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Stewart L, Advanced Ovarian Cancer Trialists Group

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[Intervention Review]

Chemotherapy for advanced ovarian cancer

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ABSTRACT

Background

Ovarian carcinoma is the seventh commonest female cancer worldwide and is responsible for the greatest number of deaths from gynaecological malignancy in Europe and North America. Although many studies have explored the use of chemotherapy in this disease, most individual trials have been too small to show clear benefit of any one type of chemotherapy.

Objectives

The type and intensity of chemotherapy used routinely for women with advanced ovarian cancer has varied because of uncertainty about the effectiveness of the different regimens. The objective of this review was to compare single drugs versus combinations of drugs, platinum versus non-platinum, and carboplatin versus cisplatin-based chemotherapy in women with advanced ovarian cancer.

Search methods

We searched MEDLINE, and CancerLit bibliographic databases and the National Cancer Institute and the UK Co-ordinating Committee on Cancer Research registers of trials. We also handsearched the proceedings of meetings and contacted experts in the field and drug companies.

Selection criteria

Randomised trials of:

(1) single non-platinum versus non-platinum combination chemotherapy

(2) single non-platinum versus platinum combination chemotherapy

(3) non-platinum regimen versus the same regimen plus cisplatin

(4) single platinum versus platinum combination chemotherapy

(5) cisplatin versus carboplatin-based chemotherapy

in women with advanced ovarian cancer.

Data collection and analysis

Individual patient data were obtained from the trial investigators, checked by the reviewers and verified by the trial investigator.

Main results

Forty-nine trials involving 8763 women were included. The data were combined to calculate hazard ratios (HR) for survival on an intention-to-treat basis. For single non-platinum versus platinum combination chemotherapy the overall HR for survival was 0.93, 95% confidence interval (CI) 0.83 to1.05 favouring platinum-based combination chemotherapy. For non-platinum regimens compared with the same regimen plus cisplatin the survival HR was 0.88, 95% CI 0.79 to 0.98 in favour of adding platinum to drug regimens. Single platinum compared with platinum combination gave a HR of 0.91, 95% CI 0.79 to 1.05 favouring combination chemotherapy. Cisplatin versus carboplatin gave a HR of 1.02, 95% CI 0.93 to 1.12. Sub-group analyses for age, stage, grade, histology, resection, bulk of residual tumour and performance status were undertaken for cisplatin versus carboplatin only. No difference in effect was found.

Authors' conclusions

Available evidence, although not conclusive, suggests platinum-based chemotherapy is better than non-platinum therapy. There is some evidence that combination therapy improves survival compared with platinum alone. No difference in effect has been shown between cisplatin and carboplatin.

PLAIN LANGUAGE SUMMARY

Platinum-based chemotherapy shows small benefit over non-platinum for advanced ovarian cancer. Paclitaxel trials were not reviewed

Ovarian cancer is the seventh commonest female cancer worldwide. Single-drug or combination chemotherapy is used routinely to treat it. This review found a small benefit in platinum-based chemotherapy over non-platinum therapy. It also found that platinum combinations may offer improved survival over single platinum and that cisplatin and carboplatin are equally effective. The trials were done when paclitaxel (an effective new drug) was not used routinely. The results therefore, will need to be looked at in the light of new evidence from paclitaxel trials.

BACKGROUND

Ovarian carcinoma is the seventh most common cancer of women in the world. Some 140,000 new cases are diagnosed every year and the disease is responsible for the greatest number of deaths from gynaecological malignancy in Europe and North America (Parkin et al 1980).

Although many studies have explored the use of chemotherapy in this disease, most individual trials have been too small to show clear benefit of one type of chemotherapy over another. Nevertheless, many of these trials have had an important influence on clinical practice, and consequently the type and intensity of chemotherapy used routinely for patients with advanced disease have fluctuated greatly over time.

In 1989 the British Medical Research Council (MRC) Gynaecological Cancer Working Party initiated an individual patient data meta-analysis to combine the results from all available randomised trials examining the role of platinum and of combination chemotherapy in the treatment of advanced ovarian cancer. At the outset the MRC secretariat contacted the investigators responsible for each trial, inviting their collaboration. In so doing it established the Advanced Ovarian Cancer Trialists Group (AOCTG), under whose auspices the meta-analysis was conducted. The first cycle of analyses was published in the British Medical Journal in 1991 (AOCTG 1991).

The AOCTG recognised the importance of updating these results especially for the comparison of carboplatin and cisplatin, where the initial data were relatively immature. The comparison of platinum analogues was considered of such clinical importance that further new investigations were initiated to identify whether any particular type of women or tumour would benefit more from either cisplatin or carboplatin-based chemotherapy. These analyses were completed in 1996 and were published in the British Journal of Cancer in 1998 (AOCTG 1998).

OBJECTIVES

To compare, in terms of overall survival

(1) Single non-platinum versus non-platinum combination chemotherapy

(2) Single non-platinum versus platinum combination chemotherapy

(3) Non-platinum regimen versus the same regimen plus cisplatin

(4) Single platinum versus platinum combination chemotherapy

(5) Cisplatin versus carboplatin

For cisplatin versus carboplatin trials, to investigate whether any particular type of women or tumour would benefit more from either cisplatin or carboplatin-based chemotherapy

METHODS

Criteria for considering studies for this review

Types of studies

Trials (published and unpublished) were eligible for inclusion provided they examined first-line treatment for advanced ovarian cancer and made one of the treatment comparisons described under objectives. Each had to have been properly randomised such that the treatment to be assigned was not known in advance. Trials that allocated treatment by quasi-random methods, for example, by date of birth were not included.

Types of participants

Women with advanced ovarian cancer. Individual data from all randomised patients were included in the meta-analysis. Where possible data were obtained for individuals who had been excluded from the original trial analyses. These women were included in the meta-analysis.

Types of interventions

Chemotherapy as categorised
(1) Single non-platinum versus non-platinum combination chemotherapy
(2) Single non-platinum versus platinum combination chemotherapy
(3) Non-platinum regimen versus the same regimen plus cisplatin
(4) Single platinum versus platinum combination chemotherapy
(5) Cisplatin versus carboplatin

Types of outcome measures

Survival

Search methods for identification of studies

Trials were identified by bibliographic searches using MEDLINE and CancerLit. This was supplemented by searching the trial registers produced by the National Cancer Institute (Physicians Data Query) and the United Kingdom Co-ordinating Committee on Cancer Research. Trials were also identified by hand searching relevant meeting proceedings, by writing to experts in the field and pharmaceutical companies and by discussion within the AOCTG. Initial bibliographic searches were done using a simple search strategy (AOCTG 1991), but for the update (AOCTG 1998) a modified version of the Cochrane optimal search strategy was used.

Data collection and analysis

This review is based on individual patient data obtained directly from the responsible trialist or data centre. The methods used were prespecified in a protocol.
Data were sought for all patients randomised in all eligible randomised trials (published or unpublished) and updated follow-up was requested. For all comparisons the following data were collected: patient identifier, treatment allocated, date of randomisation, survival status, date of last follow-up or death and whether the individual was excluded from the original analyses. For trials comparing cisplatin with carboplatin further data on age, stage, grade, histology, extent of operation, residual tumour bulk and performance status were collected at the second cycle of analyes
All data were checked thoroughly and the final database entries for each trial were verified by the responsible trialist or data centre.
All analyses were based on intention to treat. Survival analyses were stratified by trial, and the log rank expected number of deaths and variance used to calculate individual and pooled hazard ratios (HRs) using the fixed effect model (Yusuf et al 1985). HRs (representing the overall chance of dying on treatment as compared to control) were also calculated for pre-specified subgroups of patients using similar stratified methodology. Chi-squared tests were used to test for gross statistical heterogeneity over all trials in a comparison and between subsets of trials using the test for interaction or trend as appropriate. These tests are aimed primarily at detecting differences in effect size rather than direction and were chosen because qualitative differences were not anticipated. Survival curves were drawn as simple (non-stratified) Kaplan-Meier curves. These are not currently reproducable in the Cochrane Library but can be found in the meta-analysis publications (AOCTG 1991; AOCTG 1998). Improvements or detriments to absolute survival were calculated by applying the HR to baseline survival (Freedman 1982); proportional hazards are assumed. Baseline survivals of 45% at two years and 25% at five years were used based on the survival curves for the carboplatin/cisplatin comparison. All p-values quoted are two-sided and unless otherwise specified chi-square values are on one degree of freedom.

RESULTS

Description of studies

At the first cycle of analysis (AOCTG 1991) 53 eligible randomised trials were identified. Two additional potentially eligible studies were excluded on the grounds that they were judged not to be appropriately randomised. At the second cycle of analysis four new trials were identified. In total, information was available from 49 eligible trials (8763 patients) and unavailable from eight eligible trials (502 patients). Thus data were available from 95% of all individuals randomised in known randomised trials.

In the first cycle of analyses, five treatment comparisons were made. However, the comparison of single-agent versus combination non-platinum drugs was not updated as it was likely to yield minimal additional data and was primarily of historical interest. For the remaining four comparisons, data were available for all but three trials (256 women) and most were able to provide updated survival information.

Risk of bias in included studies

Only trials with adequate methods of randomisation (those which did not allow prior knowledge of treatment assignment) were included. All data received were checked thoroughly to ensure both the accuracy of the meta-analysis database and the quality of randomisation and follow up in the trial. Any queries were resolved in discussion with and the final database entries verified by the responsible trial investigator or statistician.

Effects of interventions

(1) Single non-platinum versus non-platinum combination chemotherapy

Data were available from 16 trials, comparing 1379 women randomised to receive a single non-platinum agent and 1767 to receive non-platinum combinations. The reason for the imbalance in numbers is that some trials used two or more combination arms. A total of 2817 deaths were observed. Data were not available from six trials which included a total of 403 patients. With the exception of a single trial [SCOCG1] which indicated a significant improvement in survival with combination chemotherapy, all the trials had wide confidence intervals and were inconclusive. The overall results were inconclusive, providing no clear evidence that for non-platinum based therapies, a single drug or combination of drugs provides greater overall survival (HR = 0.98, 95% CI 0.91-1.05, p = 0.42).

There was no gross statistical heterogeneity between trials chi-square(18) = 20.46, p = 0.31).

(2) Single non-platinum versus platinum combination chemotherapy

Data were included from a total of 11 trials including 1329 women and 1169 deaths. Data were not available for two trials which included a total of 99 patients. One trial (b/c OCSG 77-61-02) of 42 patients showed a conventionally significant benefit for combination chemotherapy, the remainder had wide confidence intervals and were inconclusive. The overall results are inconclusive (p = 0.23) but favour combination chemotherapy with an HR of 0.93 (95% CI 0.83-1.05), representing a 7% reduction in the overall risk of death. This translates to a suggested 3% benefit in absolute survival at both two and five years, improving survival from 45% to 48% and from 25% to 28% respectively (95% CI, 7% benefit to 2% detriment).

There was no gross statistical heterogeneity between trials (chi-square(10) = 16.42, p = 0.09). Excluding the small trial with the positive result (b/c OCSG 77-61-02) gives an overall HR of 0.96 (p = 0.51).

(3) Non-platinum regimen versus the same regimen plus cisplatin

Data were available from all nine eligible trials, that compared a non-platinum drug regimen with the same regimen plus cisplatin . A total of 1704 patients and 1428 deaths were included. The overall HR of 0.88 (95%CI 0.79 - 0.98) favours the addition of platinum and is marginally significant (p = 0.02). The suggested 12% reduction in the risk of death translates to a 5% improvement in survival at both two (45-50%) and five (25-30%) years (95% CI 1 to 8% benefit). Although the best evidence of a benefit is shown in the trials with a combination control arm (HR = 0.85), there is no clear evidence that the results between the two subsets of trials differ (Interaction chi-square = 0.64, p = 0.42).

There is no gross statistical heterogeneity between those trials with a combination control arm (p = 0.43) but, for those with single-agent control arms there is evidence of statistical heterogeneity (p = 0.02). Excluding the small positive trial (b/c OCSG 77-61-02) reduces the heterogeneity within this subset of trials (chi-square(3) = 2.18, p = 0.54) and does not alter the main results materially, with an overall HR of 0.90 (p = 0.05).

(4) Single platinum versus platinum combination chemotherapy

Data were available from all nine eligible trials and a total of 1095 patients and 894 deaths were included. One trial [GICOG 1992] showed a conventionally significant result at the 5% level, the remainder were inconclusive. Overall the results favour the use of combination chemotherapy with a HR of 0.91 (95%CI = 0.79-1.05) suggesting a 9% reduction in the overall risk of death, although this is inconclusive (p=0.21). This is equivalent to a 3% benefit in survival at both two (45-48%) and five years (25-28%) (95% CI, 8% benefit to 2% detriment).

There is no evidence of gross statistical heterogeneity between trials (chi-square(8) = 10.35, p = 0.24).There is perhaps some visual suggestion of a qualitative interaction, that cisplatin-based trials favour combination chemotherapy (HR = 0.86, p = 0.07) whereas carboplatin-based trials favour single drug therapy (HR = 1.05, p = 0.21). However, the carboplatin result is based on a relatively small number of events and confidence intervals are wide such

that there is no clear evidence of a difference in effect between the results for these groups of trials (Interaction chi-square = 1.76, p = 0.18)

If the Royal Marsden trial [Royal Marsden 1986] is excluded from the analysis, because it compared a high dose cisplatin on its own with low dose cisplatin plus chlorambucil, the overall HR is 0.88 (p = 0.08) and the HR for cisplatin-based trials is 0.80 (p = 0.02).

(5) Cisplatin versus carboplatin

Data were available from all 12 eligible trials which compared cisplatin and carboplatin either as single agents or each in combination with the same drugs in multi-drug regimens. In total this includes 2219 patients and 1745 deaths. Data from one further trial (Belpomme 1992) including 157 women were unavailable. The results of individual trials are very consistent and there is no evidence of statistical heterogeneity. There is no good evidence of any difference between cisplatin and carboplatin when given either as a single drug (HR = 1.01, p = 0.92) or in combination (HR = 1.02, p = 0.74) (Interaction chi-square = 0.003, p=0.96). The overall HR of 1.02 (p = 0.74) suggests a 2% benefit of cisplatin, but the confidence intervals are such that it could be consistent with modest benefits of either drug. In terms of absolute survival at both two and five years, the 95% confidence interval is consistent with improvements in overall survival of 3% benefit for cisplatin and 4% benefit for carboplatin.

Survival curves for the above comparisons are presented in the meta-analysis publications (AOCTG 1991; AOCTG 1998)

Treatment effects in different sub-groups

Different patient subgroups were analysed using data provided for 11 of the trials included in the carboplatin/cisplatin comparison (all except one trial [Japan] for which this information was not available.) There is no good evidence that any group of women specified by age (interaction chi-square = 0.18, p = 0.67), stage (trend chi-square = 0.64, p = 0.42), performance status (interaction chi-square = 0.68, p = 0.41), residual tumour bulk (interaction chi-square = 0.68, p = 0.41), extent of operation (trend chi-square = 0.04, p = 0.84), histology (interaction chi-square(6) = 11.56, p = 0.07) or grade (interaction chi-square = 2.30, p = 0.13) do any better or worse when treated with either cisplatin or carboplatin. There is perhaps some suggestion that stage II tumours may benefit more from cisplatin. However, very few stage II tumours were included, the confidence intervals are wide and it is difficult to draw any conclusions from the result

DISCUSSION

The results for the comparison of single non-platinum drugs versus platinum-based combinations, which is undoubtedly the most clinically heterogeneous comparison, tend to favour platinum combination chemotherapy. However, the confidence limits are such that the results remain inconclusive. For the comparison of the addition of platinum to otherwise similar drug regimens, the results are marginally significant (at conventional levels) in favour of platinum. An absolute benefit of around 5%, at two and five years is suggested. Given that there are now few patients at risk for whom additional follow up will be possible in either of these comparisons, it is unlikely that these results will change over time unless further large trials emerge. Thus these results will probably remain the best and least biased estimates of the benefits of platinum-based therapy over non-platinum regimens (which were mostly based on alkylating agents). When interpreting these results, however, it should be appreciated that many women in these trials are likely to have received platinum on relapse from which they may have derived a late benefit, and that drugs were sometimes administered at doses and schedules that would not be considered adequate today. Thus, in effect these comparisons are likely to be comparing a policy of immediate versus delayed platinum-based therapy. The results therefore suggest that the policy of giving immediate platinum-based treatment results in better overall survival than delaying such treatment until relapse.

The results for the comparison of single-agent platinum with platinum in combination are inconclusive, but for the cisplatin-based trials there is a strong trend in favour of combination chemotherapy. These results are driven largely by the GICOG multi-centre Italian trial [GICOG 1992] which contributes 50% of the total information. In most of these studies the dose of platinum used as a single-agent was lower than is currently standard and the observed difference could be attributable to the higher total drug dose in the muliple drugarms rather than combination chemotherapy per se. For these trials there are reasonable numbers of patients for whom further follow up is possible. It may therefore be important to update this analysis in future and to incorporate data from currently ongoing trials. If, as these results suggest, there may be a modest advantage of combination chemotherapy, then it is important to have a good estimate of effect with tight confidence intervals as the trade-offs involved and the subsequent choice between the two types of treatment is not necessarily straightforward. In such circumstances precise estimates of any survival differences are essential.

The comparison of cisplatin and carboplatin show no obvious advantage of one compound over the other in terms of survival. These results appear very consistent across trials. Data were not available for one trial (Belpomme 1992) whose preliminary results showed a significant prolongation of median survival for cisplatin. As far as is known this trial, which prohibited the crossover to cisplatin, has never been published in full. As in other comparisons, this meta-analysis compares treatment policy, in this case the policy of immediate cisplatin versus immediate carboplatin. The individual patient data collected for this meta-analysis shows that crossover rates during the treatment period were not excessive and are comparable on each treatment arm. With the exception of two trials (e Royal Marsden 1981 , e Mayo Clinic 846151), comprising 10.6% of the total patients, such crossover rates were

less than 10%. However, it remains likely that patients may have been treated with the alternative platinum analogue on relapse if this happened outside the period of primary treatment. Thus the comparison could in fact be one of immediate versus delayed treatment with the two platinum compounds. It will be important to update this analysis in future, looking at long-term survival, especially since the results are somewhat inconsistent with those found in testicular cancer, where cisplatin has been shown to be superior to carboplatin (Bajorin et al 1993 Horwich et al 1994). However, the consistency of the results in the sub-group analyses lends support to the interpretation that neither drug is superior in terms of improving overall survival in advanced ovarian cancer. There was no good evidence that cisplatin was more or less effective in any particular pre-defined subgroup of patients and therefore no good grounds for selecting women on the basis of age, performance status, extent of operation, tumour stage, residual bulk, grade or histology to receive one or other treatment. The somewhat extreme HR in favour of cisplatin in stage II tumours is based on very small numbers of patients. Owing to this, and the increased possibility of false positive results owing to multiplicity of subgroup analysis, this result should certainly not be regarded as anything more than hypothesis generating. It should be noted that trials included in the meta-analysis do not include recent and ongoing randomised trials using taxanes as a component of combination chemotherapy. Future updates will aim to include data from these trials.

AUTHORS' CONCLUSIONS

Implications for practice

Just as no clinical trial can provide prescriptions of how to treat individual cases, neither can a meta-analysis. Although not conclusive the results suggest that platinum based chemotherapy is better than non-platinum therapy, that platinum combinations may offer improved survival over single-agent platinum and that cisplatin and carboplatin are equally effective. However patients are not uniform in their preferences and the trade-offs between choosing more and less intensive therapy are not always straightforward. Ultimately the treatment chosen is to be decided by the patient and clinician and will depend on many factors including toxicity and quality of life in addition to survival estimates. However the results of this meta-analysis provide the current most reliable estimates of the relative survival benefits of the treatments studied to be used as part of this decision making process.

Implications for research

Currently much research effort is focussed on paclitaxel, but it is still not clear what should be used as the appropriate 'control' arm in these trials. These results sugest that this should be either platinum as a single-agent or in combination. If the latter, this should probably be the CAP regimen which a separate meta-analysis has shown to be superior to CP (OCMP 1991). However, in that meta-analysis, the doses of cisplatin and cyclophosphamide were similar in the two treatment arms and the observed difference could therefore have been attributable to either the addition of doxorubicin or to higher total doses of drug on the CAP arm. The full results of ICON2 (Torri 1996), comparing CAP with single-agent carboplatin, are awaited with interest. When these results are available, taken together with the results presented here, the best 'standard' therapy may be identified which can be used as the baseline against which to measure current and future drug development.

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f <=50 years ***{published data only}***

f > 50 years ***{published data only}***

g FIGO II ***{published data only}***

g FIGO III ***{published data only}***

g FIGO IV ***{published data only}***

h Borderline/well ***{published data only}***

h Moderate/poor ***{published data only}***

i Good ***{published data only}***

i Poor ***{published data only}***

j Low ***{published data only}***

j High ***{published data only}***

k Complete ***{published data only}***

k Incomplete ***{published data only}***

k None ***{published data only}***

l Clear cell ***{published data only}***

l Endemetroid ***{published data only}***

l Mixed ***{published data only}***

l Mucinous ***{published data only}***

l Other ***{published data only}***

l serous ***{published data only}***

l Undifferentiated ***{published data only}***

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

a Copenhagan

Methods	RCT Allocation by sealed envelope
Participants	179 participants Stage IIB, III, IV ovarian adenocarcinoma
Interventions	- cyclophosphamide - busulphan vs - cyclophosphamide + doxorubicin + fluouracil
Outcomes	survival
Notes	3 arm trial, single drug arms 1 and 2 combined as control group

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

a ECOG E1172

Methods	RCT
Participants	409 participants Stage III, IV or recurrent stage I, II adenocarcinoma
Interventions	- melphalan vs - cyclophosphamide + fluouracil + methotrexate
Outcomes	survival
Notes	Includes data on 35 women excluded from the original analyses Data on 1 patient "cancelled" after randomisation with no treatment or followup were not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

a ECOG E2875

Methods	RCT
Participants	331 participants Stage III, IV or recurrent epithelial ovarian cancer
Interventions	- melphalan vs - methotrexate + thiotepa - doxorubicin + cyclophosphamide + fluouracil - doxorubicin + cyclophosphamide + fluouracil + methotrexate+ thiotepa
Outcomes	survival
Notes	4 arm trial, 3 combination chemotherapy arms 2,3 and 4 combined as experimental group Includes data on 13 women excluded from the original analyses Data on 15 women randomised, but then "cancelled" with no follow up or from excluded institution were not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

a GOG22

Methods	RCT
Participants	339 participants Stage III, IV suboptimal epithelial ovarian cancer
Interventions	- melphalan vs - melphalan + hexamethylmelamine + doxorubicin + cyclophosphamide
Outcomes	survival
Notes	3 arm trial, combination chemotherapy arms 2 and 3 combined as treatment group

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

a GOG3

Methods	RCT Allocation by sealed envelope
Participants	418 participants Stage IV primary ovarian cancer or recurrent stage III, IV
Interventions	- melphalan vs - melphalan + fluouracil - melphalan + fluouracil + actinomycin-D - fluouracil + actinomycin-D + cyclophosphamide
Outcomes	survival
Notes	4 arm trial, combination arms 2,3 and 4 combined as treatment group. Arms suspended and reactivated at various points therefore trial split into 3 epochs of randomisation, analysed separately for each epoch and then combined in stratified analysis to give results for whole trial

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

a Mayo Clinic 703015

Methods	RCT
Participants	69 participants Stage IIIB, IV epithelial ovarian cancer
Interventions	- cyclophosphamide vs - cyclophosphamide + doxorubicin
Outcomes	survival
Notes	Includes data on 3 women excluded from the original analyses

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

a MD Anderson 1974a

Methods	RCT
Participants	75 participants Stage III, IV epithelial ovarian cancer
Interventions	- melphalan vs - cyclophosphamide + hexamethylmelamine + doxorubicin + hexamethylmelamine
Outcomes	survival
Notes	2 trials reported in same paper 4 arm trial of which 3 are relevant. combination chemotherapy arms 2 and 3 are combined as treatment group

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

a MD Anderson 1974b

Methods	RCT
Participants	128 participants Stage III, IV epithelial ovarian cancer
Interventions	- melphalan - hexamethylmelmine - doxorubicin vs - cyclophosphamide + hexamethylmelamine
Outcomes	survival
Notes	2 trials reported in same paper 4 arm trial, single drug arms 1,2 and 3 combined as control group Includes data on 30 women excluded from the original analyses

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

a Milan

Methods	RCT
Participants	74 participants Stage III, IV epithelial ovarian cancer
Interventions	- cyclophosphamide vs - cyclophospamide + doxorubicin
Outcomes	survival
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

a MRC 1976

Methods	RCT
Participants	344 participants Epithelial ovarian cancer not completely excised because of extension to upper abdomen or beyond
Interventions	- cyclophosphamide vs - hexamethylmelamine + methotrexate
Outcomes	survival
Notes	Includes data from 49 patients who were randomised after publication of trial report and on 38 patients who were excluded from the original analyses

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

a NCICCTC OV1

Methods	RCT
Participants	254 participants Stage III, IV epithelial ovarian cancer
Interventions	- melphalan vs - melphalan + fluorouracil + methotrexate
Outcomes	survival
Notes	Includes data on 14 women excluded from the original analyses

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

a NCOG5091

Methods	RCT
Participants	48 participants Stage III, IV epithelial ovarian cancer
Interventions	- melphalan vs - doxorubicin + cyclophosphamide
Outcomes	survival
Notes	Published as abstract only Includes data on 3 women excluded from the original analyses

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

a SCOCG 1979

Methods	RCT
Participants	168 participants Suboptimal stage III and stage IV epithelial ovarian cancer
Interventions	- melphalan vs - melphalan + doxorubicin
Outcomes	survival
Notes	Includes data on 6 women excluded from the original analyses

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

a Zagreb

Methods	RCT
Participants	69 participants Stage III, IV epithelial ovarian cancer
Interventions	- cyclophosphamide vs - doxorubicin + cyclophosphamide + fluorouracil + methotrexate
Outcomes	survival
Notes	Includes data on 13 women excluded from the original analyses

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

a/b Princess Margare

Methods	RCT
Participants	124 participants Stage III, IV epithelial ovarian cancer

a/b Princess Margare (*Continued*)

Interventions	- melphalan vs - cyclophosphamide + fluouracil + hexamethylmelamine+ methotrexate vs - cyclophosphamide + doxorubicin + cisplatin
Outcomes	survival
Notes	Published as abstract only 3 arm trial, arms 1 and 2 are relevant to comparison of single vs combination non-platinum ; arms 1 and 3 to single non-platinum vs platinum combination Includes 3 patients excluded from original analyses

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

a/b/c MRC 1981

Methods	RCT
Participants	149 participants Stage III, IV epithelial ovarian cancer
Interventions	- cyclophosphamide vs - doxorubicin + cyclophosphamide vs - cyclophosphamide + cisplatin
Outcomes	survival
Notes	Unpublished Trial had 3 arms and 2 randomisation options. Arms 1 and 2 are relevant to comparison of single vs combination non platinum. Arms 1 and 3 are relevant to comparison of single non platinum vs platinum combinations and addition of platinum to a regimen. Option A randomised between 2 non platinum arms. Option B randomised between all 3 arms. Only patients randomised under option B to above treatments are included in the latter 2 comparisons. For the first comparison randomisation options A and B are analysed seperately and results combined in stratified analysis to give results for entire trial. Includes 15 women excluded from the original analyses

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

a/b/c MRC 1981 (*Continued*)

Allocation concealment?	Low risk	A - Adequate

b COSA 1978

Methods	RCT
Participants	38 participants Stage III, IV epithelial ovarian cancer
Interventions	- cyclophosphamide vs - chlorambucil + cisplatin [cisplatin 50mg/m2/cycle]
Outcomes	survival
Notes	Includes 5 women excluded from original analyses

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

b ECOG EST2878

Methods	RCT
Participants	250 participants Stage III, IV epithelial ovarian cancer
Interventions	- melphalan vs - cyclophosphamide + doxorubicin + hexamethylmelamine + cisplatin [cisplatin 50mg/m2/cycle]
Outcomes	survival
Notes	Published as abstract Includes 5 women excluded from original analyses No data available from 3 women "cancelled" with no treatment or follow up

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

b ECOG EST2878 (*Continued*)

Allocation concealment?	Low risk	A - Adequate

b Edinburgh

Methods	RCT
Participants	80 participants Stage III, IV epithelial ovarian cancer
Interventions	- predinamustine vs - predinamustine + hexamethylmelamine + fluorouracil, + cisplatin [cisplatin 60mg/m2/cycle]
Outcomes	survival
Notes	Includes 4 women excluded from original analyses

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

b MOCCSG 1980

Methods	RCT
Participants	109 participants Stage IIB -I IV epithelial ovarian cancer
Interventions	- cyclophosphamide vs - cyclophosphamide + bleomycin + cisplatin cisplatin 100mg/m2/cycle]
Outcomes	survival
Notes	Unpublished

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

b Southampton

Methods	RCT
Participants	89 participants Stage III, IV epithelial ovarian cancer
Interventions	- chlorambucil vs - cyclophosphamide + doxorubicin + cisplatin [cisplatin 80mg/m2/cycle]
Outcomes	survival
Notes	Includes 1 woman excluded from original analyses

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

b/c COSA 1979

Methods	RCT
Participants	370 participants Stage III, IV epithelial ovarian cancer
Interventions	- chlorambucil vs - chlorambucil + cisplatin [cisplatin 50mg/m2/cycle]
Outcomes	survival
Notes	Includes 1 woman excluded from original analyses Combination chemotherapy was given sequentially

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

b/c Leo Laboratories

Methods	RCT
Participants	157 participants Stage IC - IV epithelial ovarian cancer
Interventions	- treosulphan vs - treosulphan + cisplatin [cisplatin 50mg/m2/cycle]
Outcomes	survival
Notes	Includes data on 22 women excluded from original analyses of which 16 had < 3 cycles of treatment judged inadequate No data availablefrom 25 women randomised with no registration forms received and not followed up

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

b/c Loma Linda

Methods	RCT Allocation by sealed envelope
Participants	11 participants Stage III, IV epithelial ovarian cancer
Interventions	- cyclophosphamide vs - cyclophosphamide + cisplatin [cisplatin 40mg/m2/cycle]
Outcomes	survival
Notes	Second randomisation to BCG vs No BCG BCG patients were not included Includes1 patient excluded from original analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

b/c OCSG 77-61-02

Methods	RCT
Participants	42 participants Stage III, IV epithelial ovarian cancer
Interventions	- cyclophosphamide vs - cyclophosphamide + cisplatin [cisplatin 50mg/m2/cycle]
Outcomes	survival
Notes	Stopped early on basis of benefit to combination chemotherapy

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

c EORTC 55731

Methods	RCT
Participants	149 participants Stage III, IV epithelial ovarian cancer
Interventions	- doxorubicin + cyclophosphamide vs - doxorubicin + cyclophosphamide + cisplatin [cisplatin 50mg/m2/cycle]
Outcomes	survival
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

c GOG 47

Methods	
Participants	495 participants sub-optimal stage III, stage IV, other recurrent cases
Interventions	- doxorubicin + cyclophosphamide vs - doxorubicin + cyclophosphamide + cisplatin [cisplatin 50mg/m2/cycle]
Outcomes	survival
Notes	Includes 74 women excluded from original analyses

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

c NCOG 5091

Methods	
Participants	84 participants Stage III, IV epithelial ovarian cancer
Interventions	- doxorubicin + cyclophosphamide vs - doxorubicin + cyclophosphamide + cisplatin [cisplatin 50mg/m2/cycle]
Outcomes	survival
Notes	Unpublished Includes 9 women excluded from original analyses

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

c SCOCSG 1981

Methods	RCT
Participants	296 participants
Interventions	- doxorubicin + melphalan vs - doxorubicin + melphalan + cisplatin [cisplatin 50mg/m2/cycle]
Outcomes	survival
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

d GICOG 1980

Methods	RCT
Participants	562 participants Stage III, IV epithelial ovarian cancer
Interventions	- cisplatin vs - cisplatin + cyclophosphamide - cisplatin + cyclophosphamide + doxorubicin [cisplatin single 50mg/m2/cycle; combination 50mg/m2/cycle]
Outcomes	survival
Notes	Includes 18 women excluded from original analyses Three arm trial, both combination chemotherapy arms are combined as the treatment group

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

d HECOG 1987

Methods	RCT
Participants	130 participants Stage III, IV epithelial ovarian cancer
Interventions	- carboplatin vs - carboplatin + doxorubicin + cyclophospamide [carboplatin: single 400mg/m2/cycle combination 300mg/m2/cycle]
Outcomes	survival
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

d Milan

Methods	RCT
Participants	44 participants Stage III, IV epithelial ovarian cancer
Interventions	- cisplatin vs - cisplatin + doxorubicin + cyclophosphamide [cisplatin: single 60mg/m2/cycle combination 50mg/m2/cycle]
Outcomes	survival
Notes	Includes 8 women excluded from the original analyses

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

d Mount Sinai

Methods	RCT
Participants	36 participants Stage III, IV epithelial ovarian cancer
Interventions	- cisplatin vs - cisplatin + doxorubicin [cisplatin: single 50mg/m2/cycle combination 50mg/m2/cycle]
Outcomes	survival
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

d Piraeus

Methods	RCT
Participants	40 participants Stage Ic - IV epithelial ovarian cancer
Interventions	- carboplatin vs - carboplatin + bleomycin + ifosfamide [carboplatin: single 400mg/m2/cycle combination 350mg/m2/cycle]
Outcomes	survival
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

d Royal Marsden 1979

Methods	RCT
Participants	87 participants Stage III, IV epithelial ovarian cancer
Interventions	- cisplatin vs - cisplatin + chlorambucil [cisplatin: single 50mg/m2/cycle combination 20mg/m2/cycle]
Outcomes	survival
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

d SGCTG 1986

Methods	RCT
Participants	161 participants
Interventions	- carboplatin vs - carboplatin + chlorambucil [carboplatin: single 400mg/m2/cycle combination 300mg/m2/cycle]
Outcomes	survival
Notes	Includes 9 women excluded from the original analyses

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

d UK South West a

Methods	RCT
Participants	30 participants Stage II - IV epithelial ovarian cancer
Interventions	- cisplatin vs - cisplatin + ifosfamide [cisplatin: single 60mg/m2/cycle combination 60mg/m2/cycle]
Outcomes	survival
Notes	Unpublished This trial had 2 independent randomisations for cisplatin and carboplatin and therefore has been treated as 2 separate trials a & b

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

d UK South West b

Methods	RCT
Participants	5 participants Stage II - IV epithelial ovarian cancer
Interventions	- carboplatin vs - carboplatin + ifosfamide
Outcomes	survival
Notes	Unpublished This trial had 2 independent randomisations for cisplatin and carboplatin and therefore has been treated as 2 separate trials a & b

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

e Athens

Methods	RCT
Participants	149 participants Stage III, IV epithelial ovarian cancer
Interventions	- cisplatin + epirubicin + cyclophosphamide vs - carboplatin + epirubicin + cyclophosphamide [cisplatin 100mg/m2/cycle carboplatin 300mg/m2/cycle]
Outcomes	survival
Notes	Published as abstract only

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

e EORTC 55836

Methods	RCT
Participants	339 participants Stage IIB - IV epithelial ovarian cancer
Interventions	- cisplatin + doxorubicin + cyclophosphamide + hexamethylmelamine vs - carboplatin + doxorubicin + cyclophosphamide + hexamethylmelamine [cisplatin 100mg/m2/cycle carboplatin 350mg/m2/cycle]
Outcomes	survival
Notes	Includes data on 20 women who were excluded from the original analyses

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

e GICOG 1984

Methods	RCT
Participants	173 participants Stage III, IV epithelial ovarian cancer
Interventions	- cisplatin vs - carboplatin [cisplatin 100mg/m2/cycle carboplatin 400mg/m2/cycle]
Outcomes	survival
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

e GOCA

Methods	RCT
Participants	173 participants Stage III, IV epithelial ovarian cancer
Interventions	- cisplatin + cyclophosphamide vs - carboplatin + cyclophosphamide [cisplatin 80mg/m2/cycle carboplatin 350mg/m2/cycle]
Outcomes	survival
Notes	Includes data on 12 women who were excluded from the original analyses

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

e GONO

Methods	RCT	
Participants	165 participants Stage III, IV epithelial ovarian cancer	
Interventions	- cisplatin + doxorubicin + cyclophosphamide vs - carboplatin + doxorubicin + cyclophosphamide [cisplatin 50mg/m2/cycle carboplatin 200mg/m2/cycle]	
Outcomes	survival	
Notes	Includes data on 1woman who was excluded from the original analyses	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

e Japan

Methods	RCT	
Participants	52 participants Stage II - IV epithelial ovarian cancer	
Interventions	- cisplatin + cyclophosphamide + doxorubicin vs - carboplatin + cyclophosphamide + doxorubicin [cisplatin 50mg/m2/cycle carboplatin 250mg/m2/cycle]	
Outcomes	survival	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

e Mayo Clinic 846151

Methods	RCT
Participants	104 participants Stage III, IV epthelial ovarian cancer
Interventions	- cisplatin + cyclophosphamide vs - carboplatin + cyclophosphamide [cisplatin 100mg/m2/cycle carboplatin 350mg/m2/cycle]
Outcomes	survival
Notes	Includes data on 1 woman who was excluded from the original analyses

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

e MOCCSG 1984

Methods	RCT
Participants	56 participants Residual stage IIB/C, stage III, IV epithelial ovarian cancer
Interventions	- cisplatin + cyclophosphamide vs - carboplatin + cyclophosphamide [cisplatin 100mg/m2/cycle carboplatin 300mg/m2/cycle]
Outcomes	survival
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

e NCIC CTC 0v.8

Methods	RCT
Participants	447 participants Ovarian cancer patients with macroscopic residual disease (mostly stage III)
Interventions	- cisplatin + cyclophosphamide vs - carboplatin + cyclophosphamide [cisplatin 75mg/m2/cycle carboplatin 300mg/m2/cycle]
Outcomes	survival
Notes	Includes data on 28 women who were excluded from the original analyses

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

e Royal Marsden 1981

Methods	RCT
Participants	131 participants Stage III, IV epithelial ovarian cancer
Interventions	- cisplatin vs - carboplatin [cisplatin 100mg/m2/cycle carboplatin 400mg/m2/cycle]
Outcomes	survival
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

e SWOG 8412

Methods	RCT
Participants	342 participants Stage III, IV epithelial ovarian cancer
Interventions	- cisplatin + cyclophosphamide vs - carboplatin + cyclophosphamide [cisplatin 100mg/m2/cycle carboplatin 300mg/m2/cycle]
Outcomes	survival
Notes	Includes data on 51 women who were excluded from the original analyses

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

e Wales

Methods	RCT
Participants	88 participants Stage IIB - IV epithelial ovarian cancer
Interventions	- cisplatin vs - carboplatin [cisplatin 100mg/m2/cycle carboplatin 400mg/m2/cycle]
Outcomes	survival
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

f <=50 years

Methods	Age sub group analysis
Participants	
Interventions	
Outcomes	
Notes	Stratified analysis of data from a number of trials

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

f > 50 years

Methods	Age sub group analysis
Participants	
Interventions	
Outcomes	
Notes	Stratified analysis of data from a number of trials

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

g FIGO II

Methods	Stage sub group analysis
Participants	
Interventions	
Outcomes	
Notes	Stratified analysis of data from a number of trials

Risk of bias

g FIGO II (*Continued*)

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

g FIGO III

Methods	Stage sub group analysis
Participants	
Interventions	
Outcomes	
Notes	Stratified analysis of data from a number of trials

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

g FIGO IV

Methods	Stage sub group analysis
Participants	
Interventions	
Outcomes	
Notes	Stratified analysis of data from a number of trials

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

h Borderline/well

Methods	Grade subgroup analysis	
Participants		
Interventions		
Outcomes		
Notes	Stratified analysis of data from a number of trials	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	D - Not used

h Moderate/poor

Methods	Grade subgroup analysis	
Participants		
Interventions		
Outcomes		
Notes	Stratified analysis of data from a number of trials	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	D - Not used

i Good

Methods	Performance status sub group analysis
Participants	
Interventions	
Outcomes	
Notes	Stratified analysis of data from a number of trials
Risk of bias	

i Good (*Continued*)

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

i Poor

Methods	Performance status sub group analysis
Participants	
Interventions	
Outcomes	
Notes	Stratified analysis of data from a number of trials

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

j Low

Methods	Residual bulk sub group analysis
Participants	
Interventions	
Outcomes	
Notes	Stratified analysis of data from a number of trials

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

j High

Methods	Residual bulk subgroup analysis	
Participants		
Interventions		
Outcomes		
Notes	Stratified analysis of data from a number of trials	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	D - Not used

k Complete

Methods	Extent of resection sub group analysis	
Participants		
Interventions		
Outcomes		
Notes	Stratified analysis of data from a number of trials	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	D - Not used

k Incomplete

Methods	Extent of resection sub group analysis	
Participants		
Interventions		
Outcomes		
Notes	Stratified analysis of data from a number of trials	
Risk of bias		

k Incomplete (*Continued*)

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

k None

Methods	Extent of resection sub group analysis
Participants	
Interventions	
Outcomes	
Notes	Stratified analysis of data from a number of trials

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

l Clear cell

Methods	Histology sub group analysis
Participants	
Interventions	
Outcomes	
Notes	Stratified analysis of data from a number of trials

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

l Endemetroid

Methods	Histology sub group analysis	
Participants		
Interventions		
Outcomes		
Notes	Stratified analysis of data from a number of trials	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	D - Not used

l Mixed

Methods	Histology sub group analysis	
Participants		
Interventions		
Outcomes		
Notes	Stratified analysis of data from a number of trials	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	D - Not used

l Mucinous

Methods	Histology sub group analysis
Participants	
Interventions	
Outcomes	
Notes	Stratified analysis of data from a number of trials
Risk of bias	

l Mucinous (*Continued*)

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

l Other

Methods	Histology sub group analysis
Participants	
Interventions	
Outcomes	
Notes	Stratified analysis of data from a number of trials

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

l serous

Methods	Histology sub group analysis
Participants	
Interventions	
Outcomes	
Notes	Stratified analysis of data from a number of trials

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

l Undifferentiated

Methods	Histology sub group analysis	
Participants		
Interventions		
Outcomes		
Notes	Stratified analysis of data from a number of trials	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	D - Not used

RCT = randomised controlled trial; vs = versus; MRC = British Medical Research Council; ECOG = Eastern Cooperative Oncology Group: EORTC = European Organisation for Research and Treatment of Cancer; GOCA = German Ovarian Cancer Study Group; GICOG = Gruppo Intergionale Cooperativo Ginecologia; GONO = Gruppo Oncologica Nord Ovest; GOG = Gynecologic Oncology Group; COSA = Gynaecological Group Clinical Oncological Society of Australia; HECOG = Hellenic Cooperative Oncology Group; MOCSG = Manchester Ovarian Cancer Study Group; NCICCTG = National Cancer Institute of Canada Clinical Trials Group; NCOG = Norther Californian Oncology Group; SGCTG = Scottish Gynaecological Cancer Trials Group; SWOG = Southwest Oncology Group; SCOCSG = Swedish Cooperative Ovarian Cancer Study Group

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

Study	Reason for exclusion
Adams 1982	Eligible - data no longer available from investigator (lost)
Barlow 1985	Eligible - trialist unable to collaborate in meta-analysis
Belpomme 1992	Eligible - trialist unable to collaborate in meta-analysis
Carmo-Pereira 1981	Eligible - trialist unable to collaborate in meta-analysis
Carmo-Pereira 1983	Eligible - trialist unable to collaborate in meta-analysis
De Palo 1977	Eligible - trialist unable to collaborate in meta-analysis
Delgado 1985	Ineligible - trial did not appear to be properly randomised
Gronroos 1984	Ineligible - trial did not appear to be properly randomised

(*Continued*)

Harvey 1982	Eligible - trialist unable to collaborate in meta-analysis
Senn 1980	Eligible - data destroyed and therefore unavailable
Young 1978	Eligible - trialist unable to collaborate in meta-analysis

DATA AND ANALYSES

Comparison 1. single vs combination non-platinum

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 survival	16	3146	Peto Odds Ratio (95% CI)	0.98 [0.91, 1.06]

Comparison 2. single non-platinum vs platinum combination

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 survival	11	1329	Peto Odds Ratio (95% CI)	0.93 [0.83, 1.05]

Comparison 3. non-platinum vs same regimen + platinum

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 survival	9	1704	Peto Odds Ratio (95% CI)	0.88 [0.79, 0.98]
1.1 Added to single-agent	5	680	Peto Odds Ratio (95% CI)	0.93 [0.78, 1.10]
1.2 Added to combination	4	1024	Peto Odds Ratio (95% CI)	0.85 [0.74, 0.97]

Comparison 4. single platinum vs platinum combination

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 survival	9	1095	Peto Odds Ratio (95% CI)	0.91 [0.79, 1.05]
1.1 Cisplatin	5	759	Peto Odds Ratio (95% CI)	0.86 [0.72, 1.01]
1.2 Carboplatin	4	336	Peto Odds Ratio (95% CI)	1.05 [0.82, 1.35]

Comparison 5. carboplatin versus cisplatin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 survival	12	2219	Peto Odds Ratio (95% CI)	1.02 [0.93, 1.12]
1.1 single agent	3	392	Peto Odds Ratio (95% CI)	1.01 [0.81, 1.26]
1.2 combination	9	1827	Peto Odds Ratio (95% CI)	1.02 [0.92, 1.14]
2 Age subgroup	2		Peto Odds Ratio (95% CI)	Totals not selected
3 Stage subgroup	3		Peto Odds Ratio (95% CI)	Totals not selected
4 Grade subgroup	2		Peto Odds Ratio (95% CI)	Totals not selected
5 Performance status subgroup	2		Peto Odds Ratio (95% CI)	Totals not selected
6 Residual bulk subgroup	2		Peto Odds Ratio (95% CI)	Totals not selected
7 Extent of operation subgroup	3		Peto Odds Ratio (95% CI)	Totals not selected
8 Histology subgroup	7		Peto Odds Ratio (95% CI)	Totals not selected

Analysis 1.1. Comparison 1 single vs combination non-platinum, Outcome 1 survival.

Review: Chemotherapy for advanced ovarian cancer

Comparison: 1 single vs combination non-platinum

Outcome: 1 survival

Study or subgroup	Combination n/N	Single agent n/N	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI	Weight	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI
a Copenhagan	87/97	73/82		6.1 %	0.92 [0.67, 1.25]
a Milan	32/37	33/37		2.5 %	0.99 [0.61, 1.61]
a ECOG E1172	188/199	199/210		14.9 %	1.07 [0.88, 1.31]
a ECOG E2875	233/245	78/86		9.2 %	1.08 [0.84, 1.39]
a Zagreb	33/34	32/35		2.5 %	1.21 [0.75, 1.97]
a Mayo Clinic 703015	52/55	52/56		4.0 %	0.92 [0.62, 1.35]
a NCICCTC OV1	116/125	118/129		9.0 %	1.01 [0.78, 1.31]
a MRC 1976	148/173	145/171		11.3 %	0.94 [0.75, 1.18]
a˙x002f˙b˙x002f˙c MRC 1981	46/57	51/59		3.7 %	1.07 [0.72, 1.60]
a GOG22	199/229	95/110		9.9 %	1.02 [0.80, 1.31]
a GOG3	237/288	101/130		10.8 %	1.00 [0.79, 1.26]
a/b Princess Margare	40/40	39/43		3.0 %	1.36 [0.87, 2.12]

(*Continued* . . .)

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Study or subgroup	Combination n/N	Single agent n/N	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI	Weight	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI
a SCOCG 1979	76/81	83/87		6.0 %	0.60 [0.44, 0.82]
a NCOG5091	24/24	20/24		1.7 %	1.21 [0.67, 2.19]
a MD Anderson 1974a	41/50	21/25		2.1 %	0.81 [0.48, 1.39]
a MD Anderson 1974b	28/33	88/95		3.4 %	0.86 [0.56, 1.30]
Total (95% CI)				**100.0 %**	**0.98 [0.91, 1.06]**

Heterogeneity: Chi² = 15.67, df = 15 (P = 0.40); I² =4%

Test for overall effect: Z = 0.41 (P = 0.68)

Test for subgroup differences: Not applicable

Analysis 2.1. Comparison 2 single non-platinum vs platinum combination, Outcome 1 survival.

Review: Chemotherapy for advanced ovarian cancer

Comparison: 2 single non-platinum vs platinum combination

Outcome: 1 survival

Study or subgroup	Platinum combination n/N	Single non-platinum n/N	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI	Weight	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI
b/c Loma Linda	4/4	7/7		0.7 %	1.60 [0.41, 6.28]
b/c OCSG 77-61-02	19/21	21/21		2.6 %	0.31 [0.15, 0.64]
a/b Princess Margare	37/40	40/43		6.7 %	0.83 [0.53, 1.30]
b COSA 1978	14/18	18/20		2.6 %	0.54 [0.26, 1.11]
b ECOG EST2878	120/128	110/122		20.1 %	0.97 [0.74, 1.25]
b Southampton	42/45	43/44		7.2 %	0.84 [0.55, 1.29]
b/c COSA 1979	167/183	165/187		28.9 %	1.05 [0.84, 1.30]
b/c Leo Laboratories	49/81	52/76		8.7 %	0.78 [0.52, 1.15]

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Study or subgroup	Platinum combination n/N	Single non-platinum n/N	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI	Weight	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI
b MOCCSG 1980	52/57	43/52		8.2 %	1.27 [0.85, 1.91]
b Edinburgh	40/42	38/38		6.7 %	0.94 [0.60, 1.48]
a˙x002fˆb˙x002fˆc MRC 1981	44/51	44/49		7.6 %	0.98 [0.64, 1.50]
Total (95% CI)				**100.0 %**	**0.93 [0.83, 1.05]**

Heterogeneity: Chi² = 16.42, df = 10 (P = 0.09); I² =39%

Test for overall effect: Z = 1.16 (P = 0.25)

Test for subgroup differences: Not applicable

Analysis 3.1. Comparison 3 non-platinum vs same regimen + platinum, Outcome 1 survival.

Review: Chemotherapy for advanced ovarian cancer

Comparison: 3 non-platinum vs same regimen + platinum

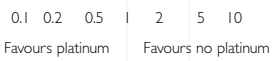
Outcome: 1 survival

Study or subgroup	platinum n/N	no platinum n/N	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI	Weight	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI
1 Added to single-agent					
b/c Loma Linda	4/4	7/7		0.6 %	1.60 [0.41, 6.28]
b/c OCSG 77-61-02	19/21	21/21		2.1 %	0.31 [0.15, 0.64]
b/c COSA 1979	167/183	165/187		23.5 %	1.05 [0.84, 1.30]
b/c Leo Laboratories	49/81	52/76		7.1 %	0.78 [0.52, 1.15]
a˙x002fˆb˙x002fˆc MRC 1981	44/51	44/49		6.1 %	0.98 [0.64, 1.50]
Subtotal (95% CI)	**340**	**340**		**39.4 %**	**0.93 [0.78, 1.10]**

Heterogeneity: Chi² = 11.42, df = 4 (P = 0.02); I² =65%

Test for overall effect: Z = 0.89 (P = 0.38)

2 Added to combination



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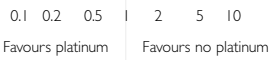
Study or subgroup	platinum n/N	no platinum n/N	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI	Weight	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI
c EORTC 55731	52/72	52/77		7.4 %	1.00 [0.68, 1.47]
c GOG 47	208/244	215/251		30.0 %	0.90 [0.75, 1.09]
c NCOG 5091	30/40	34/44		4.5 %	0.84 [0.52, 1.38]
c SCOCSG 1981	125/143	140/153		18.6 %	0.72 [0.57, 0.92]
Subtotal (95% CI)	**499**	**525**		**60.6 %**	**0.85 [0.74, 0.97]**
Heterogeneity: Chi^2 = 2.73, df = 3 (P = 0.43); I^2 =0.0%					
Test for overall effect: Z = 2.37 (P = 0.018)					
Total (95% CI)				**100.0 %**	**0.88 [0.79, 0.98]**
Heterogeneity: Chi^2 = 14.78, df = 8 (P = 0.06); I^2 =46%					
Test for overall effect: Z = 2.40 (P = 0.017)					
Test for subgroup differences: Chi^2 = 0.64, df = 1 (P = 0.43), I^2 =0.0%					

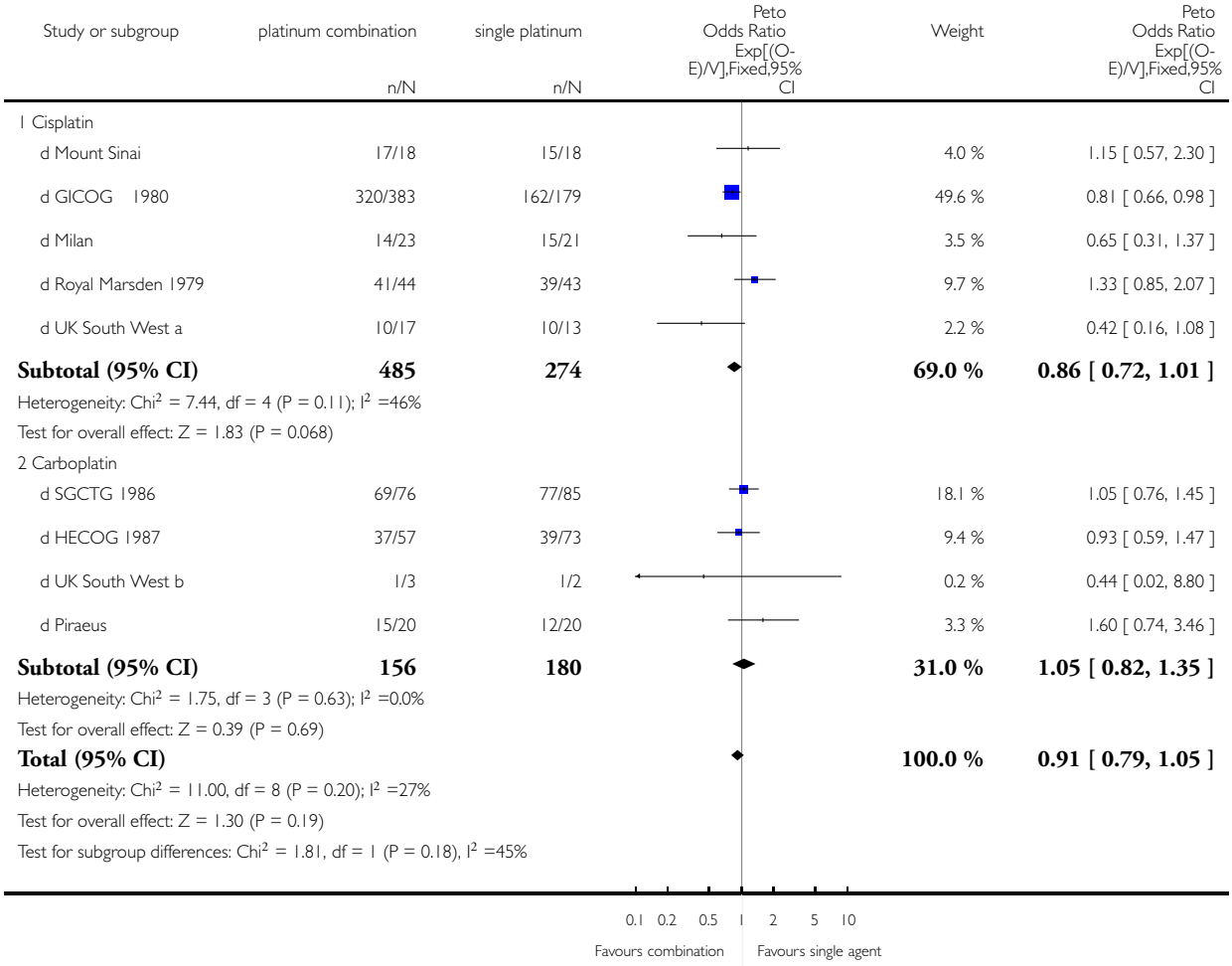


Analysis 4.1. Comparison 4 single platinum vs platinum combination, Outcome 1 survival.

Review: Chemotherapy for advanced ovarian cancer

Comparison: 4 single platinum vs platinum combination

Outcome: 1 survival



Analysis 5.1. Comparison 5 carboplatin versus cisplatin, Outcome 1 survival.

Review: Chemotherapy for advanced ovarian cancer

Comparison: 5 carboplatin versus cisplatin

Outcome: 1 survival

Study or subgroup	carboplatin n/N	cisplatin n/N	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI	Weight	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI
1 single agent					
e Royal Marsden 1981	58/67	57/64		6.6 %	1.00 [0.69, 1.44]
e Wales	37/45	33/43		4.0 %	1.04 [0.65, 1.66]
e GICOG 1984	72/88	73/85		8.4 %	1.01 [0.73, 1.39]
Subtotal (95% CI)	**200**	**192**		**19.0 %**	**1.01 [0.81, 1.26]**
Heterogeneity: Chi² = 0.02, df = 2 (P = 0.99); I² =0.0%					
Test for overall effect: Z = 0.10 (P = 0.92)					
2 combination					
e MOCCSG 1984	23/27	23/29		2.6 %	0.93 [0.52, 1.67]
e EORTC 55836	126/169	120/170		14.2 %	1.07 [0.83, 1.38]
e Mayo Clinic 846151	42/50	43/54		4.8 %	1.24 [0.81, 1.91]
e GONO	65/83	67/82		7.6 %	0.92 [0.66, 1.30]
e NCIC CTC 0v.8	189/224	188/223		21.7 %	0.97 [0.79, 1.19]
e SWOG 8412	156/171	149/171		17.5 %	1.06 [0.85, 1.33]
e GOCA	44/87	41/86		4.9 %	1.11 [0.73, 1.70]
e Athens	62/73	64/76		7.1 %	1.00 [0.70, 1.42]
e Japan	5/29	5/23		0.5 %	0.61 [0.17, 2.20]
Subtotal (95% CI)	**913**	**914**		**81.0 %**	**1.02 [0.92, 1.14]**
Heterogeneity: Chi² = 2.54, df = 8 (P = 0.96); I² =0.0%					
Test for overall effect: Z = 0.44 (P = 0.66)					
Total (95% CI)				**100.0 %**	**1.02 [0.93, 1.12]**
Heterogeneity: Chi² = 2.57, df = 11 (P = 1.00); I² =0.0%					
Test for overall effect: Z = 0.44 (P = 0.66)					
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.92), I² =0.0%					

Analysis 5.2. Comparison 5 carboplatin versus cisplatin, Outcome 2 Age subgroup.

Review: Chemotherapy for advanced ovarian cancer

Comparison: 5 carboplatin versus cisplatin

Outcome: 2 Age subgroup

Study or subgroup	carboplatin n/N	cisplatin n/N	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI
f <=50 years	197/262	204/283		1.05 [0.86, 1.28]
f > 50 years	674/817	650/789		1.00 [0.89, 1.11]

Analysis 5.3. Comparison 5 carboplatin versus cisplatin, Outcome 3 Stage subgroup.

Review: Chemotherapy for advanced ovarian cancer

Comparison: 5 carboplatin versus cisplatin

Outcome: 3 Stage subgroup

Study or subgroup	carboplatin n/N	cisplatin n/N	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI
g FIGO II	20/32	9/28		2.33 [1.11, 4.88]
g FIGO III	656/829	633/810		1.02 [0.91, 1.14]
g FIGO IV	194/215	208/230		1.01 [0.83, 1.24]

Analysis 5.4. Comparison 5 carboplatin versus cisplatin, Outcome 4 Grade subgroup.

Review: Chemotherapy for advanced ovarian cancer

Comparison: 5 carboplatin versus cisplatin

Outcome: 4 Grade subgroup

Study or subgroup	carboplatin n/N	cisplatin n/N	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI
h Borderline/well	133/189	118/177		1.21 [0.94, 1.56]
h Moderate/poor	665/804	651/794		0.98 [0.88, 1.09]

Analysis 5.5. Comparison 5 carboplatin versus cisplatin, Outcome 5 Performance status subgroup.

Review: Chemotherapy for advanced ovarian cancer

Comparison: 5 carboplatin versus cisplatin

Outcome: 5 Performance status subgroup

Study or subgroup	carboplatin n/N	cisplatin n/N	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI
i Good	657/843	629/825		1.03 [0.93, 1.15]
i Poor	153/166	164/177		0.93 [0.74, 1.17]

Analysis 5.6. Comparison 5 carboplatin versus cisplatin, Outcome 6 Residual bulk subgroup.

Review: Chemotherapy for advanced ovarian cancer

Comparison: 5 carboplatin versus cisplatin

Outcome: 6 Residual bulk subgroup

Study or subgroup	carboplatin n/N	cisplatin n/N	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI
j Low	225/338	218/320		0.96 [0.79, 1.16]
j High	352/389	351/393		1.06 [0.91, 1.23]

Analysis 5.7. Comparison 5 carboplatin versus cisplatin, Outcome 7 Extent of operation subgroup.

Review: Chemotherapy for advanced ovarian cancer

Comparison: 5 carboplatin versus cisplatin

Outcome: 7 Extent of operation subgroup

Study or subgroup	carboplatin n/N	cisplatin n/N	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI
k Complete	322/410	323/413		1.02 [0.87, 1.19]
k Incomplete	48/54	51/59		0.97 [0.65, 1.45]
k None	34/36	25/26		1.12 [0.66, 1.91]

Analysis 5.8. Comparison 5 carboplatin versus cisplatin, Outcome 8 Histology subgroup.

Review: Chemotherapy for advanced ovarian cancer

Comparison: 5 carboplatin versus cisplatin

Outcome: 8 Histology subgroup

Study or subgroup	carboplatin n/N	cisplatin n/N	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI
1 serous	429/539	430/548		1.06 [0.93, 1.22]
1 Endemetroid	84/114	81/104		0.75 [0.54, 1.04]
1 Mucinous	59/79	60/72		0.77 [0.52, 1.15]
1 Undifferentiated	44/46	38/46		1.56 [1.00, 2.44]
1 Clear cell	31/34	29/33		1.28 [0.73, 2.25]
1 Mixed	2/3	6/6		0.49 [0.11, 2.13]
1 Other	50/65	54/74		1.25 [0.83, 1.89]

WHAT'S NEW

Date	Event	Description
21 July 2009	Review declared as stable	IPD data

HISTORY

Date	Event	Description
13 October 2008	Amended	Converted to new review format.
7 September 1998	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Members of the AOCTG provided raw data from their own trials for re-analysis and contributed to the development of the project and paper publications

DECLARATIONS OF INTEREST

There is no known conflict of interest

SOURCES OF SUPPORT

Internal sources

- Medical Research Council, UK.

External sources

- No sources of support supplied

NOTES

This review was converted from an Individual Patient Data review originally intended for paper publication. It will, therefore, be updated as per the schedule of the IPD reviewers, rather than according to Cochrane guidelines.

INDEX TERMS

Medical Subject Headings (MeSH)

Antineoplastic Agents [*therapeutic use]; Antineoplastic Combined Chemotherapy Protocols [therapeutic use]; Carboplatin [therapeutic use]; Cisplatin [therapeutic use]; Ovarian Neoplasms [*drug therapy]

MeSH check words

Female; Humans