
Outcomes	Survival
Notes	-

Risk of bias

RLW 8351 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stated as randomised in paper, checks run on IPD suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Central randomisation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Individual patient data obtained and checked for all outcomes
Selective reporting (reporting bias)	Low risk	Individual patient data obtained and checked for all outcomes
Other bias	Low risk	Study appears to be free of other sources of bias

Southampton

Methods	1983 to 1986 Randomised controlled trial
Participants	32 patients Stage IIIB
Interventions	Supportive care versus supportive care and chemotherapy Cisplatin, vinblastine
Outcomes	Survival
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stated as randomised in paper, checks run on IPD suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Central randomisation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Individual patient data obtained and checked for all outcomes
Selective reporting (reporting bias)	Low risk	Individual patient data obtained and checked for all outcomes

Southampton (*Continued*)

Other bias	Low risk	Study appears to be free of other sources of bias

UCLA

Methods	1984 to 1986 Randomised controlled trial	
Participants	63 patients Stage IV	
Interventions	Supportive care versus supportive care and chemotherapy Cisplatin, vinblastine	
Outcomes	Survival	
Notes	-	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Stated as randomised in paper, checks run on IPD suggest adequate sequence generation
Allocation concealment (selection bias)	Low risk	Central randomisation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Individual patient data obtained and checked for all outcomes
Selective reporting (reporting bias)	Low risk	Individual patient data obtained and checked for all outcomes
Other bias	Low risk	Study appears to be free of other sources of bias

IPD: individual patient data

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

Study	Reason for exclusion
Gasparini 1991	Data not available
Roszkowski 2000	Adequate contact with investigator could not be established
Thongprasert 1999	Data not available

DATA AND ANALYSES

Comparison 1. Chemotherapy and supportive care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	16	2714	Hazard Ratio (95% CI)	0.77 [0.71, 0.83]
1.1 Platinum + vinca alkaloid/ etoposide	9	1201	Hazard Ratio (95% CI)	0.77 [0.68, 0.86]
1.2 Other platinum regimens	3	709	Hazard Ratio (95% CI)	0.73 [0.63, 0.85]
1.3 Vinca alkaloid/etoposide only	2	347	Hazard Ratio (95% CI)	0.80 [0.64, 1.01]
1.4 Anti-metabolic agent only	1	300	Hazard Ratio (95% CI)	0.91 [0.70, 1.17]
1.5 Taxane only	1	157	Hazard Ratio (95% CI)	0.69 [0.49, 0.97]

FEEDBACK

Amendment, 8 December 2010

Summary

The plain language summary stated that 'this study showed that chemotherapy in addition to supportive care helped the majority of patients to live longer, even the elderly and less fit'. Given that it reported that 'After 12 months, 29 out of every 100 who were given chemotherapy and best supportive care were alive compared to 20 out of every 100 who just had best supportive care', using the term 'the majority of patients' is misleading.

Reply

In agreement with the author we decided to change 'the majority of patients' by 'some patients'.

Contributors

Dr Stephen McCabe

WHAT'S NEW

Last assessed as up-to-date: 8 August 2012.

Date	Event	Description
8 August 2012	Review declared as stable	Review updated after updating searches, no new RCTs were found. Risk of bias was re-assessed following updated guidelines It is unlikely that any new RCTs will be carried out in this area, therefore this review will not be updated in future

HISTORY

Protocol first published: Issue 3, 2008

Review first published: Issue 5, 2010

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DECLARATIONS OF INTEREST

No conflict of interest.

SOURCES OF SUPPORT

Internal sources

- Medical Research Council, UK.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.

INDEX TERMS

Medical Subject Headings (MeSH)

Antineoplastic Agents [*therapeutic use]; Carcinoma, Non-Small-Cell Lung [mortality; *therapy]; Life Expectancy; Lung Neoplasms [mortality; *therapy]; Palliative Care [*methods]; Randomized Controlled Trials as Topic

MeSH check words

Humans